14 December 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

RXULTI

Brexpiprazole

Procedure no: EMEA/H/C/003841/P46/004

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	20 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	n/a	☐
☒	CHMP adoption of conclusions:	14 Dec 2023	14 Dec 2023	☐

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1. Introduction

On 29th September 2023, the MAH submitted a completed paediatric study for RXULTI (brexpiprazole), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation

measure. A short critical expert overview has also been

provided.

Rxulti tablets was approved in EU in 2018 and is currently indicated for the treatment of schizophrenia in adults.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that trial 331-10-234 was conducted to determine the safety and efficacy of brexpiprazole for the acute treatment of adolescents (13 years and older) with schizophrenia, in accordance with the EU Paediatric Investigation Plan (EMEA-001185-PIP01-11-M08). The type II variation application, consisting of the full relevant data package (i.e containing several studies), is expected to be submitted by March 2025. A line listing of all the concerned studies is annexed.

In adolescents with schizophrenia and bipolar spectrum disorder, a dose escalation pharmacokinetic (PK) trial (Trial 331-10-233) was conducted and its results, as stated by the MAH, supported the dosing (2 to 4 mg) for this trial (Trial 331-10-234). However, data coming from Trial 331-10-233 will be submitted and assessed within the type II variation for the extension of indication.

2.2. Information on the pharmaceutical formulation used in the study

Brexpiprazole is supplied as 0.25-, 0.5-, 1.0-, 2.0-, 3.0-, and 4.0-mg tablets for oral use. No changes have been made to the current approved formulations of brexpiprazole.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study 331-10-234.

2.3.2. Clinical study number and title

Study number 331-10-234

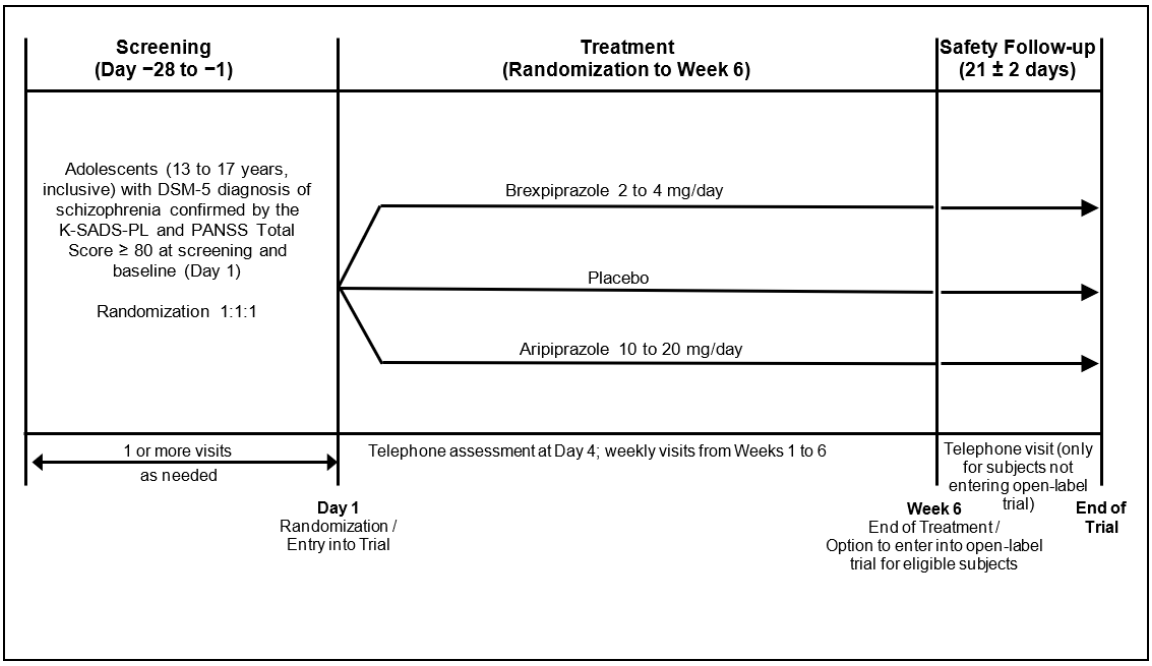
Title: Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial to Evaluate the Efficacy of Brexpiprazole Monotherapy for the Treatment in Adolescents (13-17 years old) With Schizophrenia.

Description

Trial 331-10-234 was a phase 3, multicentre, multi-national, randomized, double-blind, placebo- and active-controlled trial evaluating the short-term efficacy and safety of brexpiprazole monotherapy compared with placebo in adolescents 13 to 17 years old with a diagnosis of schizophrenia. The trial consisted of a screening period (28 days), a 6-week double-blind treatment period, and a 21-day safety follow-up period. For the 6-week double-blind treatment period, subjects were randomized 1:1:1 to 1 of 3 treatment arms: 2-4 mg/day brexpiprazole, 10-20 mg/day aripiprazole, or placebo.

After completing treatment, subjects had the option to enter the open-label trial, Trial

331-10-236. A schematic of the trial design is provided in Figure below.



DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version; PANSS = Positive and Negative Syndrome Scale.

Methods

Study participants

The trial population comprised adolescent subjects (13 to 17 years of age) with a Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) diagnosis of schizophrenia and which was confirmed by Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL), a Positive and Negative Syndrome Scale (PANSS) Total Score ≥ 80 at screening and at baseline (Day 1), and a history of the illness (diagnosis or symptoms) for at least 6 months prior to screening.

Treatments

Subjects were randomized 1:1:1 to 1 of 3 double-blind treatment arms in the 6-week treatment double-blind period:

- Brexpiprazole 0.5 mg tablet daily from Day 1 to Day 4; 1 mg brexpiprazole daily from

Day 5 to Day 7; and 2 mg brexpiprazole daily (minimum dose) from Day 8 to Day 14. From Day 15 to Day 21, the dose was either changed from 2 mg to 3 mg, or it was kept at 2 mg. After this titration period, the investigators either kept the subject at a maintenance dose, increased the dose by 1 mg to a maximum of 4 mg/day, or decreased the dose by 1 mg.

- Aripiprazole 2 mg tablet daily from Day 1 to Day 4; 5 mg aripiprazole daily from Day 5 to Day 7; and 10 mg aripiprazole daily from Day 8 to Day 14. Beginning on Day 15, the dose was either changed from 10 mg to 15 mg, or it was kept at 10 mg.

  After Day 21, the investigators either kept the subject at a maintenance dose, increased the dose by 5 mg to a maximum of 20 mg, or decreased the dose by 5 mg.

- Placebo tablet daily.

All doses of the double blinded IMPs were taken orally QD and were administered without regard to meals.

Objective(s)

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

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to Week 6 in PANSS Total Score.

The secondary efficacy endpoints were as follows:

- Change in the PANSS Positive and Negative Subscale Scores
- Percentage of subjects achieving response. Response is defined as at least 30% improvement from baseline in PANSS Total Score or Clinical Global Impression - Improvement (CGI-I) score of 1 or 2.
- Percentage of subjects achieving remission. Remission is defined as a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6).
- Change in the Children's Global Assessment Scale (CGAS) score
- Change in the Clinical Global Impression - Severity of Illness (CGI-S) scale
- Clinical Global Impression - Improvement scale

Safety was assessed by the following secondary endpoints:

- The frequency and severity of adverse events (AEs), serious AEs (SAEs) (clinical and laboratory), and discontinuation from the trial due to AEs
- Weight, height, body mass index, and waist circumference
- Analysis of potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C- SSRS)
- Clinical laboratory tests and urinalysis results (including serum prolactin), vital signs, physical examinations, and electrocardiogram (ECG) parameters
- Changes on the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS)
- Comprehensive psychotropic side effects as assessed by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale
- Cognitive adverse effects as assessed by the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY AACENT)

Exploratory endpoints included the following:

[redacted]

Sample size and Randomisation

Determination of Sample Size*:*

The treatment effect of brexpiprazole in the sample size assumption was obtained from the estimated treatment effect in the aripiprazole trial conducted in adolescent subjects with schizophrenia (study 31- 03-239). In this trial, two fixed doses of aripiprazole 10 mg/day (N=99) and 30 mg/day (N=97) were compared to placebo (N=98). The placebo-subtracted LS mean changes from baseline to Week 6 in PANSS Total score were -7.4 for aripiprazole 30 mg/day and -5.5 for aripiprazole 10 mg/day respectively, and the within-group standard deviation estimate was around 19.

