Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial to Evaluate the Efficacy of Brexpiprazole Monotherapy for the Treatment in Adolescents (13-17 Years old) With Schizophrenia

Summary

EudraCT number	2017-001447-12
Trial protocol	HU ES PL BG FR IT RO
Global end of trial date	03 April 2023

Results information

Result version number	v1 (current)
This version publication date	15 October 2023
First version publication date	15 October 2023

Trial information

Trial identification

Sponsor protocol code	331-10-234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03198078
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001185-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the short-term efficacy and safety of brexpiprazole monotherapy in the treatment of adolescents with schizophrenia.

Protection of trial subjects:

Written informed consent, assent, or both were obtained from a legally acceptable representative (eg, guardian) or subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Mexico: 95
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	Ukraine: 102
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	316
EEA total number of subjects	34

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)	315
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at investigational sites in the United States, Mexico, France, Italy, Poland, Romania, Serbia, Spain, Ukraine, and Russia from 30 June 2017 to 03 April 2023.

Pre-assignment

Screening details:

A total of 376 subjects were screened, of which 316 subjects were enrolled and randomised to brexpiprazole, aripiprazole, or placebo groups in 1:1:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole

Arm description:

Subjects were administered with brexpiprazole oral tablets, daily, dose titrated up to 0.5 mg by Day 4, 1 mg by Day 7, 2 mg by Day 14, then between 2-4 mg after Day 21 up to Week 6 with a 1 mg increase or decrease, based on the Investigator's decision.

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

Dosage and administration details:

Brexpiprazole tablets, flexible dosing from 0.5 to 4 mg/day administered orally up to Week 6.

Arm title	Aripiprazole

Arm description:

Subjects were administered with aripiprazole oral tablets, daily, dose titrated up to 2 mg by Day 4, 5 mg by Day 7, 10 mg by Day 14, then 10, 15 or 20 mg after Day 21 up to Week 6 with a 5 mg increase or decrease, based on the Investigator's decision.

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

Dosage and administration details:

Aripiprazole tablets, flexible dosing from 2 to 20 mg/day administered orally up to Week 6.

Arm title	Placebo

Arm description:

Subjects were administered with brexpiprazole or aripiprazole matching placebo oral tablets, daily up to Week 6.

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:

Matching placebo tablets were administered orally up to Week 6.

Number of subjects in period 1	Brexpiprazole	Aripiprazole	Placebo
Started	110	102	104
Completed	107	97	92
Not completed	3	5	12
Adverse Event	-	1	2
Pregnancy	-	1	-
Withdrawal by Subject	1	-	2
Lost to follow-up	1	-	-
Withdrawal by Caregiver	1	3	5
Lack of efficacy	-	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole
Reporting group description:	
Subjects were administered with brexpiprazole oral tablets, daily, dose titrated up to 0.5 mg by Day 4, 1 mg by Day 7, 2 mg by Day 14, then between 2-4 mg after Day 21 up to Week 6 with a 1 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Aripiprazole
Reporting group description:	
Subjects were administered with aripiprazole oral tablets, daily, dose titrated up to 2 mg by Day 4, 5 mg by Day 7, 10 mg by Day 14, then 10, 15 or 20 mg after Day 21 up to Week 6 with a 5 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered with brexpiprazole or aripiprazole matching placebo oral tablets, daily up to Week 6.	

Reporting group values	Brexpiprazole	Aripiprazole	Placebo
Number of subjects	110	102	104
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	15.3	15.3	15.2
standard deviation	± 1.5	± 1.4	± 1.4
Gender categorical Units: Subjects			
Female	58	57	51
Male	52	45	53
Race Units: Subjects			
White	70	66	68
Black or African American	8	7	6
American Indian or Alaska Native	2	1	4
Asian	1	1	0
Other	29	27	25
Missing	0	0	1
Ethnicity Units: Subjects			

Hispanic or Latino	34	32	34
Not Hispanic or Latino	75	70	68
Other	1	0	1
Missing	0	0	1
Positive and Negative Syndrome Scale (PANSS) Total Score			
The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) to 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranges from 30 (best possible outcome) to 210 (worst possible outcome). Higher scores indicate worsening of symptoms.			
Units: score on a scale			
arithmetic mean	101.1	101.0	102.1
standard deviation	± 14.9	± 13.0	± 16.3

Reporting group values	Total		
Number of subjects	316		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	166		
Male	150		
Race			
Units: Subjects			
White	204		
Black or African American	21		
American Indian or Alaska Native	7		
Asian	2		
Other	81		
Missing	1		
Ethnicity			
Units: Subjects			
Hispanic or Latino	100		
Not Hispanic or Latino	213		
Other	2		
Missing	1		

Positive and Negative Syndrome Scale (PANSS) Total Score			
The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) to 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranges from 30 (best possible outcome) to 210 (worst possible outcome). Higher scores indicate worsening of symptoms.			
Units: score on a scale arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Brexpiprazole
Reporting group description:	
Subjects were administered with brexpiprazole oral tablets, daily, dose titrated up to 0.5 mg by Day 4, 1 mg by Day 7, 2 mg by Day 14, then between 2-4 mg after Day 21 up to Week 6 with a 1 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Aripiprazole
Reporting group description:	
Subjects were administered with aripiprazole oral tablets, daily, dose titrated up to 2 mg by Day 4, 5 mg by Day 7, 10 mg by Day 14, then 10, 15 or 20 mg after Day 21 up to Week 6 with a 5 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered with brexpiprazole or aripiprazole matching placebo oral tablets, daily up to Week 6.	

Primary: Change From Baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score
End point description:	
The PANSS consisted of three subscales: total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) to 7 (extremely severe symptoms). PANSS total score was sum of rating scores for 7 positive scale items, 7 negative scale items, & 16 general psychopathology scale items from PANSS panel. PANSS total score ranges from 30 (best possible outcome) to 210 (worst possible outcome). Higher scores indicate worsening of symptoms. Least squares (LS) mean was determined by Mixed-effect model repeated measures (MMRM) method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value and baseline visit interaction as a covariate, & with an unstructured covariance. Efficacy sample included all randomised subjects who received at least 1 dose of investigational medicinal product (IMP),had a baseline assessment, & at least one post-baseline assessment of the PANSS Total Score.	
End point type	Primary
End point timeframe:	
Baseline to Week 6	

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)	-22.75 (± 1.49)	-23.95 (± 1.57)	-17.42 (± 1.58)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136 [1]
Method	MMRM
Parameter estimate	Least squares (LS) mean Difference
Point estimate	-5.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.55
upper limit	-1.1

Notes:

[1] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [2]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-6.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-2.21

Notes:

[2] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Secondary: Change From Baseline to Week 6 in PANSS Positive and Negative Sub-scales Scores

End point title	Change From Baseline to Week 6 in PANSS Positive and Negative Sub-scales Scores

End point description:

PANSS has 7 positive symptom constructs: delusions, conceptual disorganisation, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility; and 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. Each item`s severity was rated on 7-point scale, with score of 1 (absence of symptoms) to 7 (extremely severe symptoms). PANSS positive & negative subscale scores were the sum of rating scores for 7 positive & 7 negative items respectively. Both scores range from 7 (best possible outcome) to 49 (worst possible outcome). Higher scores denote worsening of symptoms. LS mean was determined by MMRM method. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)				
Change From Baseline in PANSS Positive Score	-6.58 (± 0.43)	-7.29 (± 0.45)	-5.14 (± 0.46)	
Change From Baseline in PANSS Negative Score	-4.70 (± 0.41)	-4.77 (± 0.43)	-3.82 (± 0.44)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Statistical analysis description: PANSS positive sub-scale score	
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0205 [3]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	-0.22