As a result, a -7.4-point reduction (based on the estimated treatment effect for aripiprazole 30 mg/day) and a within-group standard deviation=19 in the mean change from baseline to Week 6 in PANSS Total score for brexpiprazole vs placebo are used in the sample size calculation.

A sample size of 105 subjects per arm was considered adequate for this trial. It provided at least 80% power at a 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 versus placebo, assuming a standard deviation (SD) of 19. With a 1:1:1 allocation ratio, the overall sample size of this trial was planned to be 315 subjects.

This provided a sample size comparable to other similar trials. A total of 376 subjects were screened for this trial and 316 subjects were randomized to double blind investigational medicinal product (IMP) (110 subjects to brexpiprazole, 102 subjects to aripiprazole, and 104 subjects to placebo). All 316 subjects (100.0%) who were randomized, received at least 1 dose of IMP and, accordingly, were analysed for safety. Of the 316 subjects, 314 subjects (99.4%) were analysed for efficacy. One subject (1.0%) each in the aripiprazole group and the placebo group were included in the Safety Sample but excluded from the Efficacy Sample because they did not have valid postbaseline assessments for PANSS Total Score.

Subject disposition for the randomized sample is presented in Table 0-1.

Table 0-1 Subject Disposition (Randomized Sample)

Number of Subjects	Brexpiprazole (N = 110) n (%)[a]	Aripiprazole (N = 102) n (%)[a]	Placebo (N = 104) n (%)[a]	Total (N = 316) n (%)[a]
Screened				376
Randomized	110 (100.0)	102 (100.0)	104 (100.0)	316 (100.0)
Treated	110 (100.0)	102 (100.0)	104 (100.0)	316 (100.0)
Completed	107 (97.3)	97 (95.1)	92 (88.5)	296 (93.7)
Discontinued	3 (2.7)	5 (4.9)	12 (11.5)	20 (6.3)
Analyzed For Safety[b]	110 (100.0)	102 (100.0)	104 (100.0)	316 (100.0)
Analyzed For Efficacy[c]	110 (100.0)	101 (99.0)	103 (99.0)	314 (99.4)

IMP = investigational medicinal product; PANSS = Positive and Negative Syndrome Scale.

[a]Percentages are based on the number of randomized subjects.

[b]Subjects receiving at least one dose of IMP are included in the safety analysis.

[c]Subjects who were randomized, treated and had baseline and post-baseline observations on PANSS Total Score.

A total of 20 subjects (6.3%) discontinued during the trial, including 3 (2.7%) brexpiprazole subjects, 5 (4.9%) aripiprazole subjects, and 12 (11.5%) placebo subjects. There were no deaths in the trial. Primary reasons for discontinuations included withdrawal by caregiver (9 subjects [2.8%]), withdrawal by subject (3 subjects [0.9%]), lack of efficacy (3 subjects [0.9%]), and AEs (3 subjects [0.9%]).

Blinding (masking)

The randomized treatments were administered in a double-blind fashion. All doses of double-blind IMP were taken orally once daily and were administered without regard to meals.

Statistical Methods

Subject Samples: The following analysis samples were defined for this trial:

- Enrolled Sample: All subjects who signed an informed consent/assent form.
- Randomized Sample: All subjects who were randomized into the trial. Subjects were considered randomized when they were assigned a treatment group by IWRS.
- Safety Sample: All subjects who were randomized into the trial and who received at least 1 dose of IMP. Subjects were only excluded from this population if there was documented evidence that the subject did not take IMP (ie, drug dispensed = drug returned or no IMP dispensed). If a subject was dispensed IMP and was lost to follow up, he/she were considered exposed.
- Efficacy Sample: All subjects who were randomized into the trial, took at least 1 dose of IMP, and had a baseline and at least 1 postbaseline efficacy evaluation for the PANSS Total score.

The observed case (OC) dataset will be used in the primary analysis of efficacy endpoints.

Handling of missing data: missing data will be handled by analysis of mixed model repeated measures (MMRM) methodology based on all data from protocol-specified visits in the efficacy

sample OC dataset under the assumption of missing at random (MAR).

The OC dataset will consist of actual observations recorded at each visit during double-blind treatment and no missing data will be imputed.

In order to explore the robustness of the primary analysis based on the MAR assumption, **sensitivity analyses** of the primary efficacy endpoint under MNAR (Missing not at Random) assumption will be conducted using pattern-mixture model.

In addition, in order to **assess sensitivity** of results due to missing data, a last observation carried forward (LOCF) analysis will be performed as a sensitivity analysis.

Efficacy: The primary efficacy endpoint was the change from baseline to Week 6 in PANSS Total Score.

The primary statistical comparison of interest is brexpiprazole 2 - 4 mg versus placebo based on all available data (observed cases, OC dataset). All randomized subjects who have both baseline and post-baseline PANSS total score will be included in the primary efficacy analysis.

A mixed model repeated measures (MMRM) analysis was applied to the change from baseline from Week 1 to Week 6 in PANSS Total Score with fixed-effect factors of treatment, trial site (pooled), visit, treatment by visit interaction, and fixed effect covariates of baseline and baseline by visit interaction.

The difference in least-square means between brexpiprazole and placebo at the Week 6 visit serves as the primary treatment comparison. Significance testing was based on the contrast (ie, difference in least-square means between brexpiprazole and placebo) at the Week 6 visit by using a two-sided 0.05 level. 95% CI.

Subgroup Analyses of the primary endpoint: from baseline in PANSS Total score at every study week will be conducted by sex, race (White and Other races), age category (< 15, ≥ 15 years) and region (US, European [continent], Mexico) using MMRM analysis with factors of treatment, visit, treatment by visit interaction, and baseline and baseline by visit interaction as covariate with an unstructured variance covariance structure.

In addition, change in PANSS Positive and Negative subscale Scores, change in CGAS Score and CGI-S scale at Week 6 (MMRM analysis with factors of treatment, visit, treatment by visit interaction, and baseline and baseline by visit interaction as covariates, (with LS Mean and 95% CI), percentage of subjects achieving response and remission (with relative risk and 95% CI), and CGI-I (difference and 95% CI) will also be computed by age category (< 15, ≥ 15 years).

Pharmacokinetics: Mean (SD) plasma concentrations versus nominal time were plotted for brexpiprazole.

Safety: The incidence of AEs and the incidence of abnormal findings in vital signs, ECGs, clinical laboratory tests, and physical examinations were analyzed. In addition, data from EPS scales (including SAS, AIMS, and BARS), UKU scale, NY AACENT scale, and potential suicide events recorded on the C- SSRS were analyzed. Percentage of subjects with clinically significant changes in weight, BMI, and waist circumference were also analyzed.

Results

Baseline data

The demographics and baseline characteristics

A total of 150 subjects (47.5%) were male and 166 subjects (52.5%) were female. The subjects' mean (SD) age at baseline was 15.3 (1.5) years. Subjects in the < 15-year-old age group were well-represented with 101 subjects (32.0%). The number of subjects in the ≥ 15-year-old age group (215 subjects [68.0%]) was higher than that in the < 15-year-old age group. The subjects' mean (SD) weight at baseline was 64.7 (16.6) kg, with the placebo group subjects having a slightly higher mean weight (68.0 kg) than the overall mean weight. The subjects' mean (SD) height, BMI, and waist circumference were 166.3 (10.2) cm, 23.8 (5.0) kg/m2, and 78.6 (13.8) cm, respectively.

The highest proportion of subjects randomized in this trial were White (204 subjects [64.6%]) and were not Hispanic or Latino (213 subjects [67.4%]). There were 81 subjects (25.6%) whose race was documented as other. Most of these were of multiple races.

There was a lower proportion of subjects in the US (43 subjects [13.6%]) and in Mexico (95 subjects [30.1%]) than in Europe (178 subjects [56.3%]).

Demographics and baseline characteristics were similar for most parameters across the three treatment groups.
A summary of the demographic and baseline characteristics and scale scores is presented in Table 0-3.

Table 0-2 Demographic and Baseline Characteristics (Randomized Sample)

Demographic Characteristic	Brexpiprazole (N = 110)	Aripiprazole (N = 102)	Placebo (N = 104)	Total (N = 316)
Age (yrs)				
n	110	102	104	316
Mean (SD)	15.3 (1.5)	15.3 (1.4)	15.2 (1.4)	15.3 (1.5)
Median	16.0	16.0	15.0	15.5
Min, Max	13,17	13,17	13,18	13,18
Age Group (n [%])				
<15 Years	36 (32.7%)	30 (29.4%)	35 (33.7%)	101 (32.0%)
>=15 Years	74 (67.3%)	72 (70.6%)	69 (66.3%)	215 (68.0%)

Table 0-2 Demographic and Baseline Characteristics (Randomized Sample)

Demographic Characteristic	Brexpiprazole (N = 110)	Aripiprazole (N = 102)	Placebo (N = 104)	Total (N = 316)
Height (cm)				
n	110	102	104	316
Mean (SD)	166.3 (10.8)	165.0 (10.0)	167.7 (9.8)	166.3 (10.2)
Median	166.5	166.0	168.5	167.0
Min, Max	140.0,194.0	145.0,183.0	146.0,195.0	140.0,195.0
Weight (kg)				
n	110	102	104	316
Mean (SD)	64.6 (16.9)	61.4 (14.7)	68.0 (17.7)	64.7 (16.6)
Median	61.6	59.3	66.1	61.6
Min, Max	30.0,114.8	35.3,110.0	39.2,125.0	30.0,125.0
Body Mass Index (kg/m^2)				
n	110	102	104	316
Mean (SD)	23.2 (5.2)	22.4 (4.2)	24.1 (5.2)	23.2 (5.0)
Median	22.1	22.3	22.9	22.4
Min, Max	15.3,46.6	14.8,36.3	14.1,38.4	14.1,46.6
Waist Circumference (cm)				
n	110	102	104	316
Mean (SD)	78.7 (13.4)	76.3 (12.2)	80.8 (15.5)	78.6 (13.8)
Median	78.0	75.0	78.5	77.0
Min, Max	54.0,122.0	50.0,114.0	52.0,125.0	50.0,125.0
Race [n (%)]				
White n (%)	70 (63.6%)	66 (64.7%)	68 (65.4%)	204 (64.6%)
Black or African American n (%)	8 (7.3%)	7 (6.9%)	6 (5.8%)	21 (6.6%)
American Indian or Alaska Native n (%)	2 (1.8%)	1 (1.0%)	4 (3.8%)	7 (2.2%)
Asian n (%)	1 (0.9%)	1 (1.0%)	0 (0.0%)	2 (0.6%)
Native Hawaiian or Other Pacific Islander n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other n (%)	29 (26.4%)	27 (26.5%)	25 (24.0%)	81 (25.6%)
Missing n (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.3%)
Ethnicity [n (%)]				
Hispanic or Latino	34 (30.9%)	32 (31.4%)	34 (32.7%)	100 (31.6%)
Not Hispanic or Latino	75 (68.2%)	70 (68.6%)	68 (65.4%)	213 (67.4%)
Other	1 (0.9%)	0 (0.0%)	1 (1.0%)	2 (0.6%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

SD = standard deviation.

The baseline disease characteristics

The baseline means (SD) for PANSS Total Score, Negative Subscale score and Positive

Subscale score were 101.4 (14.7), 25.5 (5.6) and 24.3 (4.8), respectively. For CGAS and CGI-S scores, the baseline means (SD) were 48 (11.8) and 4.8 (0.7), respectively. The parameters for baseline disease characteristics were similar across the three treatment groups.

A summary of the baseline disease characteristics and scale scores is presented in Table 0-3.

Table 0-3 Baseline Disease Characteristics (Randomized Sample)

Parameter	Brexpiprazole (N = 110)	Aripiprazole (N = 102)	Placebo (N = 104)	Total (N = 316)
PANSS Negative Sub-Score				
Mean (SD)	25.8 (5.6)	25.1 (5.2)	25.7 (6)	25.5 (5.6)
Min, Max	12, 45	11, 38	14, 45	11, 45
PANSS Positive Sub-Score				
Mean (SD)	24.2 (5.1)	24.9 (4)	23.9 (5.2)	24.3 (4.8)

Table 0-3 Baseline Disease Characteristics (Randomized Sample)				
Parameter	**Brexpiprazole (N = 110)**	**Aripiprazole (N = 102)**	**Placebo (N = 104)**	**Total (N = 316)**
Min, Max	12, 40	16, 38	11, 37	11, 40
PANSS Total Score				
Mean (SD)	101.1 (14.9)	101 (13)	102.1 (16.3)	101.4 (14.7)
Min, Max	80, 150	81, 138	81, 152	80, 152
CGI-S Severity Score				
Mean (SD)	4.8 (0.7)	4.7 (0.7)	4.7 (0.7)	4.8 (0.7)
Min, Max	3, 6	4, 6	3, 6	3, 6
CGAS Assessment Score				
Mean (SD)	48.1 (11.4)	48.1 (12.3)	47.7 (11.9)	48 (11.8)
Min, Max	22, 74	25, 80	30, 73	22, 80
P-Q-LES-Q Total Score				
Mean (SD)	40.8 (9)	41.4 (8.6)	41.3 (9.6)	41.1 (9)
Min, Max	19, 70	21, 60	25, 70	19, 70
Age Of First Diagnosis For Schizophrenia (Years)				
Mean (SD)	13.9 (2)	13.9 (1.9)	14.1 (1.8)	14 (1.9)
Min, Max	6, 17	8, 17	9, 17	6, 17

CGAS = Children's Global Assessment Scale; CGI-S = Clinical Global Impression-Severity of Illness Scale; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; P-Q-LES-Q = Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

Prior medication

Previous medications taken within 30 days of screening were recorded. Lifetime antipsychotic use was recorded. The aripiprazole group had a lower proportion of subjects who had taken psychoanaleptics compared to the brexpiprazole and placebo groups (8.2%, 2.9%, and 7.7% in the brexpiprazole, aripiprazole, and placebo groups, respectively).

Primary psycholeptics taken prior to the start of study therapy were as follows in the brexpiprazole, aripiprazole, and placebo groups, respectively:

- Risperidone: Taken by 58.2% of the subjects (59.1%, 52.0%, and 63.5%)
- Olanzapine: Taken by 19.9% of the subjects (25.5%, 15.7%, and 18.3%)
- Haloperidol: Taken by 14.6% of the subjects (10.9%, 15.7%, and 17.3%)
- Aripiprazole: Taken by 13.9% of the subjects (10.9%, 13.7%, and 17.3%)

An adequate washout of prohibited medications (including antipsychotics, antidepressants and mood stabilizers) was required before the trial.

Number analysed

A total of 376 subjects were screened for this trial and 316 subjects were randomized to double-blind IMP (110 subjects to brexpiprazole, 102 subjects to aripiprazole, and 104 subjects to placebo). All 316 subjects (100.0%) who were randomized received at least 1 dose of IMP and, accordingly, were analyzed for safety. Of the 316 subjects, 314 subjects (99.4%) were analyzed for efficacy. One subject (1.0%) in the aripiprazole group and 1 subject (1.0%) in the placebo group were included in the Safety Sample but excluded

from the Efficacy Sample because they did not have valid postbaseline assessments for PANSS Total Score. In the Randomized Sample (N = 316), 20 subjects (6.3%) discontinued during the trial.

Efficacy results

A summary of Efficacy Results at week 6 is presented in Table 0-3.