Notes:

[3] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Aripiprazole vs Placebo
Statistical analysis description: PANSS positive sub-scale score	
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [4]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-0.91

Notes:

[4] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Brexpiprazole vs Placebo
Statistical analysis description:	
PANSS negative sub-scale score	
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136 [5]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.04
upper limit	0.28

Notes:

[5] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Aripiprazole vs Placebo
Statistical analysis description:	
PANSS negative sub-scale score	
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1158 [6]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	0.24

Notes:

[6] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Secondary: Percentage of Subjects Achieving Response

End point title	Percentage of Subjects Achieving Response

End point description:

Response was defined as at least 30% improvement from baseline in PANSS Total Score or CGI score of 1 or 2. The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel, and ranges from 30 (best possible outcome) to 210 (worst possible outcome). The CGI scale is an investigator-rated evaluation that assesses the severity of a subject's illness on a 7-point scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). Percentage of subjects achieving response was determined by Last Observation Carried Forward (LOCF) method. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score. Percentages are rounded off to the nearest decimal point.

End point type	Secondary

End point timeframe:

Up to 6 weeks

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: percentage of subjects				
number (not applicable)	43.64	43.56	28.16	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response rate
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	2.2

Notes:

[7] - P-value was analysed by Cochran-Mantel-Haenszel (CMH) general association test controlling for (pooled) centers.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0224 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Response rate
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.16

Notes:

[8] - P-value was analysed by CMH general association test controlling for (pooled) centers.

Secondary: Percentage of Subjects Achieving Remission

End point title	Percentage of Subjects Achieving Remission

End point description:

Remission was defined as a score of ≤ 3 on each of the following specific PANSS items: delusions (positive scale item [P] 1), unusual thought content (general scale item [G] 9), hallucinatory behavior (P3), conceptual disorganisation (P2), mannerisms/posturing (G5), blunted affect (negative scale item [N] 1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6). Each item`s severity was rated on 7-point scale, with score of 1 (absence of symptoms) to 7 (extremely severe symptoms). Percentage of subjects achieving remission was determined by LOCF method. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score. Percentages are rounded off to the nearest decimal point.

End point type	Secondary

End point timeframe:

Up to 6 weeks

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: percentage of subjects				
number (not applicable)	29.09	35.64	23.30	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4415 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Remission Rate
Point estimate	1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.81

Notes:

[9] - P-value was analysed by CMH general association test controlling for (pooled) centers.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0472 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Ratio of Remission Rate
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.16

Notes:

[10] - P-value was analysed by CMH general association test controlling for (pooled) centers.

Secondary: Change From Baseline to Week 6 in Children’s Global Assessment Scale (CGAS) Total Score

End point title	Change From Baseline to Week 6 in Children’s Global Assessment Scale (CGAS) Total Score

End point description:

The CGAS is a 100-point rating scale measuring psychological, social, and school functioning for children aged 6-17 years and provides a global measure of the severity of disturbance. The scale is separated into 10-point sections that are headed with a description of the level of functioning and followed by examples matching the interval. The score ranges from 0-100, 1 to 10 indicates the need for constant supervision and 91 to 100 indicates superior functioning in all areas. Higher scores indicate better functioning. LS mean was determined by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)	10.56 (± 1.00)	12.07 (± 1.05)	8.08 (± 1.06)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0854 [11]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	5.31

Notes:

[11] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072 [12]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	3.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	6.88

Notes:

[12] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Secondary: Change From Baseline to Week 6 in Clinical Global Impression Severity (CGI-S) Score

End point title	Change From Baseline to Week 6 in Clinical Global Impression Severity (CGI-S) Score

End point description:

The CGI-S scale is an investigator-rated evaluation that assesses the severity of a subject’s illness on a 7-point scale, ranging from 1 to 7. The investigator answered the question: “Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?”. Response

choices were: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects. Higher scores indicate worse condition. LS mean was determined by the MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)	-0.92 (± 0.09)	-1.01 (± 0.09)	-0.80 (± 0.09)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3589 [13]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.13

Notes:

[13] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1118 [14]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.05

Notes:

[14] - P-value was analysed by MMRM method with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as a covariate, and with an unstructured covariance.