Table 0-4 Summary of Efficacy Results at Week 6 (Efficacy Sample)

Variable	Brexpiprazole	Aripiprazole	Placebo
PANSS Total Score, MMRM	N=110	N=101	N=103
Mean at Baseline (SD)	101.06 (14.87)	101.03 (13.08)	102.17 (16.30)
LS Mean (SE) Change at Week 6	-22.75 (1.49)	-23.95 (1.57)	-17.42 (1.58)
LS Mean Difference (95% CI)[a]	-5.33 (-9.55, -1.10)	-6.53 (-10.8, -2.21)	-
P-value[b]	0.0136	0.0032	-
CGI-S Severity Score, MMRM	N=110	N=101	N=103
Mean at Baseline (SD)	4.76 (0.66)	4.75 (0.65)	4.74 (0.73)
LS Mean (SE) Change at Week 6	-0.92 (0.09)	-1.01 (0.09)	-0.80 (0.09)
LS Mean Difference (95% CI)[a]	-0.11 (-0.36,0.13)	-0.20 (-0.45,0.05)	-
P-value[b]	0.3589	0.1118	-
PANSS Positive Score, MMRM	N=110	N=101	N=103
Mean at Baseline (SD)	24.20 (5.12)	24.87 (4.01)	23.96 (5.19)
LS Mean (SE) Change at Week 6	-6.58 (0.43)	-7.29 (0.45)	-5.14 (0.46)
LS Mean Difference (95% CI)[a]	-1.44 (-2.65, -0.22)	-2.15 (-3.40, -0.91)	-
P-value[b]	0.0205	0.0008	-
PANSS Negative Score, MMRM	N=110	N=101	N=103
Mean at Baseline (SD)	25.77 (5.62)	25.11 (5.24)	25.75 (5.97)
LS Mean (SE) Change at Week 6	-4.70 (0.41)	-4.77 (0.43)	-3.82 (0.44)
LS Mean Difference (95% CI)[a]	-0.88 (-2.04,0.28)	-0.95 (-2.14,0.24)	-
P-value[b]	0.1360	0.1158	-
CGAS Total Score, MMRM	N=110	N=101	N=103
Mean at Baseline (SD)	48.10 (11.36)	47.89 (12.14)	47.63 (12.00)
LS Mean (SE) Change at Week 6	10.56 (1.00)	12.07 (1.05)	8.08 (1.06)
LS Mean Difference (95% CI)[a]	2.48 (-0.35,5.31)	3.99 (1.09,6.88)	-
P-value[b]	0.0854	0.0072	-
CGI-I Score, LOCF	N=110	N=101	N=103
Mean (SD) at Week 6	2.86 (0.95)	2.79 (0.97)	3.17 (1.08)
Treatment Mean Difference (95% CI)	-0.29 (-0.56, -0.03)	-0.34 (-0.62, -0.06)	-
P-value[c]	0.0287	0.0184	-
Response Rate, LOCF	N=110	N=101	N=103
Proportion (%) of Responders at Week 6	48 (43.64%)	44 (43.56%)	29 (28.16%)
RR (95% CI)	1.55 (1.09,2.20)	1.51 (1.06,2.16)	-
P-value[d]	0.0111	0.0224	-
Remission Rate, LOCF	N=110	N=101	N=103
Proportion (%) of Remitters at Week 6	32 (29.09%)	36 (35.64%)	24 (23.30%)
RR (95% CI)	1.18 (0.77,1.81)	1.48 (1.01,2.16)	-
P-value[d]	0.4415	0.0472	-

CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression-Improvement Scale CGI-S = Clinical Global Impression-Severity of Illness Scale; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; LOCF = last observation carried forward; LS = least squares; MMRM = mixed model repeated measures; PANSS = Positive and

Negative Syndrome Scale; RR = ratio of response rate: brexpiprazole / placebo or aripiprazole / placebo; SD = standard deviation; SE = standard error.

[a]LS mean difference = difference in LS mean change.

[b]Derived from MMRM analysis with fixed effect of treatment, (pooled) clinical center visit, treatment visit interaction, baseline value, and baseline visit interaction as covariate, and with an unstructured covariance.

[c]CMH Row Mean Scores Differ test controlling for study center.

[d]CMH General Association test controlling for study center.

Primary Efficacy Variable

The brexpiprazole group showed a statistically significant improvement compared with the placebo group for the primary efficacy endpoint, mean change from baseline to Week 6 in the PANSS Total Score (least squares [LS] mean difference = −5.33 [95% confidence interval [CI]: −9.55, −1.10], p = 0.0136).

The aripiprazole group showed a numerical improvement in the PANSS Total Score at Week 6 compared with the placebo group (LS mean difference = −6.53 [95% CI: −10.8, −2.21], nominal p = 0.0032).

Secondary Efficacy Variables

The brexpiprazole group showed a numerical improvement compared to the placebo group for the mean change from baseline in PANSS Positive Subscale score at Week 6 (LS mean difference = −1.44 [95% CI: −2.65, −0.22], p = 0.0205). Nominal p-value < 0.05 between the two groups was observed from Week 3 and throughout the remainder of the treatment period.

The brexpiprazole group showed a numerical improvement compared to the placebo group for the mean change from baseline in PANSS Negative Subscale score at Week 6 (LS mean difference = −0.88 [95% CI: −2.04, 0.28], p = 0.1360). An improvement with nominal p-value < 0.05 in the brexpiprazole group compared with the placebo group for the mean change in PANSS Negative Subscale score was observed at Week 4 only (LS mean difference = −1.29 [95% CI: −2.28, −0.30], p = 0.0111)

The aripiprazole group showed a numerical improvement compared to the placebo group for the mean change in PANSS Positive Subscale score with nominal p-value < 0.05 starting at Week 3 and throughout the remainder of the treatment period (LS mean difference at Week 6 = −2.15 [95% CI: −3.40, −0.91], p = 0.0008).

The aripiprazole group showed a numerical improvement compared to the placebo group for the mean change from baseline in PANSS Negative Subscale score at Week 6 (LS mean difference = −0.95 [95% CI: −2.14, 0.24], p = 0.1158; Table 2.5.4.5 1). An improvement with nominal p-value < 0.05 in the aripiprazole group compared to the placebo group for the mean change in PANSS Negative Subscale score was observed at Week 2 and Week 3.

For the secondary efficacy endpoints, an improvement with nominal p-value < 0.05 in the brexpiprazole group versus placebo group at Week 6, was seen in PANSS Positive Subscale scores, CGI-I scores, and response rates. A numerical

improvement was seen in PANSS Negative Subscale scores, CGAS scores, CGI-S scores, and remission rates.

Examination of Subgroups

Subgroups analyses by age, sex, region, race, and ethnicity were performed in this trial.

Age Subgroups

In the placebo group, the mean change from baseline in PANSS Total score was of larger magnitude in the < 15 year-old age subgroup than in the ≥ 15-year-old age subgroup. Therefore, the mean difference (brexpiprazole group vs placebo group) at Week 6 in the PANSS Total Score showed numerically more improvement in the ≥ 15-year-old age subgroup than in the < 15-year-old age subgroup. A similar pattern was observed for the aripiprazole age subgroups (Table 2.5.4.7 1).

Table 0-5 Summary of Mean Change from Baseline to Week 6 in PANSS Total Score by age group – MMRM (Efficacy Sample)

Variable	Brexpiprazole	Aripiprazole	Placebo
PANSS Total Score < 15 Years old	N=36	N=29	N=34
Mean at Baseline (SD)	99.89 (14.83)	99.79 (12.75)	101.35 (16.00)
LS Mean (SE) Change at Week 6	-20.62 (2.55)	-21.95 (2.91)	-20.52 (2.65)
LS Mean Difference (95% CI)[a]	-0.10 (-7.41,7.21)	-1.43 (-9.25,6.38)	-
PANSS Total Score >= 15 Years old	N=74	N=72	N=69
Mean at Baseline (SD)	101.64 (14.96)	101.53 (13.26)	102.57 (16.55)
LS Mean (SE) Change at Week 6	-22.98 (1.83)	-23.99 (1.85)	-14.92 (1.94)
LS Mean Difference (95% CI)[a]	-8.05 (-13.3, -2.80)	-9.07 (-14.3, -3.79)	-

CI = confidence interval; LS = least squares; MMRM = mixed model repeated measures; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = standard error.

[a]Derived from MMRM analysis with fixed effect of treatment, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariate, and with an unstructured covariance.

Sex Subgroups

The LS mean difference in PANSS Total Score at Week 6 (brexpiprazole group versus placebo group) in the female subgroup was −5.24 (95% CI: −11.1, 0.58) and in the male subgroup was −5.26 (95% CI: −11.5, 0.94).

Region Subgroups

The majority of subjects came from Europe (approximately 56%) and had a LS mean difference at Week 6 (brexpiprazole versus placebo) of −7.33 (95% CI: −12.6, −2.02. Subjects in the US comprised approximately 14% of the total number of subjects and had a LS mean difference at Week 6 (brexpiprazole versus placebo) of −11.9 (95% CI: −27.6, 3.82). Subjects in Mexico comprised approximately 30% of subjects. The response of Mexican subjects was the lowest when compared to Europe and to US. The LS mean difference at Week 6 (brexpiprazole versus placebo) for subjects in Mexico was 1.07 (95% CI: −6.27, 8.42).

Race Subgroups

The majority of the subjects were of White race (64.6%) and had a LS mean difference at Week 6 (brexpiprazole group versus placebo group) of −5.71 (95% CI: −10.9, -0.54).

In the subgroup of all other races, the LS mean difference at Week 6 (brexpiprazole group versus placebo group) was −4.81 (95% CI: −12.5, 2.88).

Ethnicity Subgroups

The majority of the subjects were in the not Hispanic/Latino subgroup (67.4%). For this subgroup, the
LS mean difference at Week 6 (brexpiprazole group versus placebo group) was −7.17 (95% CI: −12.4,
−1.93).
Subjects in the Hispanic/Latino subgroup comprised approximately 31.6% of subjects. The response in Hispanic/Latino subjects was the lower when compared to the not Hispanic/Latino subgroup. The LS mean difference at Week 6 (brexpiprazole versus placebo) was −0.01 (95% CI: −7.31, 7.28).

Safety results

All subjects who were randomized into the trial and received at least 1 dose of IMP were included in the Safety Sample. A total of 110 subjects were exposed to brexpiprazole. The majority of subjects in the Safety Sample were exposed to brexpiprazole, aripiprazole, or placebo for at least 42 days.

During the trial at least 1 treatment-emergent adverse event (TEAE) was reported by 44 subjects (40.0%) in the brexpiprazole group, 53 subjects (52.0%) in the aripiprazole group, and 42 subjects (40.4%) in the placebo group (Table 2.5.5.2 1).

The IMP was discontinued due to TEAEs in 1 subject (1.0%) in the aripiprazole group and 2 subjects (1.9%) in the placebo group. None of the subjects in the brexpiprazole group discontinued the IMP due to TEAEs.

No deaths were reported during this trial. Severe TEAEs were reported in 2 subjects (1.8%) in the brexpiprazole group and 1 subject (1.0%) in the placebo group. Serious TEAEs were reported in 1 subject (0.9%) in the brexpiprazole group, 1 subject (1.0%) in the aripiprazole group, and 3 subjects (2.9%) in the placebo group (Table 2.5.5.2 1).

Table 0-6 Summary of Adverse Events (Safety Sample)

Event	Brexpiprazole (N=110) n (%)[a]	Aripiprazole (N=102) n (%)[a]	Placebo (N=104) n (%)[a]	Total (N=316) n (%)[a]
Subjects treated	110 (100.0)	102 (100.0)	104 (100.0)	316 (100.0)
Subject days of IMP exposure	4632	4252	4209	13093
Subjects with adverse events	46 (41.8)	56 (54.9)	44 (42.3)	146 (46.2)
Adverse events (number of events)	86	147	100	333
Subjects with TEAEs	44 (40.0)	53 (52.0)	42 (40.4)	139 (44.0)
Treatment-emergent adverse events (number of events)	76	125	76	277
Subjects with serious TEAEs	1 (0.9)	1 (1.0)	3 (2.9)	5 (1.6)
Subjects with non-serious TEAEs	43 (39.1)	53 (52.0)	42 (40.4)	138 (43.7)
Subjects with severe TEAEs	2 (1.8)	0 (0.0)	1 (1.0)	3 (0.9)
Subjects discontinued IMP due to adverse events	0 (0.0)	1 (1.0)	2 (1.9)	3 (0.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event; IMP = investigational medicinal product; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a]Percentages were based on the number of treated subjects.
A TEAE is defined as an AE that started after start of 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. Multiple occurrences of TEAEs are counted once, per specific MedDRA (version 25.1) preferred term.

Treatment-emergent Adverse Events

Treatment-emergent AEs with an incidence rate of ≥ 5% in the brexpiprazole group and greater than that in the placebo group included nausea (6.4% versus 3.8% for the placebo group) and headache (6.4% versus 4.8% for the placebo group). Table 2.5.5.3 1 displays the TEAEs with an incidence rate of ≥ 2% in the brexpiprazole group and greater than that in the placebo group.

Table 0-1 Incidence of TEAE of at Least 2% in Brexpiprazole Group and Greater Than Placebo by System Organ Class and MedDRA Preferred Term (Safety Sample)

System Organ Class MedDRA Preferred Term	Brexpiprazole (N = 110) n (%)	Aripiprazole (N = 102) n (%)	Placebo (N = 104) n (%)	Total (N = 316) n (%)
Gastrointestinal Disorders				
Nausea	7 (6.4)	4 (3.9)	4 (3.8)	15 (4.7)
Nervous System Disorders				
Akathisia	4 (3.6)	7 (6.9)	3 (2.9)	14 (4.4)
Headache	7 (6.4)	5 (4.9)	5 (4.8)	17 (5.4)
Hypersomnia	3 (2.7)	5 (4.9)	2 (1.9)	10 (3.2)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Treatment-emergent Adverse Events Potentially Related to the Investigational Medicinal Product

The incidence of subjects with potentially drug-related TEAEs (per investigator judgment) was 21.8% in the brexpiprazole group compared to 16.3% in the placebo group. In the brexpiprazole group, potentially drug-related TEAEs with an incidence rate of ≥ 2% were nausea (4.5% versus 3.8% for the placebo group), headache (4.5% versus 1.0% for the placebo group), somnolence (4.5% versus 4.8% for the placebo group), and akathisia (3.6% versus 2.9% for the placebo group) (Table 2.5.5.4 1).

The incidence of subjects with potentially drug-related TEAEs (per investigator judgment) was 38.2% in the aripiprazole group compared to 16.3% in the placebo group.

Table 0-1	Incidence of Potentially Drug-related Treatment-emergent Adverse Events During the Double-blind Treatment Period by System Organ Class and MedDRA Preferred Term (Safety Sample)			
	Brexpiprazole (N = 110)	**Aripiprazole (N = 102)**	**Placebo (N = 104)**	**Total (N = 316)**
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
At least one TEAE[a]	24 (21.8)	39 (38.2)	17 (16.3)	80 (25.3)
Cardiac Disorders	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.6)
Palpitations	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.6)
Ear and Labyrinth Disorders	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Vertigo	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Eye Disorders	2 (1.8)	3 (2.9)	0 (0.0)	5 (1.6)
Blepharospasm	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Eye Movement Disorder	1 (0.9)	1 (1.0)	0 (0.0)	2 (0.6)
Vision Blurred	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.6)
Gastrointestinal Disorders	7 (6.4)	10 (9.8)	4 (3.8)	21 (6.6)
Dry Mouth	1 (0.9)	1 (1.0)	0 (0.0)	2 (0.6)
Nausea	5 (4.5)	2 (2.0)	4 (3.8)	11 (3.5)
Salivary Hypersecretion	2 (1.8)	4 (3.9)	1 (1.0)	7 (2.2)
Tongue Disorder	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)

Table 0-1	Incidence of Potentially Drug-related Treatment-emergent Adverse Events During the Double-blind Treatment Period by System Organ Class and MedDRA Preferred Term (Safety Sample)			
	Brexpiprazole (N = 110)	**Aripiprazole (N = 102)**	**Placebo (N = 104)**	**Total (N = 316)**
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Vomiting	1 (0.9)	2 (2.0)	1 (1.0)	4 (1.3)
General Disorders and Administration Site Conditions	2 (1.8)	7 (6.9)	0 (0.0)	9 (2.8)
Asthenia	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.6)
Fatigue	2 (1.8)	6 (5.9)	0 (0.0)	8 (2.5)
Investigations	1 (0.9)	2 (2.0)	3 (2.9)	6 (1.9)
Alanine Aminotransferase Increased	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Weight Increased	1 (0.9)	1 (1.0)	2 (1.9)	4 (1.3)
White Blood Cell Count Decreased	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Metabolism and Nutrition Disorders	0 (0.0)	3 (2.9)	2 (1.9)	5 (1.6)
Decreased Appetite	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.6)
Increased Appetite	0 (0.0)	2 (2.0)	1 (1.0)	3 (0.9)
Musculoskeletal and Connective Tissue Disorders	2 (1.8)	4 (3.9)	2 (1.9)	8 (2.5)
Arthralgia	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Muscle Rigidity	1 (0.9)	3 (2.9)	1 (1.0)	5 (1.6)
Musculoskeletal Stiffness	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Pain In Extremity	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders	15 (13.6)	26 (25.5)	14 (13.5)	55 (17.4)
Akathisia	4 (3.6)	6 (5.9)	3 (2.9)	13 (4.1)
Cognitive Disorder	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Disturbance In Attention	1 (0.9)	0 (0.0)	1 (1.0)	2 (0.6)
Dizziness	0 (0.0)	3 (2.9)	2 (1.9)	5 (1.6)
Dizziness Postural	1 (0.9)	1 (1.0)	0 (0.0)	2 (0.6)
Dystonia	0 (0.0)	2 (2.0)	0 (0.0)	2 (0.6)
Extrapyramidal Disorder	2 (1.8)	1 (1.0)	0 (0.0)	3 (0.9)
Headache	5 (4.5)	4 (3.9)	1 (1.0)	10 (3.2)
Hypersomnia	2 (1.8)	3 (2.9)	2 (1.9)	7 (2.2)
Hypoaesthesia	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Hypokinesia	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Psychomotor Hyperactivity	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Sedation	2 (1.8)	4 (3.9)	0 (0.0)	6 (1.9)
Somnolence	5 (4.5)	11 (10.8)	5 (4.8)	21 (6.6)
Tremor	1 (0.9)	3 (2.9)	0 (0.0)	4 (1.3)
Psychiatric Disorders	1 (0.9)	6 (5.9)	2 (1.9)	9 (2.8)
Abnormal Dreams	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Anxiety	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.6)
Insomnia	1 (0.9)	2 (2.0)	1 (1.0)	4 (1.3)
Irritability	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Restlessness	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Tension	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)