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

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

End point description:

The efficacy of brexpiprazole in the treatment was rated for each subject using the CGI-I. The investigator rated the subject's total improvement whether or not it was entirely due to drug treatment on a 7-point scale, ranging from 0 to 7. 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. Higher scores indicate worse condition. Mean CGI-I scale score was determined by LOCF method. Efficacy sample included all randomised subjects who received at least 1 dose of IMP, had a baseline assessment, and at least one post-baseline assessment of the PANSS Total Score.

End point type	Secondary

End point timeframe:

Week 6

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
arithmetic mean (standard deviation)	2.86 (± 0.95)	2.79 (± 0.97)	3.17 (± 1.08)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0287 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.03

Notes:

[15] - P-value was analysed by CMH row mean scores differ test controlling for study center.

Statistical analysis title	Aripiprazole vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0184 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.06

Notes:

[16] - P-value was analysed by CMH row mean scores differ test controlling for study center.

Secondary: Number of Subjects With Adverse Events (AEs) and Trial Discontinuations Due to AEs

End point title	Number of Subjects With Adverse Events (AEs) and Trial Discontinuations Due to AEs

End point description:

An AE was defined as any untoward medical occurrence in a subject administered with a medicinal product that does not necessarily have a causal relationship with the treatment. Safety sample included all randomised subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 21 days after the last dose of study drug (up to approximately 9 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	102	104	
Units: subjects				
AEs	46	56	44	
Trial Discontinuation Due to AEs	0	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent AEs (TEAEs), Serious

TEAEs, and TEAEs Graded by Severity

End point title	Number of Subjects With Treatment-emergent AEs (TEAEs), Serious TEAEs, and TEAEs Graded by Severity

End point description:

AE is any untoward medical occurrence in subject administered with medicinal product that does not necessarily have a causal relationship with treatment. An SAE is any AE that results in appearance of (or worsening of any pre-existing) undesirable signs, symptoms/medical conditions which is fatal, life-threatening, result in persistent/significant disability/incapacity, constitutes congenital anomaly/birth defect, and requires inpatient hospitalisation/prolongation of existing hospitalisation. TEAE is AE after start of treatment/if event was continuous from baseline, medicinal product related, or resulted in death, discontinuation, interruption/reduction of medicinal product. TEAEs were graded on a 3-point scale: 1(Mild:Discomfort noticed, but no disruption to daily activity), 2(Moderate:Discomfort sufficient to reduce/affect normal daily activity), 3(Severe:Inability to work/perform normal daily activity). Safety sample=all randomized participants who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 21 days after the last dose of study drug (up to approximately 9 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	102	104	
Units: subjects				
Serious TEAEs	1	1	3	
Mild TEAEs	33	47	32	
Moderate TEAEs	17	16	13	
Severe TEAEs	2	0	1	
TEAEs	44	53	42	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Relevant Abnormalities in Vital Signs

End point title	Number of Subjects With Potentially Clinically Relevant Abnormalities in Vital Signs

End point description:

Vital sign measurements included body weight measured in kilograms (kg), systolic blood pressure (SBP), and diastolic blood pressure (DBP), measured in millimetres of mercury (mmHg). Blood pressure measurements were made in the supine, sitting, and standing positions after the subject had been in each position for at least 3 minutes. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with at least one post-baseline result for the specified vital signs.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: subjects				
SBP Sitting (mmHg): Low	0	0	1	
SBP Standing (mmHg): Low	1	1	0	
SBP Supine (mmHg): Low	0	0	1	
DBP Standing (mmHg): Low	1	0	0	
DBP Supine (mmHg): Low	0	1	0	
Weight (kg): Low	5	2	4	
Weight (kg): High	9	5	5	
Orthostatic Hypotension (mmHg): Low	2	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Weight