Table 0-1	Incidence of Potentially Drug-related Treatment-emergent Adverse Events During the Double-blind Treatment Period by System Organ Class and MedDRA Preferred Term (Safety Sample)			
	Brexpiprazole (N = 110)	**Aripiprazole (N = 102)**	**Placebo (N = 104)**	**Total (N = 316)**
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Renal and Urinary Disorders	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Polyuria	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Skin and Subcutaneous Tissue Disorders	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.6)
Hyperhidrosis	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Pruritus	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Vascular Disorders	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Orthostatic Hypotension	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)

AE = adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event.
[a]Subjects with AEs in multiple SOCs were counted only once towards the total.

Deaths

No deaths were reported during this trial.

Serious Adverse Events

Serious TEAEs were reported for a total of 5 subjects (1.6%). The incidence of subjects with serious TEAEs was 1 subject (0.9%) in the brexpiprazole group, 1 subject (1.0%) in the aripiprazole group, and 3 subjects (2.9%) in the placebo group (Table 2.5.5.6 1).

One subject in the brexpiprazole group had a serious TEAE of schizophrenia (verbatim: worsening of symptoms of schizophrenia) which was considered to be severe in severity and not related to the IMP.

One subject in the aripiprazole group had a serious TEAE of psychotic disorder (verbatim: worsening of psychotic symptoms) which was considered to be mild in severity and not related to the IMP.

One subject in the placebo group had a serious TEAE of schizophrenia (verbatim: worsening of schizophrenia) which was considered to be mild in severity and not related to the IMP. One subject in the placebo group had a serious TEAE of schizophrenia (verbatim: worsening of schizophrenia symptoms) which was considered to be moderate in severity and not related to the IMP. One subject in the placebo group had a serious TEAE of psychotic disorder (verbatim: worsening of psychotic symptoms) which was considered to be moderate in severity and not related to the IMP.

Table 0-1	Incidence of Serious Treatment-emergent Adverse Events in Any Treatment Group by System Organ Class and MedDRA Preferred Term (Safety Sample)			
	Brexpiprazole (N = 110)	**Aripiprazole (N = 102)**	**Placebo (N = 104)**	**Total (N = 316)**
System Organ Class MedDRA Preferred Term	**n(%)**	**n (%)**	**n (%)**	**n (%)**
At least one TEAE[a]	1 (0.9)	1 (1.0)	3 (2.9)	5 (1.6)
Psychiatric Disorders	1 (0.9)	1 (1.0)	3 (2.9)	5 (1.6)
Psychotic Disorder	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.6)
Schizophrenia	1 (0.9)	0 (0.0)	2 (1.9)	3 (0.9)

AE = adverse event; SOC = system organ class; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a]Subjects with AEs in multiple SOCs were counted only once towards the total.

Adverse Events Leading to Discontinuation of Investigational Medicinal Product

The IMP was discontinued due to TEAEs in 1 subject (1.0%) in the aripiprazole group and 2 subjects (1.9%) in the placebo group. There were no TEAEs that led to discontinuations in the brexpiprazole group (Table 2.5.5.7 1).

Table 0-1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuations by System Organ Class and MedDRA Preferred Term (Safety Sample)

	Brexpiprazole (N = 110)	Aripiprazole (N = 102)	Placebo (N = 104)	Total (N = 316)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
At least one TEAE[a]	0 (0.0)	1 (1.0)	2 (1.9)	3 (0.9)
Nervous System Disorders	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Akathisia	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders	0 (0.0)	0 (0.0)	2 (1.9)	2 (0.6)
Psychotic Disorder	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Schizophrenia	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)

AE = adverse event; SOC = system organ class; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a]Subjects with AEs in multiple SOCs were counted only once towards the total.

Treatment-emergent Adverse Events Related to Extrapyramidal Symptoms

Extrapyramidal related events were reported in 7 subjects (6.4%) in the brexpiprazole group, 11 subjects (10.8%) in the aripiprazole group, and 5 subjects (4.8%) in the placebo group (Table 2.5.5.8.1 1). All TEAEs related to extrapyramidal symptoms in the brexpiprazole group were considered mild or moderate in severity.

Table 0-1 Incidence of EPS-related TEAEs by EPS Category and MedDRA Preferred Term (Safety Sample)

	Brexpiprazole (N = 110)	Aripiprazole (N = 102)	Placebo (N = 104)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**
At least one TEAE[a]	7 (6.4)	11 (10.8)	5 (4.8)
EPS - Akathisia Events	4 (3.6)	7 (6.9)	5 (4.8)
Akathisia	4 (3.6)	7 (6.9)	3 (2.9)
Psychomotor Hyperactivity	0 (0.0)	0 (0.0)	2 (1.9)
EPS - Dystonic Events	1 (0.9)	5 (4.9)	1 (1.0)
Dystonia	0 (0.0)	2 (2.0)	0 (0.0)
Muscle Rigidity	1 (0.9)	4 (3.9)	1 (1.0)
EPS - Parkinsonian Events	4 (3.6)	3 (2.9)	0 (0.0)
Extrapyramidal Disorder	2 (1.8)	1 (1.0)	0 (0.0)
Hypokinesia	1 (0.9)	0 (0.0)	0 (0.0)
Tremor	1 (0.9)	3 (2.9)	0 (0.0)

AE = adverse event; EPS = extrapyramidal symptom; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAEs = treatment-emergent adverse events

[a]Subjects with AEs in multiple SOCs were counted only once towards the total.

Pregnancy

There were 2 events of pregnancy in this trial, one in the brexpiprazole group and another in the aripiprazole group. Both subjects gave live birth to normal babies via caesarean section.

Clinical Laboratory Results

There were no trends or meaningful differences observed in liver enzyme parameters, metabolic parameters, creatine phosphokinase and renal parameters, hematology laboratory results, or urinalysis results between the brexpiprazole and placebo groups or between the aripiprazole and placebo groups.

Prolactin

In females, the mean value for prolactin showed a mild increase in the brexpiprazole group (mean increase from baseline to last visit was 3.55 ng/ml).

In the aripiprazole group, mean changes in prolactin values from baseline were −14.41 ng/ml and −6.31 ng/ml in female and male subjects respectively (decrease in mean prolactin values from baseline).

None of the potentially clinically relevant (PCR) prolactin test results were considered by the investigator as a TEAE. There was one TEAE of galactorrhoea reported by one male subject (0.9%) in the brexpiprazole group. The TEAE was considered mild in severity and not related to the IMP. No action was taken to the IMP and the TEAE resolved within the same day. Prolactin levels were within normal range and were not clinically significant for this subject.

Body Weight and Body Mass Index

A total of 8 subjects (2.5%) experienced weight increased TEAEs (2 subjects [1.8%] in the brexpiprazole group, 2 subjects [2.0%] in the aripiprazole group, and 4 subjects [3.8%] in the placebo group). None of the TEAEs related to weight increase were serious, and none were severe.

A Z-score change of < 0.5 SD is considered not clinically significant. Weight Z-Score increases by ≥ 0.5 from baseline during double-blind period were recorded for 5 subjects (4.5%) in the brexpiprazole group, 3 subjects (2.9%) in the aripiprazole group, and 4 subjects (3.8%) in the placebo group.
Weight Z-Score decreases by ≥ 0.5 from baseline were recorded for 6 subjects (5.5%) in the brexpiprazole group and 1 subject (1.0%) in the placebo group.

Body mass index Z-Score increases by ≥ 0.5 at the last visit were recorded for 8 subjects (7.3%) in the brexpiprazole group, 5 subjects (4.9%) in the aripiprazole group, and 2 subjects (1.9%) in the placebo group. Body mass index Z-Score decreases by ≥ 0.5 at the last visit were recorded for 6 subjects (5.5%) in the brexpiprazole group, 4 subjects (3.9%) in the aripiprazole group, and 3 subjects (2.9%) in the placebo group.

Extrapyramidal Symptoms Rating Scale

- **Simpson Angus Scale**

The SAS Total Score showed little change from baseline during the treatment period.

The LS mean change in SAS Total Score between the baseline and the last visit was 0.04 in the brexpiprazole group and −0.03 in the placebo group, with a LS mean difference of 0.07 at the last visit.

In the aripiprazole group, the LS mean change in SAS Total Score between the baseline and the last visit was 0.15, with a LS mean difference (aripiprazole versus placebo) of 0.18 at the last visit.

- **Abnormal Involuntary Movement Scale**

The AIMS Total Score showed little change from baseline during the treatment period.

The LS mean change in AIMS Total Score between the baseline and the last visit was −0.12 in the brexpiprazole group and −0.06 in the placebo group, with a LS mean difference of −0.06 at the last visit.

In the aripiprazole group, the LS mean change in AIMS Total Score between the baseline and the last visit was 0.05, with a LS mean difference (aripiprazole versus placebo) of 0.11 at the last visit.

- **Barnes Akathisia Rating Scale**

The BARS Global Score showed little change from baseline during the treatment period.

The LS mean change in BARS Global Score between the baseline and the last visit was 0.01 in the brexpiprazole group and 0.01 in the placebo group, with a LS mean difference of 0.00 at the last visit.

In the aripiprazole group, the LS mean change in BARS Global Score between the baseline and the last visit was 0.06, with a LS mean difference (aripiprazole versus placebo) of 0.05 at the last visit.

- **Suicidality**

No suicidal behaviour was reported during the treatment or follow-up period of this trial based on the C-SSRS, however, suicidal ideation was reported for 1 subject (0.9%) in the brexpiprazole group, 2 subjects (2.0%) in the aripiprazole group, and 2 subjects (1.9%) in the placebo group. None of the reported suicidal ideations was considered as a TEAE.

- **Udvalg for Kliniske Undersogelser (Adverse Event Questionnaire)**

The majority of side effects with symptoms present were reported in the psychic section. Most subjects reporting symptoms reported moderate concentrations difficulties than any other symptom (brexpiprazole 40%, 42.1% in the aripiprazole group, and 33.6% in the placebo group). There were slight differences between reporting of side effects using the UKU between the brexpiprazole, placebo, and aripiprazole groups. Subjects with side effects with probable connection to IMP reported mostly mild symptoms in all groups and most subjects reported no side effect. Where present, side effects were mostly

considered to be mild and not interfere with the patient's performance and the doctor and patient assessment of interference correlated well.

- **New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment**

The percentage of subjects reporting at least one event of adverse cognitive effects was similar between the treatment groups. The majority of subjects in all groups reporting symptoms reported them as moderate. Drug-related Signs/Symptoms reported by > 5% of the subjects in the brexpiprazole or aripiprazole group and > placebo group were: attention/vigilance (4.5% in the brexpiprazole group, 5.8% in the aripiprazole group, and 3.8% in the placebo group) and speed of processing (2.7% in the brexpiprazole group, 7.8% in the aripiprazole group, and 2.8% in the placebo group). A total of 8.1% brexpiprazole, 14.7% aripiprazole, and 11.5% placebo subjects reported any signs/symptoms that were drug-related. Drug-related signs/symptoms were mostly mild or moderate in the brexpiprazole group with no severe signs/symptoms. The majority of drug-related signs/symptoms in the aripiprazole group were mild or moderate, with some severe symptoms also reported. The majority of drug-related signs/symptoms in the placebo group were moderate with some subjects reporting severe signs/symptoms. The percentage of subjects with any signs/symptoms causing function to be impaired was 84.5% in the brexpiprazole group, 78.4% in the aripiprazole group, and 75.0% in the placebo group, and the majority of these signs/symptoms were considered to be moderate in all 3 treatment groups. The mean change from baseline in the NY AACENT total score at Week 6 showed improvement in the 3 treatment groups (total score mean change from baseline was -1.64 in the brexpiprazole group, -1.57 in the aripiprazole group, and -1.05 in the placebo group).

2.3.3. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No1901/2006, the MAH has submitted the results of Study 331-10-234.

Trial 331-10-234 was a phase 3, multicentre, multi-national, randomized, double-blind, placebo- and active-controlled trial evaluating the short-term efficacy and safety of brexpiprazole monotherapy compared with placebo in adolescents 13 to 17 years old with a diagnosis of schizophrenia. The study is part of the Paediatric Investigation Plan (EMEA-001185-PIP01-11-M08).

The trial consisted of a screening period (28 days), a 6-week double-blind treatment period, and a 21- day safety follow-up period. For the 6-week double-blind treatment period, subjects were randomized 1:1:1 to 1 of 3 treatment arms: 2-4 mg/day brexpiprazole, 10-20 mg/day aripiprazole, or placebo.

After completing treatment subjects had the option to enter the open-label trial, Trial 331-10-236.

In adolescents with schizophrenia, a multicenter, open-label, dose escalation pharmacokinetic (PK) trial (Trial 331-10-233) was conducted. The MAH's conclusion is that the target brexpiprazole dose of 2-4 mg/day in adults with schizophrenia is also suitable for adolescents. Results will be evaluated at the time of type 2 variation submission.

The 331-10-234 study design is compliant with EMA Guidelines (EMA/CHMP/40072/2010/Rev1).

Trial population: a total of 316 subjects were randomized to 1 of 3 treatment arms. All randomized subjects (100.0%) received at least 1 dose of IMP and, accordingly, were analysed for safety; 314 out of 316 subjects (99.4%) were analysed for efficacy. A total of 296 (93.7%) subjects completed the trial.

Sample size: a sample size of 105 subjects per arm was considered adequate for this trial. It provided at least 80% power at a 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 versus placebo, assuming a standard deviation (SD) of 19. The main assumption made for calculation derived from the aripiprazole adolescent study and it is considered acceptable.

Population: criteria for diagnosis of schizophrenia (DSM V) are adequate.

The highest proportion of subjects randomized in this trial were White (64.6%) and were not Hispanic or Latino (67.4%). There 25.6% whose race was documented as other. Most of these were of multiple races. There was a lower proportion of subjects in the US (13.6%) and in Mexico (30.1%) than in Europe (56.3%).

The demographics and baseline characteristics were similar across the treatment groups, reflecting the population of interest. Specifically, stratification of patients according to cut off age of 15 years is supported and consistent with EMA GL (EMA/CHMP/40072/2010/Rev1) recommendation in view of the fact that clinical features and incidence of schizophrenia may differ between these two strata; in addition, the higher percentage of number of subjects in the ≥ 15-year-old age group (68.0%) as compared to the < 15-year-old age group is expected.

Baseline disease characteristics identified a population of adolescents affected by moderate-severe schizophrenia: baseline means (SD) for PANSS Total Score 101.4 (14.7). These were similar across the three treatment groups.

Statistical methods: selection of primary and secondary endpoints is adequate for the aim of the study. Handling of missing data and methods to analyse primary endpoint (MMRM analysis, the primary statistical comparison of interest based on OC dataset), including definition of sensitivity analyses performed to assess the robustness of trial results (based on the MAR assumption) are considered adequate.

In the SAP no pre-specified analysis is reported regarding the comparative arm with aripiprazole.

Results:

The primary efficacy endpoint was the change from baseline to Week 6 in PANSS Total Score.