End point title	Mean Change From Baseline in Weight

End point description:

Change in weight was reported, in kg. Safety sample included all randomised subjects who received at least 1 dose of IMP. ‘Number of subjects analysed’ indicates the number of subjects with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: kg				
arithmetic mean (standard deviation)	0.8 (± 2.6)	0.5 (± 2.7)	0.0 (± 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Height

End point title	Mean Change From Baseline in Height

End point description:

Change in height was reported in centimeters (cm). Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for the endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	99	96	
Units: cm				
arithmetic mean (standard deviation)	0.2 (± 1.1)	0.2 (± 2.9)	0.3 (± 0.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Body Mass Index (BMI)

End point title	Mean Change From Baseline in Body Mass Index (BMI)

End point description:

Change in BMI was reported in kilograms per square metre (kg/m^2). Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	99	96	
Units: kg/m^2				
arithmetic mean (standard deviation)	0.2 (± 1.1)	0.3 (± 1.5)	0.0 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Waist Circumference

End point title	Mean Change From Baseline in Waist Circumference

End point description:

Change in waist circumference was reported in 'cm'. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: cm				
arithmetic mean (standard deviation)	0.6 (± 3.9)	-0.3 (± 4.3)	0.0 (± 5.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At Least One Occurrence of Suicidal Behavior or Suicidal Ideation as Recorded on Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With At Least One Occurrence of Suicidal Behavior or Suicidal Ideation as Recorded on Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS is a scale used to report at least one occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior was defined as reporting any of the following items: actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior. The suicidal ideation total score is the sum of intensity scores of 5 items (frequency, duration, controllability, deterrents, and reasons for ideation). The score of each intensity item ranges from 0 (none) to 5 (worst) and the total score ranges from 0 to 25. Lower scores indicate improvement. Safety sample included all randomised subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	102	104	
Units: subjects	1	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Relevant Laboratory Test Values

End point title	Number of Subjects With Potentially Clinically Relevant

	Laboratory Test Values

End point description:

Potentially clinically relevant laboratory values assessed included - serum chemistry [including blinded prolactin], hematology, and urinalysis. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for the endpoint analysis. 'Number analysed (n)' indicates the number of subjects with at least one post-baseline numeric result for the specified parameter.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	98	99	
Units: subjects				
Alanine aminotransferase (U/L): High (n=105,98,98)	1	2	0	
Bilirubin (mg/dL): High (n=105, 96, 91)	0	1	0	
Cholesterol, Fasting (mg/dL): High (n=102, 98, 96)	2	3	0	
Creatine kinase (U/L): High (n=105, 98, 98)	5	4	1	
Glucose, Fasting (mg/dL): High (n=102, 98, 96)	16	15	9	
HDL Cholesterol, Fasting (mg/dL):Low(n=100,96,94)	12	10	13	
LDL Cholesterol, Fasting (mg/dL):High(n=100,96,94)	2	3	0	
Triglycerides Fasting (mg/dL):High(n=102, 98, 96)	13	7	10	
Urate (mg/dL): High (n=105, 98, 98)	0	0	1	
Hematocrit (%): Low (n=104, 97, 98)	4	0	1	
Hemoglobin (g/dL): Low (n=104, 98, 99)	2	0	0	
Leukocytes (10^9/L): Low (n=104, 98, 99)	0	1	0	
Leukocytes (10^9/L): High (n=104, 98, 99)	0	0	1	
Protein, Urine: High (n=105, 98, 97)	2	2	0	
Eosinophils/Leukocytes (%): High (n=104,98,99)	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Parameters

End point title	Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Parameters

End point description:

Twelve-lead ECG recordings were obtained after the subject was supine and at rest for at least 5 minutes. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for the endpoint analysis. ‘Number analysed (n)’ indicates the number of subjects with at least one post-baseline numeric result for the specified parameter.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	107	97	94	
Units: subjects				
Rate: Bradycardia (n=107, 97, 93)	0	0	1	
Rhythm: Sinus Bradycardia (n=107, 97, 93)	0	0	1	
Rhythm: SupraventricularPrematureBeat(n=107, 97,94)	0	1	1	
Rhythm: Ventricular Premature Beat (n=106, 97, 93)	1	0	0	
ST/T Morphology: QTcF (n=107, 97, 93)	0	1	0	
ST/T Morphology: QTcN (n=107, 97, 93)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simpson Angus Scale (SAS) Total Score

End point title	Change From Baseline in Simpson Angus Scale (SAS) Total Score

End point description:

The SAS consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Severity of each item was rated on a 5-point scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where lower scores indicate less severe condition. LS mean was determined by Analysis of Covariance (ANCOVA) model with treatment and study center as main effects and baseline value as covariate. Safety sample included all randomised subjects who received at least 1 dose of IMP. ‘Number of subjects analysed’ indicates the number of subjects with data available for the endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)				
Change From Baseline to Last Visit	0.04 (± 0.12)	0.15 (± 0.12)	-0.03 (± 0.13)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Statistical analysis description:	
LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.	
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.39

Statistical analysis title	Aripiprazole vs Placebo
Statistical analysis description:	
LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.	
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.51

Secondary: Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point title	Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point description:

The AIMS assessment consists of 12 items rating the involuntary movements: Facial and oral movements (4 items), extremity movements (2 items), and trunk movements (1 item) were observed unobtrusively while the subject is at rest and the investigator also made global judgments on the subject's dyskinesias (2 items), and dental status (2 items). Severity of each item was rated on a 5-point scale, with a score of 0 (absence of symptoms) to 4 (severe condition). Total Score is the sum of the scores of all 12 items, ranging from 0 to 48, higher scores indicate severe condition. LS mean was determined by ANCOVA model with treatment and study center as main effects and baseline value as covariate. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for the endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)	-0.12 (± 0.09)	0.05 (± 0.09)	-0.06 (± 0.09)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo

Statistical analysis description:

LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.

Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.18

Statistical analysis title	Aripiprazole vs Placebo

Statistical analysis description:

LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.

Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.36

Secondary: Change From Baseline in Barnes Akathisia Rating Scale (BARS) Score

End point title	Change From Baseline in Barnes Akathisia Rating Scale (BARS) Score

End point description:

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point scale, with a score of 0 (absence of symptoms) to 3 (severe condition) and the global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the scores of all 4 items, ranging from 0 to 14, higher scores indicate severe condition. LS mean was determined by ANCOVA model with treatment and study center as main effects and baseline value as covariate. Safety sample included all randomised subjects who received at least 1 dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for the endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline up to last visit (approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	101	103	
Units: score on a scale				
least squares mean (standard error)	0.01 (± 0.03)	0.06 (± 0.03)	0.01 (± 0.03)	

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo

Statistical analysis description:

LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.

Comparison groups	Brexpiprazole v Placebo

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.09

Statistical analysis title	Aripiprazole vs Placebo

Statistical analysis description:

LS mean difference was analysed by ANCOVA model, with treatment and study center as main effects and baseline value as covariate.

Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.14

Secondary: Number of Subjects With Severe Psychotropic Side Effects as Assessed by Udvalg for Kliniske Undersogelser (UKU) Rating Scale

End point title	Number of Subjects With Severe Psychotropic Side Effects as Assessed by Udvalg for Kliniske Undersogelser (UKU) Rating Scale

End point description:

The UKU rating scale is a semi-structured interview used to assess the side effects of subjects being treated with antipsychotic drugs. The scale is divided into 6 sub-scales: Psychic, neurological, autonomic, other, global assessment by subject, and global assessment by doctor. The scale has a total of 48 items, each item is rated on a 4-point scale (0=not present; 1=mild; 2=moderate; 3=severe), and the total score ranges from 0 to 144. Higher ratings indicate greater impairment. The severe side effects are reported in this endpoint. Safety sample included all randomised subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	102	104	
Units: subjects				
Psychic: Concentration Difficulties	7	10	8	
Psychic: Asthenia/Lassitude	6	3	1	
Psychic: Failing Memory	2	2	4	
Psychic: Depression	0	2	1	
Psychic: Tension/Inner Unrest	4	3	9	
Psychic: Increased Duration of Sleep	0	1	0	
Psychic: Reduced Duration of Sleep	4	1	1	
Psychic: Increased Dream Activity	0	2	0	
Psychic: Emotional Indifference	3	6	6	
Neurologic: Akathisia	1	1	0	
Autonomic: Nausea/Vomiting	0	0	1	
Autonomic: Micturition Disturbances	0	1	0	
Autonomic: Palpitations/Tachycardia	1	0	1	
Autonomic: Increased Tendency to Sweating	1	0	0	
Other: Weight Gain	0	1	0	
Other: Amenorrhoea	0	1	0	
Other: Migraine	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Cognitive Adverse Effects Assessed by New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT)

End point title	Number of Subjects With Cognitive Adverse Effects Assessed by New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT)

End point description:

The NY-AACENT is used to detect changes in cognitive function subsequent to pharmacological or similar treatments for neurological or psychiatric problems, specifically designed to be used in pediatric population (ages 12 to 17), but could have been utilised with other age groups, as appropriate. Number of subjects with at least one occurrence of the corresponding signs/symptoms are reported in this endpoint. Safety sample included all randomised subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to last dose of study drug (up to approximately 6 weeks)

End point values	Brexpiprazole	Aripiprazole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	102	104	
Units: subjects				
Working Memory	88	79	83	
Attention/Vigilance	98	90	91	
Verbal Learning	71	70	69	
Visual Learning	46	46	44	
Reasoning	97	86	83	
Speed of Processing	88	84	82	
Social Cognition	91	87	84	
Any Signs/Symptoms	100	91	92	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug up to 21 days after the last dose of study drug (up to approximately 9 weeks)	
Adverse event reporting additional description:	
Safety sample included all randomised subjects who received at least 1 dose of IMP.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Brexpiprazole
Reporting group description:	
Subjects were administered with brexpiprazole oral tablets, daily, dose titrated up to 0.5 mg by Day 4, 1 mg by Day 7, 2 mg by Day 14, then between 2-4 mg after Day 21 up to Week 6 with a 1 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Aripiprazole
Reporting group description:	
Subjects were administered with aripiprazole oral tablets, daily, dose titrated up to 2 mg by Day 4, 5 mg by Day 7, 10 mg by Day 14, then 10, 15 or 20 mg after Day 21 up to Week 6 with a 5 mg increase or decrease, based on the Investigator's decision.	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered with brexpiprazole or aripiprazole matching placebo oral tablets, daily up to Week 6.	