The PANSS is an established and clinically meaningful endpoint, it is the same primary outcome measure used for all trials in adults. The brexpiprazole group showed a statistically significant improvement compared with the placebo group in PANSS at week 6 (LS mean difference = −5.33 [95% CI: −9.55, −1.10], p = 0.0136). However, the LS mean difference was lower than the assumption in treatment difference of -7.4 points made for sample size calculation.

The aripiprazole group showed an improvement in the PANSS Total Score at Week 6 compared with the placebo group (LS mean difference = −6.53 [95% CI: −10.8, −2.21], nominal p = 0.0032), with a LS mean difference closer to that used for the assumption calculation of -7.4 derived from the aripiprazole study conducted in support of the adolescent indication. The study is not powered to detect statistical differences

with the comparator but to check assay sensitivity.

Thus, the results of the primary endpoint question the relevance/clinical significance of brexpiprazole in reducing schizophrenia symptoms according to PANSS score in view of the narrow effect size.

Of note, subgroups analysis of the primary outcome by age range (cut-off ≥15-year and < 15-year) suggests not consistent results between groups: the mean difference (brexpiprazole group vs placebo group) at Week 6 in the PANSS Total Score showed significant improvement in the ≥ 15-year-old age subgroup with a LS Mean Difference of -8.05 ((95% CI -13.3, -2.80); but no/minimal the difference in the < 15-year-old age subgroup was seen (LS Mean Difference -0.10 (95% CI-7.41,7.21).

In the aripiprazole arm similar behaviour between the two age cut-offs is noted with a mean difference at Week 6 in the PANSS Total Score of -9.07 and -1.43, respectively for the ≥15-year and < 15-year cut-off. Consistently, in the aripiprazole adolescent study a treatment effect could be supported by results in the older subgroup; on the contrary, in the younger subgroup, of very limited in size, results did not allow conclusions on the presence of a treatment effect.

Although the results are obtained from limited subgroups, particularly in the one below 15 years of age, the different treatment effect noted between the two age subgroups is consistent with aripiprazole results likely suggesting a lower effect in younger patients. It could be expected from a clinical perspective in earlier onset schizophrenia characterized by a more severe/difficult to treat course.

The secondary endpoints are not type I controlled and nominal P are reported.

Regarding PANSS positive and negative subscale scores: for the positive ones an improvement with nominal p-value (< 0.05) in the brexpiprazole group versus placebo group was seen at Week 6 (LS mean difference = −1.44 [95% CI: −2.65, −0.22], p = 0.0205). On the contrary, only a numerical change (not nominal p reached) was seen in PANSS Negative Subscale scores at Week 6 (LS mean difference = −0.88 [95% CI: −2.04, 0.28], p = 0.1360). Achieving an impact on PANSS Negative subscale scores (MMRM) is challenging, representing a difficult clinical symptom to be impacted by treatment in adolescent schizophrenic patients; of note, results are consistent between brexpiprazole and aripiprazole arms.

A positive impact (nominal p) of brexpiprazole on CGI-I (Clinical global impression-improvement) scores, with a treatment mean difference from PLB of 0.29 (95% CI -0.56, -0.03) and response rates (RR 1.55 95% CI 1.09,2.20) was seen.

It is worth mentioning that the mean difference from PLB at week 6 of Clinical Global Impression- Severity of Illness Scale (CGI-S, MMRN) scores, representing an important endpoint to evaluate efficacy, were minimally impacted (-0.11 CI 95% -0.36-0.13).

A numerical, not statistically significant improvement was seen in Children's Global Assessment Scale (CGAS) scores (LS Mean Difference 2.48 (95% IC -0.35,5.31) and remission rates (RR 1.18, 95% CI
0.77,1.81).

Results regarding secondary endpoints in the aripiprazole arm suggest an equal or better efficacy as compared to brexpiprazole, although results are not aimed to make a comparison (study not powered for comparison).

Safety:

No deaths were reported during this trial.

The incidence of subjects with potentially drug-related TEAEs (per investigator judgment) was 21.8% in the brexpiprazole group and 38.2% in the aripiprazole group compared to 16.3% in the placebo group. In the brexpiprazole group, potentially drug-related TEAEs with an incidence rate of ≥ 2% were nausea (4.5% versus 3.8% for the placebo group), headache (4.5% versus 1.0% for the placebo group), somnolence (4.5% versus 4.8% for the placebo group), and akathisia (3.6% versus 2.9% for the placebo group).

The most common potentially drug-related TEAEs in both the brexpiprazole and aripiprazole groups were those affecting the central nervous system (13.6% in the brexpiprazole group and 25.5% in the aripiprazole group and 13,5% in the placebo group), with 3.6%, 5.9% and 2.9% of akathisia, 1.8%,
1% and 0.0% of extrapyramidal symptoms, 4.5%, 3.9% and 1.0% of headache, 1.8%, 3.9% and 0.0% of sedation, 4.5%, 10.8% and 4.8% of somnolence in the brexpiprazole, aripiprazole and placebo group respectively.

There were no TEAEs that led to discontinuations in the brexpiprazole group.
None of the EPS-related TEAEs in the brexpiprazole group were serious or led to discontinuation and no clinically significant changes from baseline were observed in SAS, AIMS, and BARS scores.

No TEAEs related to suicidality were reported.

Weight related TEAEs (weight increased) occurred in 2 subjects (1.8%) in the brexpiprazole group and 2 subjects (2.0%) in the aripiprazole group, and 4 subjects (3.8%) in the placebo group. None of these TEAEs were serious or led to discontinuation.

With regard to the effect on prolactin, there was a slight elevation in the brexpiprazole group, whereas aripiprazole was associated with a decrease in prolactin level. The lower intrinsic activity as D2 agonist respect aripiprazole, which makes brexpiprazole a step closer to D2 antagonism, could be responsible to this effect. Of note, none of the potentially clinically relevant prolactin test results in this trial were considered as a TEAE by the investigator.

There were no trends or meaningful differences observed in liver enzyme parameters, metabolic parameters, creatine phosphokinase and renal parameters, hematology laboratory results, or urinalysis results between the brexpiprazole and placebo groups or between the aripiprazole and placebo groups.

The safety results of brexpiprazole in adolescent appears to be consistent with the current safety profile of brexpiprazole in adults.

3. Rapporteur's CHMP overall conclusion and recommendation

Results form study 331-10-234 suggest an overall positive effect of brexpiprazole in improving symptoms of schizophrenia in adolescents, although the relevance/clinical significance of brexpiprazole effect is uncertain in particular in the younger age group (<15 years).

Although childhood-onset schizophrenia is on a continuum with the adult form of the disorder, earlier onset is usually associated with a more severe and difficult to treat illness. Moreover, adolescents are more likely to have negative symptoms which are associated with poor outcomes and recovery levels.

With regard to safety, no new safety signals were observed, and the safety results were consistent with the current safety profile of brexpiprazole in adults.

☒ Fulfilled:

No further action required; however further data are expected in the context of a type II variation for extension of indication prior any conclusion on product information amendments is made. The MAH should submit this variation application by March 2025.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: RXULTI Active substance: brexpiprazole

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, multicentre, sequential cohort dose escalation trial to assess the safety, tolerability and pharmacokinetics of oral brexpiprazole in adolescents with schizophrenia spectrum or psychotic disorder, and with other psychiatric disorders for which antipsychotic treatments are used in specialist child and adolescent psychiatry clinical practice	331-10-233 (Study 1, PIP EMEA-001185-PIP01-11-M08)	December 2016	
Randomised, multicentre, double-blind, placebo- and activecontrolled trial to evaluate the short-term efficacy of brexpiprazole monotherapy for the treatment of adolescents with schizophrenia.	331-10-234 (Study 2, PIP EMEA-001185-PIP01-11-M08)	03 April 2023	29 September 2023 (within this p46 paediatric procedure)
Open-label, long-term, multicenter trial to evaluate the safety and tolerability of flexible-dose brexpiprazole as maintenance treatment	331-10-236 (Study 3, PIP EMEA-001185-PIP01-11-M08)	Planned for December 2025	

in adolescents with schizophrenia			
Extrapolation study based on data from brexpiprazole adult and paediatric trials and literature to support the maintenance of the antipsychotic effect of brexpiprazole in adolescents with schizophrenia	331-201-00185 (study 4, PIP EMEA-001185-PIP01-11-M08)	Planned for June 2024	