Serious adverse events	Brexpiprazole	Aripiprazole	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 110 (0.91%)	1 / 102 (0.98%)	3 / 104 (2.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 110 (0.00%)	1 / 102 (0.98%)	1 / 104 (0.96%)
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	1 / 110 (0.91%)	0 / 102 (0.00%)	2 / 104 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Brexpiprazole	Aripiprazole	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 110 (17.27%)	28 / 102 (27.45%)	16 / 104 (15.38%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	4 / 110 (3.64%)	7 / 102 (6.86%)	3 / 104 (2.88%)
occurrences (all)	4	9	3
Headache			
subjects affected / exposed	7 / 110 (6.36%)	5 / 102 (4.90%)	5 / 104 (4.81%)
occurrences (all)	7	6	5
Somnolence			
subjects affected / exposed	5 / 110 (4.55%)	11 / 102 (10.78%)	5 / 104 (4.81%)
occurrences (all)	6	12	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 110 (1.82%)	8 / 102 (7.84%)	0 / 104 (0.00%)
occurrences (all)	3	9	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 110 (6.36%)	4 / 102 (3.92%)	4 / 104 (3.85%)
occurrences (all)	7	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2018	• Revised EudraCT ID • Clarified that adequately trained clinician is psychiatrist/local medical equivalent "who is experienced in treating adolescents with schizophrenia" • Clarified that subjects must be between 13 and 17 years of age, inclusive, at time of baseline(Day 1), in addition to time of informed consent/assent • Clarified that subjects must have a PANSS Total Score ≥80 at screening and baseline(Day 1) • Removed inclusion criteria for previous response to antipsychotic treatment (other than clozapine), for history of relapse/exacerbation of symptoms when not receiving antipsychotic treatment • Clarified exclusion criterion on diagnosis to exclude all subjects with Diagnostic and Statistical Manual of Mental Disorders -5th Edition (DSM-5) diagnosis other than schizophrenia that has been primary focus of treatment within 3 months of screening • Updated possible sample size to 160/arm • Modified exclusion criteria for subjects considered treatment resistant to antipsychotic medication • Added exclusion criteria for subjects known to have medication compliance issues that lead to intramuscular (IM) depot medication use and who report a true allergic response to aripiprazole or brexpiprazole • Removed exclusion of subjects exposed to brexpiprazole • Modified exclusion criteria for subjects who have been exposed to "IM depot therapy" to on IM depot therapy within 5×half-life of medication • Added: recording of lifetime antipsychotic use to screening procedure, recording of height to screening & Week 6, body temperature to vital sign measurements, dispensing of IMP at Weeks 1, 2, 3, 4, and 5 to schedule of assessments • Modified maximum allowable dose of clonazepam as rescue therapy during trial to 1.5 mg/day throughout trial • Corrected description & basis of PANSS scales rating • Modified 'Hy's Law' and drug-induced liver injury to potential serious hepatotoxicity.
16 June 2020	• Deleted text stating that translation of ICFs with back translation for confirmation will be utilised. • Clarified that stimulants are prohibited within 28 days (instead of 1 month) prior to dosing for subjects with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), for consistency. • Deleted the footnote superscript note from all assessment time points for serum pregnancy test and urine pregnancy test. • Added a single footnote superscript note next to the urine pregnancy assessment. The footnote for the urine pregnancy assessment was updated to state that if the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. • Deleted text stating that the methods of follow-up for complete withdrawal of consent will also be noted in the trial ICF.

05 July 2022	• Reduced sample size to 315 subjects (105 subjects per arm). • Deleted text "To ensure that trial is adequately powered, the estimate of the trial variability will be obtained at the blinded interim analysis. The variability will be estimated based on a blinded and pooled analysis of all treatment arms. Sample size may be adjusted up to the maximum of 160 subjects per arm." describing SD re-estimation. • Replaced the new power calculated based on the reduced sample size (80%). No changes were made to assumptions in calculation (nominal 2-sided alpha level of 0.05 to detect a −7.4-point reduction in PANSS Total Score change from baseline to Week 6 for brexpiprazole vs placebo assuming a SD of 19%). • Replaced the requirement for at least 1 post-randomisation to postbaseline efficacy evaluation for the PANSS Total Score. • Added a description of the estimand to expand on the primary efficacy analysis text. • Added a statement regarding the primary endpoint analysis that the comparison between brexpiprazole 2 – 4 mg and placebo would be tested at a significance level of 0.05 (2-sided). • Added definition for remission to the secondary efficacy endpoint that is based on the aripiprazole and brexpiprazole trials. • Deleted the use of log rank test for testing differences in time from randomisation to remission to be consistent with the analysis method used in other brexpiprazole studies. • Changed Efficacy sample to Randomisation Sample which is conventional for analysis of demographics and baseline characteristics.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported