15 January 2026
EMADOC-1700519818-2988413
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RXULTI

International non-proprietary name: Brexpiprazole

Procedure No. EMA/VR/0000307490

Note

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

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Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Netherlands B.V. submitted to the European Medicines Agency on 20 October 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.8 and 5.1 based on final results from study 331-10-236. This is a Phase 3, Long-term, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Flexible-Dose Brexpiprazole as Maintenance Treatment in Adolescents (13-17 Years Old) With Schizophrenia. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0294/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0294/2022 was completed.

2. Overall conclusion and impact on the benefit/risk balance

The MAH submitted single Type II variation application to propose targeted updates to Rxulti SmPC, limited to Annex I:

- Section 4.8: in "Description of selected adverse reaction - Paediatric population" subsection: Deletion of "ongoing" from any mention of the long-term trial (331-10-236) and numeric updates for some undesirable effects: akathisia, suicidal behaviour, weight gain, prolactin, somnolence including sedation and hypersomnia.
- Section 5.1: in "Maintenance of efficacy trial – Paediatric population" subsection: Deletion of ongoing from any mention of the long-term trial (331-10-236). Replacement of the term "interim" with the term "completed" in reference to the analyses from long-term trial.

These changes are proposed on the basis of the final safety and efficacy data from the recently completed (Apr 2025) Phase 3 long-term, multicenter, single-arm, open-label trial 331-10-236. The study tested flexible-dose brexpiprazole as maintenance treatment in adolescents (13-17 years old) with schizophrenia (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5) over a period of 24 months. The primary objective of the study was to characterise the long-term safety, while efficacy was evaluated as secondary endpoint to support maintenance of brexpiprazole monotherapy in the paediatric population.

Brexpiprazole is an atypical antipsychotic agent, approved in the EU for treatment of schizophrenia in adults in 2018. An extension of the schizophrenia indication to include treatment of schizophrenia in adolescents aged from 13 years to 17 years was recently approved in the EU (Mar 2025) based on the

results from 3 clinical trials: one phase 1 dose-escalation trial (331-10-233) and two phase 3 clinical trials (331-10-234 and 331-10-236).

Trial 331-10-236 was ongoing at the time of the paediatric indication application. On that occasion, results from an interim analysis were reviewed (latest cut-off date of 13 September 2024) comprising a total of 288 (97.6%) subjects, of whom 168 subjects having completed the study and 12 subjects ongoing in the trial.

With the current procedure, the MAH submitted the final study report (dated April 2025) of trial 331-10-236 involving 295 adolescents (ages 13 to 17) with diagnosis of schizophrenia treated with brexpiprazole 1 to 4 mg flexibly dosed. With the completion of trial 331-10-236, the MAH accomplishes all requirements of the agreed EU PIP (EMA/PE/0000183866).

With a total of 178 subjects (60.3%) completing the full 24-month treatment period and 216 (73.5%) receiving more than 12 months of treatment, the exposure reached in the trial sufficiently enabled a long-term safety profiling. The study population comprised subjects aged ≥15 (74.2%) and <15 years (25.8%), equally distributed between female (51.9%) and male (48.1%) sex, who rolled over from prior brexpiprazole (n=99), aripiprazole (n=89), placebo (n=87) or were de novo subjects (n=20). Discontinuation included a total of 117 (39.7%) subjects overall with no relevant differences among subgroups. Only a minority of subjects (3.1%) discontinued due to an AE or lack of efficacy (2.4%). Given that the discontinuation rate of antipsychotics in early-onset schizophrenia is a significant concern, related to the complex adherence issues generally observed in these patients, the observed rates are considered acceptable.

Safety data from the completion of Trial 331-10-236 were consistent with the previous paediatric trial results. The most commonly reported TEAEs (>5% overall) were weight increased, somnolence, headache, nasopharyngitis and akathisia. A total of 9 (3.1%) subjects experienced at least one serious TEAEs, none of these was causally related to the investigational medicinal product (IMP). No deaths were reported during the trial. The incidence of TEAEs was 60.3% in males and 67.3% in females, with a similar rate of TEAEs across subgroups when presented by gender, race, region, and age group (< or ≥15 years).

Overall, no new safety signals were identified and no clinically relevant trends in abnormalities were observed in any clinical laboratory results, vital signs, ECG or suicidality. The safety results were consistent with the known safety profile of brexpiprazole that is adequately reported in the SmPC.

Efficacy data from Trial 331-10-236 supports the maintenance of treatment effect of brexpiprazole when flexibly dosed 1 to 4 mg/day in adolescent subjects with schizophrenia. A favourable trend in efficacy outcomes, as evaluated by changes from baseline through Month 24 in PANSS Total Score, was observed in all groups throughout the trial showing that the proportion of responders progressively increased throughout the trial.

The proposed changes are considered acceptable and in line with the data derived from the completion of the long-term study on the adolescent patients with schizophrenia.

Overall benefit-risk balance of RXULTI remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of SmPC sections 4.8 and 5.1 based on final results from study 331-10-236. This was a Phase 3, long-term, multicenter, open-label trial to evaluate the safety and tolerability of flexible-dose brexpiprazole as maintenance treatment in adolescents (13-17 years old) with schizophrenia. The Package Leaflet is updated in drug interactions part. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

☒is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0294/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es)I, IIIB are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Rxulti-H-C-00003841-II-EMA/VR/0000307490'

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Schizophrenia is a major psychiatric disorder and a chronic debilitating illness with an approximate prevalence of 1% worldwide. The age at onset of schizophrenia typically occurs in late adolescence to early adulthood, and there is a considerable increase in prevalence during adolescence with up to one-third of patients with schizophrenia develop disease before adulthood.

The aetiology and pathogenesis of schizophrenia remain partially undefined and is considered multifactorial, involving a complex interaction between genetic vulnerability and environmental risk factors. The finding of abnormalities in neurotransmission has provided the basis for theories that identify the quantitative alteration in neurotransmission (primarily dopamine, serotonin and glutamate) as a crucial pathogenic factor.

Clinically, schizophrenia presents a heterogenous constellation of symptoms, traditionally classified as positive (mainly delusions, hallucinations), negative (alogia, avolition, anhedonia) and cognitive. The clinical course follows a fluctuating pattern with exacerbations and remissions, but a progressive and significant impairment in global functioning and quality of life. Early onset patients tend to have more severe negative symptoms and cognitive impairment compared with adult-onset schizophrenia and a longer duration of untreated psychosis is associated with lower level of functioning and a subsequently worse response to treatment.

Brexpiprazole is an atypical antipsychotic agent discovered by Otsuka. Brexpiprazole is a serotonin-dopamin activity modulator that combines partial agonist activity at dopamine D2 receptors and serotonin 5-hydroxytryptophan receptor 1 A (5-HT1A) with antagonist activities at serotonin 5-hydroxytryptophan receptor 2A (5-HT2A) and noradrenergic α1B/2C receptors.

Brexpiprazole was approved in the EU for treatment of schizophrenia in adults in 2018. An extension of the schizophrenia indication to include treatment in adolescents aged from 13 years to 17 years was recently approved in the EU (2025) based on the results from 3 clinical trials: one phase 1 dose-escalation trial (331-10-233) and two phase 3 clinical trials (331-10-234 and 331-10-236). Trial 331-10-236 was designed to evaluate long-term safety and supportive efficacy of brexpiprazole monotherapy and was ongoing at the time of the paediatric indication application.

Trial 331-10-236, recently completed (Apr 2025), provided additional results regarding efficacy and safety in long-term treatment with brexpiprazole in adolescent patients with schizophrenia.

This type II variation submitted by the MAH aims to update the SmPC in alignment with the final safety data from completed Trial 331-10-236. Proposed changes are limited to Annex I, sections 4.8 and 5.1.

Within this variation the MAH also updated Package Leaflet related to drug interactions part to clarify that ketoconazole's co-administration refers to use in Cushing's syndrome.

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

The MAH conducted a long-term, multicenter, single-arm, open-label Trial (331-10-236) involving 295 adolescents subjects (ages 13 to 17) with diagnosis of schizophrenia (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5) treated with brexpiprazole 1 to 4 mg flexibly dosed.

The trial consisted of up to a 24-month open-label treatment period and was being conducted on an outpatient basis. The trial population included subjects from completed Trial 331-10-234 and de novo subjects between 13 and 17 years of age, inclusive. For rollover subjects, Trial 331-10-236 consisted of a 24 month open-label treatment period and a 21 day follow-up period.

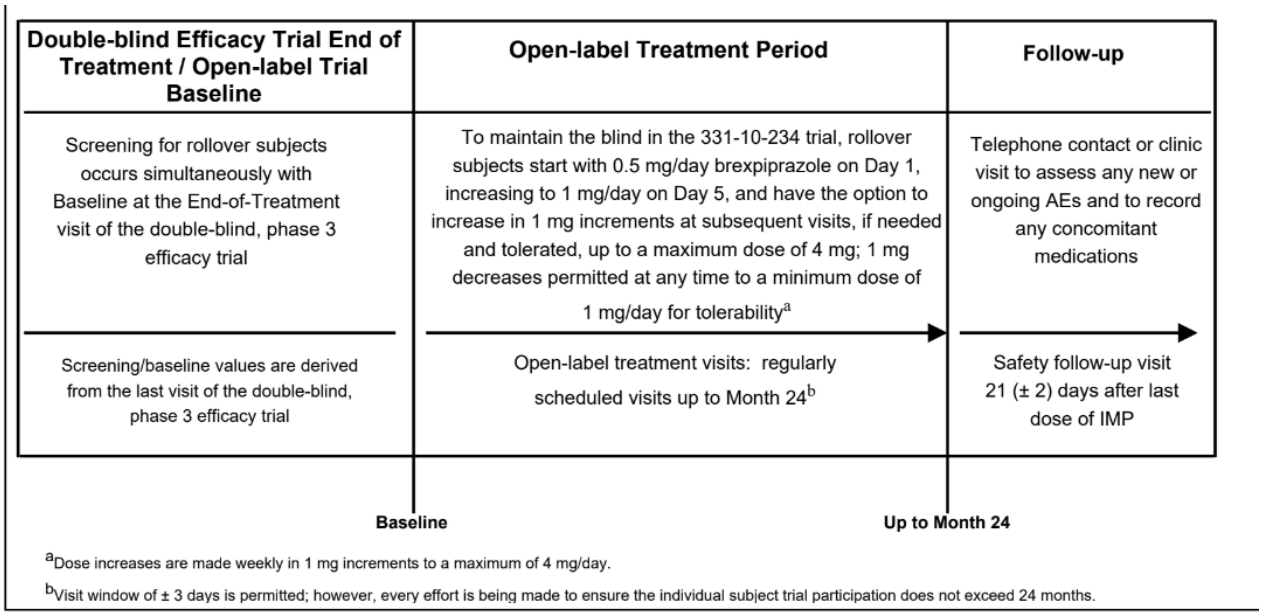

Figure 9.1-1 Trial Design Schematic - Rollover Subjects from Trial 331-10-234

For de novo subjects, Trial 331-10-236 consisted of a 3- to 28-day screening phase, a 1 to 4 weeks conversion phase (if necessary), a 24-month open-label treatment phase, and a 21 (± 2) day follow up period.

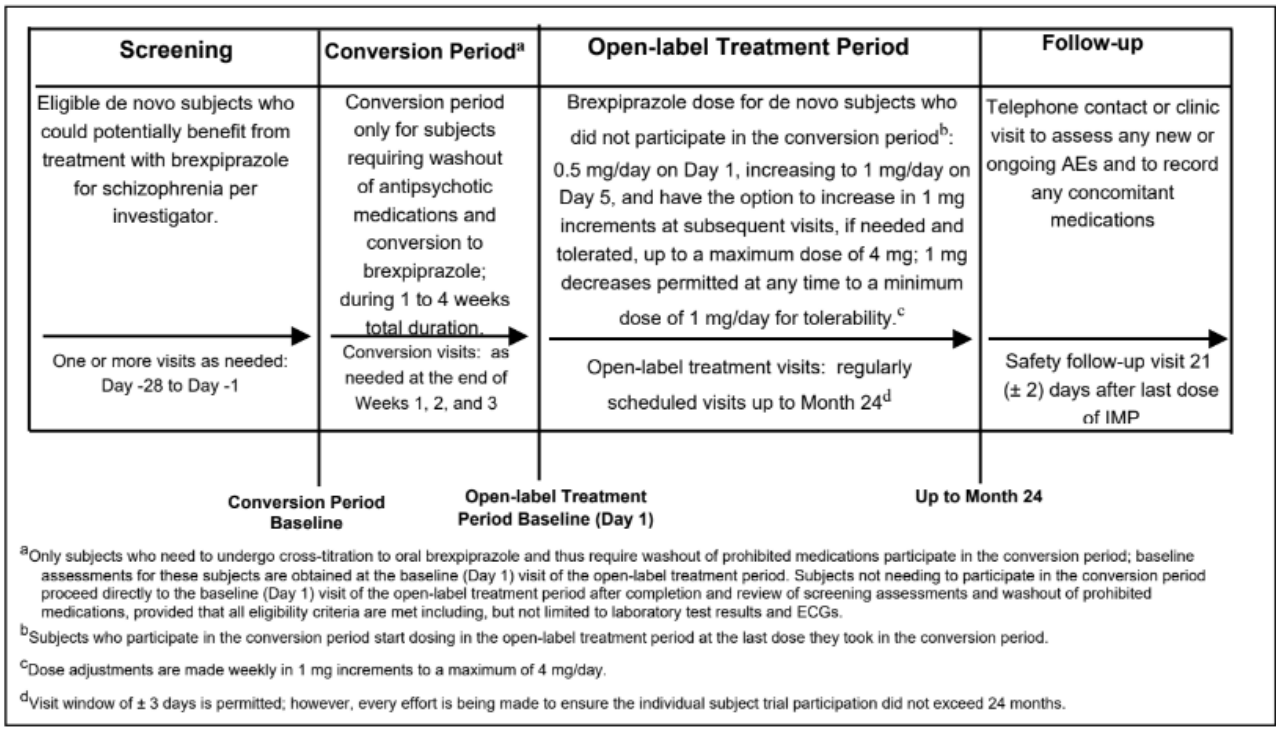

Figure 9.1-2 Trial Design Schematic - De Novo Subjects

AE = adverse event; IMP = investigational medicinal product.

Main Inclusion Criteria

- Male and female subjects 13-17 years of age, inclusive.
- Subjects who turned 18 during trial 331-10-234.
- Subjects with a current primary diagnosis of schizophrenia, as defined by DSM-5 criteria and confirmed by the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia- Present and Lifetime). For de novo subjects the initial documented diagnosis of schizophrenia was confirmed by the K-SADS-PL at screening.
- Subjects who, in the investigator's judgment, required treatment with antipsychotic medication(s).

Main Exclusion Criteria

- Subjects with a DSM-5 diagnosis other than schizophrenia that has been the primary focus of treatment within 3 months of screening.
- Subjects with a clinical presentation or history that was consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms better accounted for by another general medical condition(s) or direct effect of a substance.
- Subjects considered treatment-resistant to antipsychotic medication, history of failure of clozapine treatment, history of response to clozapine treatment only.
- Subjects with a diagnosis of neurological disorder(s) with exception of Tourette's syndrome
- History of neuroleptic malignant syndrome
- Positive drug screen (excluding known prescription of stimulant, opiates, or cannabis)

- Some relevant medical conditions (e.g. hypo and hyperthyroidism, type I diabetes).

The list of prohibited concomitant medications included: all psychotropic agents as antipsychotics, antidepressants, mood stabilizers, benzodiazepines, stimulants, ramelteon and other non-benzodiazepine sleep aides, antihistamines (except for loratadine and cetirizine), varenicline, nutritional supplements and herbal preparations with central nervous system effects, CYP2D6 inhibitors and CYP3A4 inhibitors and inducers.

Treatments

Daily dosing for this trial includes 1, 2, 3, or 4 mg of brexpiprazole, with a maximum dose of 4 mg daily.

Following the initial titration, subjects maintained the same dose or had the option to increase or decrease the dose by 1mg/day in 1-week increments. The dose of brexpiprazole could be decreased at any time based on the investigator's judgement after the start of the open-label treatment period.

- Roll-over subjects (from Trial 331-10-234):

9.4.1.1 Rollover Subjects from Trial 331-10-234

Table 9.4.1.1-1 Dose Adjustments for Brexpiprazole in the Open-label Treatment Period (Both Rollover Subjects from Trial 331-10-234 and Nonconversion De Novo Subjects)

Trial Visit	Dose Options	Dose Changes
Start of the open-label treatment period, Days 1–4	0.5 mg/day (starting dose)	Not applicable
Days 5–7	1 mg/day	Not applicable
Days 8–14	1 or 2 mg/day	Maintain same dose or option to increase to 2 mg/day if tolerated
Days 15–21	1, 2, or 3 mg/day	Maintain same dose, or option to increase or decrease by 1 mg /day (minimum dose 1 mg/day)
Day 22 (Week 3) to Month 24	1, 2, 3, or 4 mg/day	Maintain same dose, or option to increase or decrease dose by 1 mg/day (minimum dose 1 mg/day and maximum dose 4 mg/day)

- De Novo subjects: if the washout of prohibited medications per the protocol was not appropriate, in the opinion of the investigator, the subjects entered a conversion period to cross-titrate from their current antipsychotic treatment(s) to brexpiprazole monotherapy.

Table 9.4.1.2.1-1 Recommendation for Switching from Other Antipsychotics to Oral Brexpiprazole Monotherapy					
	Conversion Period[a]				
Trial Visit	Conversion Baseline	Week 1	Week 2	Week 3	Baseline of Open-label Tx[b]
Dose of brexpiprazole	0.5 mg/day	0.5 or 1 mg/day	1 or 2 mg/day	1, 2, or 3 mg/day	1, 2, or 3 mg/day
Dose of other antipsychotic(s)	No change	No change	Decrease	Discontinue	Discontinue
Dose of aripiprazole	Decrease	Decrease	Discontinue	Discontinue	Discontinue

Tx = treatment.

Note: Washout of required prohibited medications is per the protocol (Section 16.1.1, Table 4.1-1).

[a]Conversion period will last for 1 to 4 weeks.

[b]The baseline (Day 1) visit of the open-label treatment period coincides with the end of the conversion period which is up to 4 weeks in duration.

Outcomes/endpoints

The primary objective of the trial was to assess the long-term safety and tolerability of oral brexpiprazole as monotherapy in adolescents (13 to 17 years old) with schizophrenia. Secondary outcomes (such as the PANSS ratings) concerning efficacy, were assessed in patients for whom baseline and post-baseline ratings were available.

Primary safety endpoints: frequency and severity of treatment emergent adverse events (TEAEs), frequency of serious TEAEs and discontinuation from trial due to AEs.

Secondary safety endpoints: mean change from baseline and incidence of clinically significant abnormalities in clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose, insulin, serum prolactin, glycosylated hemoglobin HbA1C, creatine phosphokinase), body weight, height waist circumference and body mass index (BMI), vital signs, electrocardiogram parameters. Were also evaluated mean change from baseline on extrapyramidal symptoms (EPS) scales (namely the Abnormal Involuntary Movement Scale or AIMS, the Simpson-Angus Scale or SAS, and the Barnes Akathisia Rating Scale or BARS), special pediatric safety assessments (such as the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment or NY-AACENT, and the UKU or Udvalg for Kliniske Undersogelser Side Effects Rating Scale), potential suicide events recorded with the Columbia-Suicide Severy Rating Scale (C-SSRS), baseline and postbaseline Tanner Staging Scale data, and the time to discontinuation due to AE.

The **secondary efficacy outcomes** were assessed using the PANNS Total score, PANSS Positive subscale, PANSS Negative subscale, and the CGI (Clinical Global Impression) S-score (severity) and I-score (improvement). Each of these variables were evaluated at baseline and at week 4 and Months 2, 3, 4, 6, 8, 10, 12, 18 and 24 (when available), and the changes from baseline (except for CGI I-score) were calculated.

Sample size

Sample size was not determined by a formal computation to achieve a target power.

Sample size was planned to attain at least 100 subjects completing 1 year of exposure to brexpiprazole. The safety sample consisted of all enrolled subjects who received at least one dose of IMP.

The efficacy sample consisted of all subjects in the safety sample who had a baseline assessment and at least one postbaseline assessment of the PANSS (Positive and Negative Syndrome Scale) Total Score.

A total of 178 of 295 subjects completed the full open label treatment period of the trial. A total of 294 subjects (99.7%) were analysed for safety, and 288 (97.6%) of subjects were analysed for efficacy.

The majority of included subjects (275) rolled over from the previous double blind, phase 3 efficacy Trial (99 subjects had prior brexpiprazole, 89 subjects had prior aripiprazole, 87 subjects had prior placebo), 20 subjects were de novo.

The data analysis for the open-label treatment period was performed on the analysis sample in aggregate as well as separately on 4 subgroups define by prior treatment status:

- 3 subgroups of rollover subjects from trial 331-10-234: prior brexpiprazole, prior aripiprazole, and prior placebo.
- A subgroup of de novo subjects.

Changes in Planned Analyses

Compared to the prior (interim) CSR (data cutoff date of 10 Oct 2023; approved on 25 Mar 2024), the following changes to the summaries were made:

- Update of the compliance rate derivation, counting the number of days treated over the duration of treatment instead of the number of capsules taken, considering the flexible dose.

- Added safety topics of interest.

Changes in the Conduct of the Trial

Table 9.8.1-1 Protocol Amendments		
Amendment Number	**Date**	**Description of the Changes**
1.	01 Dec 2017	• Clarifications were added around trial procedures design throughout the protocol. • Add weekly (± 3 day) window parameters during open-label treatment period. • Delete requirement in Exclusion Criteria to have 3 time points collected for subjects with QTcF or QTcN corrections of ≥ 450 msec for males and ≥ 470 msec for females. • Add body weight and waist circumference collection at every in-clinic visit. • Add body temperature collection at every in-clinic visit. • Add serum pregnancy test collection at Week 4, Months 6, 12, and 18. • Add urine pregnancy test at Screening/Baseline for rollover subjects. • Removed SAS, AIMS, BARS, UKU, and NY-AACENT requirements during the Conversion Period. • Delete requirement of ECG collection on Day 1 (pre-dose) for de novo subjects.

Table 9.8.1-1 Protocol Amendments		
Amendment Number	**Date**	**Description of the Changes**
		• Add that a follow-up contact will not be necessary if a subject who early terminated received the last dose of IMP > 21 days (± 2 days from the ET visit). • Delete process that OMRI will provide a copy of the CGAS for source documentation use and the results will be recorded on the eSource. • Change maximum allowable dose levels of oral benzodiazepine rescue therapy during the trial. • Update restrictions to allow outpatient group therapy. • Change the assessment duration to the past 1 month in the Suicidal Ideation and Intensity of Ideation sections of the C-SSRS "Baseline/Screening" Version.
2.	13 Sep 2018	• Provided clarifications to support improved program facilitation and communication. • Added history of electroconvulsive therapy to exclusions. • Added birth control patch as an acceptable form of birth control. • Removed inclusion criteria for subjects showing previous response to an antipsychotic. • Added exclusion criteria for subjects known to have medication compliance issues that lead to intramuscular depot medication use. • Added exclusion for subjects who report a true allergic response to aripiprazole or brexpiprazole. • Added exclusion of known poor metabolizers CYP2D6 or CYP3A4. • Modified exclusion criteria for subjects considered treatment resistant to antipsychotic medication. • Added in an exclusion for "subjects who participated in any clinical trial within the last 30 days prior to screening." • Added a possible extension of screening period following discussion with the medical monitor. • Added recording of lifetime antipsychotic use to screening procedure. • Added in a serum pregnancy test. • Clarified that completion of trial will be registered by trial personnel in eSource. • Removed filing of central laboratory reports with source documents. • Added in total, low-density lipoprotein, and high-density lipoprotein for cholesterol clinical laboratory test
3.	03 Jun 2019	• Clarification was added that subjects who were hospitalized for the entire duration of the 331-10-234 study will not be terminated if they are hospitalized in the 331-10-236 study for medical or psychosocial reasons. • Added dispense investigational product to the Schedule of Assessments and clarified vital signs – refers to pulse and heart rate interchangeably throughout the protocol. • Removed "predose" from the ECG assessment for Month 12.
4.	16 Jun 2020	• Introduced a COVID-19 Addendum for any protocol-specified activities that were not able to be performed or could not be performed due to COVID-19 considerations.

6.2. Results

Subject Disposition

A total of 295 subjects entered this trial (275 subjects rolled over from Trial 331-10-234 [99 subjects had prior brexpiprazole, 89 subjects had prior aripiprazole, and 87 subjects had prior placebo], and 20 subjects were de novo). A total of 294 (99.7%) subjects have been analyzed for safety, and 288 (97.6%) subjects have been analyzed for efficacy. One rollover subject that had prior brexpiprazole was not included in the safety analysis because the subject did not receive IMP (Section 16.2.3).

A total of 178 (60.3%) subjects completed the full 2-year open-label treatment period of the trial; and 117 (39.7%) subjects discontinued during the open-label treatment period.

Table 10.1-1 Subject Disposition for Subjects Enrolled into the Open-Label Treatment Period (Enrolled Sample)

	Prior Brex (N = 99)	Prior Arip (N = 89)	Prior Placebo (N = 87)	De Novo (N = 20)	Total (N = 295)
Number of Subjects	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Screened					302
Enrolled[b]	99 (100.0)	89 (100.0)	87 (100.0)	20 (100.0)	295 (100.0)
Treated	98 (99.0)	89 (100.0)	87 (100.0)	20 (100.0)	294 (99.7)
Completed	58 (58.6)	59 (66.3)	50 (57.5)	11 (55.0)	178 (60.3)
Discontinued	41 (41.4)	30 (33.7)	37 (42.5)	9 (45.0)	117 (39.7)
Analyzed For Safety[c]	98 (99.0)	89 (100.0)	87 (100.0)	20 (100.0)	294 (99.7)
Analyzed For Efficacy[d]	96 (97.0)	87 (97.8)	85 (97.7)	20 (100.0)	288 (97.6)

Arip = aripiprazole; Brex = brexpiprazole; IMP = investigational medicinal product; PANSS = Positive and Negative Syndrome Scale.

[a]Percentages were based on the number of subjects in the Enrolled Subjects.

[b]All consented/assented subjects who met all the inclusion and none of the exclusion criteria for the current trial.

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

[d]All subjects in the safety sample who had a baseline assessment and at least one postbaseline assessment of the PANSS Total Score.

A total of 14 of 20 de novo subjects entered the conversion period and all 14 (100.0%) subjects were treated and enrolled into the open-label treatment period.

Table 10.1-2 Subject Disposition for De Novo Subjects Entering the Conversion Period (Enrolled Sample)

	De Novo With Conversion
Number of Subjects:	**n (%)[a]**
Enrolled	14 (100.0)
Treated	14 (100.0)
Enrolled Into The Open-Label Treatment Period	14 (100.0)

[a]Percentages were based on the number of subjects in the Enrolled Subjects.

Discontinuations included a total of 117 (39.7%) subjects overall (41 [41.4%] subjects that had prior brexpiprazole, 30 [33.7%] subjects that had prior aripiprazole, 37 [42.5%] subjects that had prior placebo, and 9 [45.0%] de novo subjects).

Primary reasons for discontinuations included withdrawal by subject (37 [12.5%] subjects), withdrawal by caregiver (27 [9.2%] subjects) and lost to follow-up (17 [5.8%] subjects). Discontinuations due to AEs were reported in 9 (3.1%) subjects. All reasons for discontinuation were presented. There were no deaths in the trial.

Kaplan-Meier Curves for Time to Treatment Discontinuation (for each subgroup) were performed.

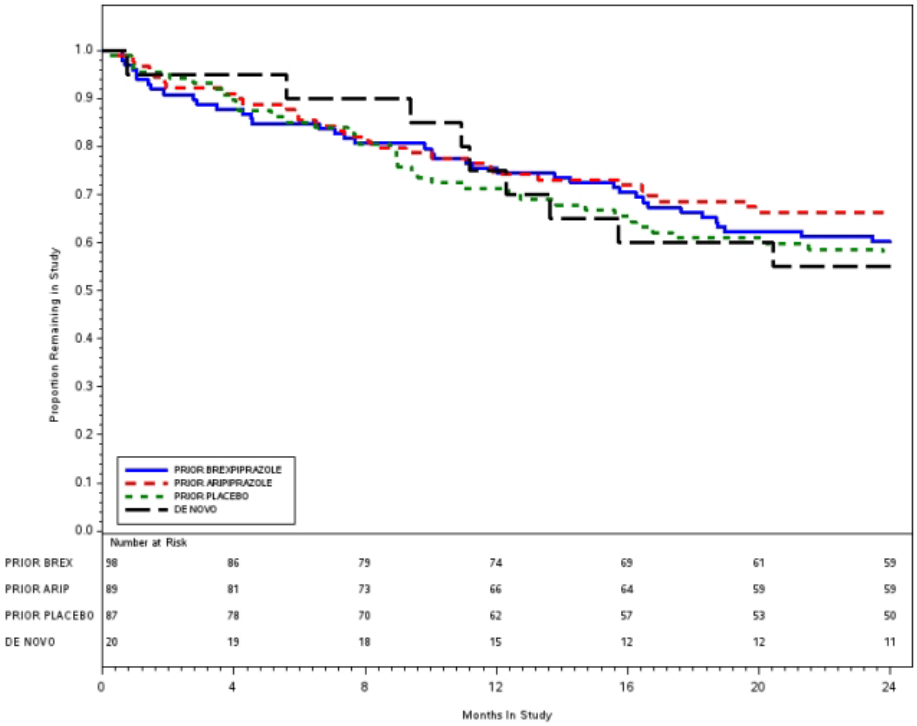

Figure 10.1-1 Kaplan-Meier Curves for Time to Treatment Discontinuation for All Reasons (Safety Sample)

Arip = aripiprazole; Brex = brexpiprazole.

Protocol deviations:

Overall, 196 (66.4%) subjects had at least one major protocol deviation. Of these subjects, a majority (121 subjects, 41.0%) had at least one COVID-related protocol deviation.

Table 10.2-1	Summary of Subjects With Major Protocol Deviations by Type of Deviation (Enrolled Sample)				
	Prior Brex (N = 99)	Prior Arip (N = 89)	Prior Placebo (N = 87)	De Novo (N = 20)	Total (N = 295)
Deviation Classification	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Any Deviation	64 (64.6)	58 (65.2)	59 (67.8)	15 (75.0)	196 (66.4)
Entry Criteria	3 (3.0)	3 (3.4)	4 (4.6)	0 (0.0)	10 (3.4)
Procedural Deviations	50 (50.5)	44 (49.4)	40 (46.0)	10 (50.0)	144 (48.8)
Dosing	14 (14.1)	19 (21.3)	21 (24.1)	3 (15.0)	57 (19.3)
Prohibited Medications	16 (16.2)	15 (16.9)	13 (14.9)	3 (15.0)	47 (15.9)
Subjects With At Least One Covid-Related Protocol Deviation[b]	50 (50.5)	36 (40.4)	30 (34.5)	5 (25.0)	121 (41.0)

Arip = aripiprazole; Brex = brexpiprazole; CRF = case report form.

[a]Percentages were based on the number of subjects in the Randomized Sample.

[b]Covid relationship is not collected directly in the CRF but is derived based on the protocol deviation description text.

Demographics and baseline characteristics

Overall, the mean (SD) age of subjects was 15.5 (1.5) years old, a total of 153 (51.9%) subjects were female, and 142 (48.1%) subjects were male. The main demographic characteristics are presented in the provided table below. MAH did not perform statistical analyses among subgroups.

Table 11.2-1 Demographic Characteristics for the Open-Label Treatment Period (Enrolled Sample)					
Demographic Characteristic	**Prior Brex (N = 99)**	**Prior Arip (N = 89)**	**Prior Placebo (N = 87)**	**De Novo (N = 20)**	**Total (N = 295)**
Age (yrs)					
n	99	89	87	20	295
Mean (SD)	15.5 (1.6)	15.5 (1.4)	15.4 (1.5)	15.5 (1.0)	15.5 (1.5)
Median	16.0	16.0	16.0	16.0	16.0
Min, Max	13,18	13,18	13,18	13,17	13,18
Age Group [n (%)]					
Age <15 n (%)	27 (27.3%)	21 (23.6%)	25 (28.7%)	3 (15.0%)	76 (25.8%)
Age >=15 n (%)	72 (72.7%)	68 (76.4%)	62 (71.3%)	17 (85.0%)	219 (74.2%)
Sex [n (%)]					
Male n (%)	46 (46.5%)	40 (44.9%)	45 (51.7%)	11 (55.0%)	142 (48.1%)
Female n (%)	53 (53.5%)	49 (55.1%)	42 (48.3%)	9 (45.0%)	153 (51.9%)
Height (cm)					
n	99	89	87	20	295
Mean (SD)	166.7 (10.7)	165.6 (9.9)	168.1 (9.9)	170.5 (8.6)	167.1 (10.2)
Median	168.0	166.0	169.0	169.0	168.0
Min, Max	140.0,194.0	145.0,185.0	146.0,195.0	153.0,188.0	140.0,195.0
Weight (kg)					
n	99	89	87	20	295
Mean (SD)	65.9 (16.9)	62.9 (14.5)	68.0 (17.0)	71.1 (14.0)	66.0 (16.2)
Median	63.0	60.7	63.8	69.1	63.4
Min, Max	29.2,116.6	39.4,109.3	40.1,122.0	45.4,97.0	29.2,122.0
Body Mass Index (kg/m2)					
n	99	89	87	20	295
Mean (SD)	23.6 (5.4)	22.9 (4.5)	23.9 (5.1)	24.5 (4.7)	23.5 (5.0)
Median	22.4	22.1	22.9	23.9	22.6
Min, Max	14.9,47.3	15.4,36.1	14.4,40.0	17.8,35.7	14.4,47.3
Waist Circumference (cm)					
n	99	89	87	20	295
Mean (SD)	79.9 (13.5)	76.9 (12.1)	80.7 (15.1)	79.1 (14.5)	79.1 (13.7)
Median	78.0	75.0	79.0	80.0	78.0
Min, Max	57.0,126.0	57.0,113.0	53.0,122.0	45.0,112.0	45.0,126.0
Race [n (%)]					
White n (%)	65 (65.7%)	64 (71.9%)	58 (66.7%)	18 (90.0%)	205 (69.5%)
Black or African American n (%)	6 (6.1%)	2 (2.2%)	3 (3.4%)	1 (5.0%)	12 (4.1%)
American Indian or Alaska Native n (%)	2 (2.0%)	1 (1.1%)	4 (4.6%)	0 (0.0%)	7 (2.4%)
Asian n (%)	1 (1.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
Native Hawaiian or Other Pacific Islander n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other n (%)	25 (25.3%)	21 (23.6%)	21 (24.1%)	1 (5.0%)	68 (23.1%)
Missing	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)

Extent of Exposure

A total of 294 subjects were exposed to at least 1 dose of brexpiprazole in the open-label treatment period at a mean daily dose of 2.45 mg for any exposure. Overall, 251 (85.4%) patients received >6 months of brexpiprazole, 216 (73.6%) subjects were exposed >12 months, 50 (17.0%) subjects were exposed >24 months.

Table 12.1-1	Extent of Exposure to Brexpiprazole During the 24-month Open-Label Treatment Period (Safety Sample)									
	Prior Brex		Prior Arip		Prior Placebo		De Novo		Total	
Days of Exposure	n (%)	Mean Avg Daily Dose (mg/day)	n (%)	Mean Avg Daily Dose (mg/day)	n (%)	Mean Avg Daily Dose (mg/day)	n (%)	Mean Avg Daily Dose (mg/day)	n (%)	Mean Avg Daily Dose (mg/day)
>= 28 Days (4 Weeks)	95 (96.9)	2.40	88 (98.9)	2.41	85 (97.7)	2.55	19 (95.0)	2.90	287 (97.6)	2.48
>= 93 Days (3 Months)	87 (88.8)	2.48	82 (92.1)	2.42	81 (93.1)	2.60	19 (95.0)	2.90	269 (91.5)	2.53
>= 186 Days (6 Months)	83 (84.7)	2.47	76 (85.4)	2.48	74 (85.1)	2.64	18 (90.0)	3.01	251 (85.4)	2.56
>= 372 Days (12 Months)	73 (74.5)	2.48	66 (74.2)	2.50	62 (71.3)	2.69	15 (75.0)	3.06	216 (73.5)	2.59
>= 465 Days (15 Months)	71 (72.4)	2.53	65 (73.0)	2.50	58 (66.7)	2.68	13 (65.0)	2.94	207 (70.4)	2.59
>= 558 Days (18 Months)	64 (65.3)	2.56	61 (68.5)	2.49	53 (60.9)	2.69	12 (60.0)	2.86	190 (64.6)	2.59
>= 651 Days (21 Months)	60 (61.2)	2.54	59 (66.3)	2.50	52 (59.8)	2.69	11 (55.0)	2.89	182 (61.9)	2.59
>= 730 Days (2 Years)	15 (15.3)	2.81	13 (14.6)	2.46	16 (18.4)	2.86	6 (30.0)	2.87	50 (17.0)	2.74
Any Exposure	98 (100.0)	2.35	89 (100.0)	2.39	87 (100.0)	2.51	20 (100.0)	2.91	294 (100.0)	2.45

Arip = aripiprazole; Brex = brexpiprazole.

Treatment-emergent Adverse Events

Overall, 188 of 294 subjects experienced at least a TEAE. A total of 58 (59.2%) subjects with prior brexpiprazole, 54 (60.7%) subjects with prior aripiprazole, 63 (72.4%) subjects with prior placebo, and 13 (65.0%) de novo subjects experienced TEAEs.

The majority of TEAEs reported were mild (156 subjects, 53.1%) or moderate (76 of subjects, 25.9%).

The most commonly reported TEAEs (>5% overall) were weight increased (32 subjects, 10.9%), somnolence (31 subjects, 10.5%), headache (30 subjects, 10.2%), nasopharyngitis (19 subjects, 6.5%) and akathisia (15 subjects, 5.1%). No inferential statistical analysis of TEAEs was performed.

Table 12.2.2.1-1 Incidence of TEAEs of at Least 2% by System Organ Class and MedDRA Preferred Term for the Open-Label Treatment Period (Safety Sample)					
	Prior Brex (N = 98)	Prior Arip (N = 89)	Prior Placebo (N = 87)	De Novo (N = 20)	Total (N = 294)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders					
Nausea	3 (3.1)	1 (1.1)	4 (4.6)	0 (0.0)	8 (2.7)
Salivary Hypersecretion	4 (4.1)	3 (3.4)	2 (2.3)	0 (0.0)	9 (3.1)
Infections and Infestations					
Influenza	4 (4.1)	5 (5.6)	0 (0.0)	2 (10.0)	11 (3.7)
Nasopharyngitis	9 (9.2)	6 (6.7)	4 (4.6)	0 (0.0)	19 (6.5)
Urinary Tract Infection	3 (3.1)	2 (2.2)	5 (5.7)	0 (0.0)	10 (3.4)
Investigations					
Blood Prolactin Increased	2 (2.0)	1 (1.1)	3 (3.4)	0 (0.0)	6 (2.0)
Musculoskeletal and Connective Tissue Disorders					
Muscle Rigidity	0 (0.0)	0 (0.0)	4 (4.6)	2 (10.0)	6 (2.0)
Nervous System Disorders					
Akathisia	6 (6.1)	4 (4.5)	4 (4.6)	1 (5.0)	15 (5.1)
Dizziness	3 (3.1)	3 (3.4)	1 (1.1)	0 (0.0)	7 (2.4)
Headache	10 (10.2)	9 (10.1)	11 (12.6)	0 (0.0)	30 (10.2)
Somnolence	9 (9.2)	7 (7.9)	9 (10.3)	6 (30.0)	31 (10.5)
Psychiatric Disorders					
Anxiety	3 (3.1)	4 (4.5)	4 (4.6)	1 (5.0)	12 (4.1)
Insomnia	1 (1.0)	4 (4.5)	8 (9.2)	1 (5.0)	14 (4.8)
Irritability	2 (2.0)	0 (0.0)	4 (4.6)	0 (0.0)	6 (2.0)
Psychotic Disorder	4 (4.1)	0 (0.0)	3 (3.4)	0 (0.0)	7 (2.4)
Schizophrenia	3 (3.1)	3 (3.4)	3 (3.4)	0 (0.0)	9 (3.1)

Arip = aripiprazole; Brex = brexpiprazole; MedDRA = Medical Dictionary for Regulatory Activities; TEAEs = treatment-emergent adverse events.

TEAEs Related to the IMP

A total of 92 of 294 (31.3% overall) subjects had at least 1 TEAE that was considered by the investigator to be potentially drug-related: 25 (25.5%) in prior brexpiprazole, 23 (25.8%) in prior aripiprazole, and 35 (40.2%) in prior placebo subgroup, 9 (45.0%) among de novo subjects.

The most commonly reported potentially related to the IMP TEAEs were somnolence (27 subjects, 9.2%), weight increased (23 subjects, 7.3%), and akathisia (15 subjects, 5.1%).

In the conversion phase, somnolence and irritability were the only potentially drug-related TEAEs occurring in more than 1 subject (2 subjects each, 14.3%, respectively).

Serious Adverse Events

Severe TEAEs were reported in 9 (3.1%) subjects overall and included the following: schizophrenia related episodes (worsening of exacerbation of psychotic symptoms, 3 subjects), other psychotic disorders (2 subjects), suicide attempt (1 subject), suicidal ideation (1 subject), agitation (1 subject),

back pain (1 subject). Three of those led to discontinuation of IMP. One event (agitation) was considered by the investigator to be potentially related to IMP.

Table 12.3.1.2-1 Incidence of Serious Treatment-emergent Adverse Events in Any Treatment Group by System Organ Class and MedDRA Preferred Term (Safety Sample)

	Prior Brex (N = 98)	Prior Arip (N = 89)	Prior Placebo (N = 87)	De Novo (N = 20)	Total (N = 294)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
At least one TEAE[a]	4 (4.1)	1 (1.1)	3 (3.4)	1 (5.0)	9 (3.1)
Eye Disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Abnormal Sensation In Eye	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Infections and Infestations	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pilonidal Disease	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous System Disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychomotor Hyperactivity	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders	3 (3.1)	1 (1.1)	3 (3.4)	1 (5.0)	8 (2.7)
Psychotic Disorder	1 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.7)
Schizophrenia	1 (1.0)	1 (1.1)	1 (1.1)	0 (0.0)	3 (1.0)
Suicidal Ideation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (0.3)
Suicide Attempt	1 (1.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.7)

AE = adverse event; Arip = aripiprazole; Brex = brexpiprazole; 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.

A total of 9 subjects discontinued the IMP due to an AE. There were no deaths in the trial.

Adverse Event of Special Interest (AESI)

- **Extrapiramidal Symptom-related TEAEs**: Overall, EPS-related TEAEs were reported for 31 (10.5%) subjects: 10 (10.2%), 8 (9.0%), and 10 (11.5%) rollover subjects that received prior brexpiprazole, prior aripiprazole, or placebo, and 3 (15.0%) de novo subjects. The most relevant EPS-related AEs were akathisia (15 subjects, 5.1%) and muscle rigidity (6 subjects, 2.0%). The TEAE of psychomotor hyperactivity was considered serious, but nonrelated to IMP. The TEAE of dystonia was considered nonserious but related to IMP and led to the discontinuation of brexpiprazole. The mean changes in SAS, AIMS and BARS scores were considered not clinically significative.
- **Suicidality**: Overall, TEAEs associated with suicidality were reported for 9 of 294 (3.1%) subjects. A total of 5 (1.7%) subjects experienced suicidal ideation, 2 (0.7%) subjects each experienced suicide attempt or intentional self-injury/overdose. Both events of suicide attempt were classified as serious, both events were resolved and considered not related to IMP, one of them resulted in trial discontinuation. The events of self-injury and overdose were considered mild or moderate. All suicidal ideation events were considered not related to IMP. For 1 subject the suicidal ideation was classified as severe and serious, the remaining 4 subjects were classified as mild and nonserious.

  The emergence of suicidal ideation measured with C-SSRS was reported in 15 subjects (5.1%), and the emergence of serious suicidal ideation was reported in 2 (0.7%) subjects.
- **Somnolence**: A total of 37 (12.6%) subjects had somnolence-related TEAEs (hypersomnia 0.7%, sedation 1.4%, somnolence 11.2%). All TEAEs related to somnolence were considered mild or moderate in severity. A total of 14 TEAEs of somnolence and 2 TEAEs of sedation resulted in a dose reduction of IMP. A total of 2 TEAEs of somnolence resulted in a dose increase.
- **Weight Gain**: A total of 32 (10.9%) subjects experienced TEAEs of weight gain. Additionally, 1 subject experienced the TEAE of BMI increase, 1 separate subject experienced waist

circumference increased, and 2 separate subjects experienced increased appetite. All TEAEs related to weight gain were considered mild or moderate in severity, 1 AE of weight gain resulted in discontinuation of IMP. None of the TEAEs related to weight gain were considered serious.

TEAEs Subgroup Analysis

Overall incidence of TEAEs was 60.3% in males and 67.3% in females. Overall, the incidence of TEAEs was similar across subgroups when presented by gender, race, region, and age group.

Psychiatric symptoms: The total incidence of anxiety was 4.1% (12 subjects, 16 total events). All events were assessed as nonserious and either mild or moderate in severity. Of the 16 total events of anxiety, 3 events were reported as related to brexpiprazole. A total of 14 subjects (4.8%) experienced insomnia. All the events were assessed as nonserious and either mild or moderate in severity. Of the total 19 events (experienced by 14 subjects) of insomnia, 4 of the events were reported as related to brexpiprazole. The total incidence of irritability was 2.0% (6 subjects). All of the events were assessed as nonserious and either mild or moderate in severity. Of the total 7 events, 3 of the events of irritability were reported as related to brexpiprazole.

Pregnancy

Two pregnancies were reported during the trial treatment period. In the first case reported the subject underwent elective termination of the pregnancy. In the second pregnancy reported the outcome of the pregnancy was unknown at the time of the report.

Clinical Laboratory Results

- **Liver Enzymes**: None of the findings about mean changes in liver enzymes over time were considered clinically meaningful. A reduction over time of alkaline phosphatase (U/L), Mean (SD)=-21.16 (57.13) was observed in the total safety sample.

  Liver enzyme results of potential clinical relevance were reported for 3 subjects for alanine aminotransferase and 2 subjects for bilirubin. TEAEs related to hepatic impairment and steatosis were mild and not related to IMP. An event of gamma-glutamyltransferase increased was considered moderate and related to IMP. All events were nonserious and recovered/resolved, all subjects continued with treatment.

- **Metabolic Parameters**: None of the findings about mean changes over time were considered clinically meaningful. Mean (SD) changes in the total safety sample in fasting cholesterol (mg/dL) was 7,39 (30.86), in fasting triglycerides (mg/dL) was 5.30 (53.90), in LDL cholesterol (mg/dL) was 5.05 (25.28), in fasting glucose (mg/dL) was 0.86 (14.09).

  Treatment-emergent significant changes in lipids and glucose were summarized as follows: Fasting cholesterol: 9.6% of subjects had a shift from normal to high; Fasting LDL cholesterol: 9.2% of subjects had a shift from normal to high; Fasting HDL cholesterol: 17.2% of subjects had a shift from normal to low; Fasting triglycerides: 24.5% of subjects had a shift from normal to high; Fasting glucose: 2.5% of subjects had a shift from normal to high, overall 39.8% of subjects had an increase of >10mg/dL.

Overall, 6 subjects (2.3%) met the criteria for treatment-emergent metabolic syndrome.

- **Creatine Phosphokinase and Renal Parameters**: In the total safety sample, mean (SD) change over time in CPK (U/L) was -15.92 (157.05), mean (SD) change over time in creatinine (mg/dL) was 0.03 (0.12), in urea nitrogen (mg/dL) was 0.50 (4.12).

  There were no TEAEs related to CPK or renal parameters reported.

- **Hematology parameters**: None of the findings about Hb1Ac (%) and others hematology parameters (basophils, eosinophils, lymphocytes, neutrophils, red blood cell count, white blood cell count, platelets) were considered clinically meaningful.

- **Urinalysis**: None of the findings about mean changes over time in urinalysis parameters (glucose, pH, protein) were considered clinically meaningful.

- **Prolactin**: Mean (SD) change in all subjects was +2.51 (15.49) ng/mL at the last visit, with similar trends observed in both female and male subjects. Prolactin-related TEAEs were reported for 2 (0.7%) subjects and an additional event of galactorrhoea was reported for 2 (0.7%) subjects. All of these prolactin-related TEAES were considered nonserious, mild in severity and related to IMP. All subjects continued treatment.

  In total, 86 (30.5%) subjects had a prolactin elevation, 69 subjects (24.5%) ≤2 x ULN, and 8 subjects (2.8%) >3 x ULN (upper limit of normal).

Vital signs

- **Blood pressure and heart rate**: Overall, mean (SD) change in systolic blood pressure supine was 1.0 (9.8) mmHg; mean (SD) change in diastolic blood pressure supine was 0.3 (7.9) mmHg; mean (SD) change in pulse rate was -0,5 beats/min.

  The mean changes from baseline in pulse rate and systolic and diastolic blood pressure were minimal and not considered clinically meaningful.

  The vital signs most commonly reported with potential clinical relevance, occurring in ≥10% of subjects overall, were: a decrease in systolic blood pressure with an increase in heart rate in 53 (18.0%) subjects at transition from supine position to standing; an increase in diastolic blood pressure in 49 (16.7%) subjects during standing, an increase in systolic blood pressure in 3 7 (12.6%) subjects during standing. TEAs related to vital signs included hypotension and orthostatic hypotension in 1 subject each (moderate and mild in severity).

- **Body weight**: Mean (SD) change in body weight was 3.9 (6.5) kg, overall. To adjust for the natural growth of paediatric patients, z-scores were derived. The mean change in z-score of body weight at Month 24 was -0.04 SD and at last visit 0.00 SD, while 21.8% of patients had an increase in age-and gender-adjusted body weight z-score of at least 0.5 SD from baseline.

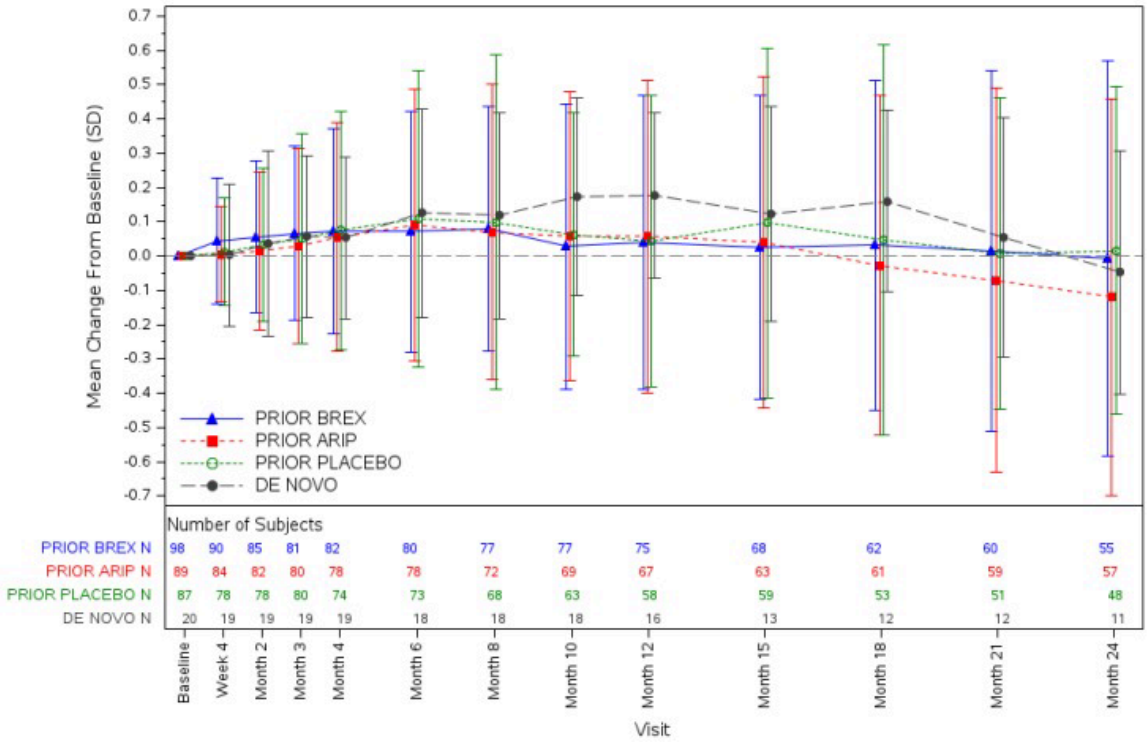

Figure 12.5.2.1-1 Change from Baseline in Body Weight Z-Score (Safety Sample)

Arip = aripiprazole; Brex = brexpiprazole; SD = standard deviation.
Week 1 and Week 2 assessments are not reported on the graph.
Bars are means +/- one standard deviation.

Salivary Hypersecretion

The total incidence of salivary hypersecretion was 3,1% (9 subjects). All the events were assessed as nonserious and mild in severity. Of the 10 events experienced by the 9 subjects, 9 events were reported as related to brexpiprazole. The dose was not changed, and no subjects were withdrawn due to salivary hypersecretion. All 10 events resolved without change to brexpiprazole except of one dose reduction.

Electrocardiogram abnormalities

Mean (SD) change in Heart Rate at last visit was -1.3 (13.9) beats/min. The Mean (SD) change in QT interval at last visit was 3.8 (27.5) and 6.1 (27.9) at Month 24. Mean changes from baseline in ECG parameters were minimal and not considered clinically meaningful.

The most frequently reported ECG abnormalities of potential clinical relevance were bradycardia and sinus bradycardia (6 subjects, 2.1%), supraventricular premature beat (4 subjects, 1.4%), and 1° atrioventricular block (3 subjects, 1.0%). TEAs related to ECG parametres included defect conduction intraventricular (2 subjects, 0.7%) and tachycardia (1 subjects, 0.3%). No TEAEs of QT prolongation were reported.

Other Safety Variables

All incidences of UKU symptoms considered to be probably related to IMP were mild to moderate in severity, except for on subject with increased salivation (severe). This event was considered nonserious and the subject continued with treatment.

Cognitive sings/symptoms measured by NY-AACENT were seen in the majority of subjects during the open-label treatment period. Overall, 260 (88.4%) subjects had any signs/symptoms of attention vigilance, social cognition, reasoning, speed of processing, working memory and verbal learning. Signs/symptoms considered to be IMP-related were speed of processing (17 subjects, 5.7%), working memory and verbal learning (10 subjects each, 3,4%), and attention/vigilance (9 subjects, 3.0%). Mean change from baseline in NY-AACENT total score was -3.21 at Month 24 and -2.52 at last visit. A total score decrease in all prior treatment groups and in de novo subjects was observed.

Secondary Efficacy Outcomes

- **PANSS Total Score**: Overall, subjects had a decrease in mean (SD) change of -19.06 (14.79), -24.45 (16.97) and -19.38 (17.66) from baseline in PANSS Total Score at Month 12, Month 24, and last visit, respectively. For subjects <15 years old, the mean (SD) change from baseline was -18.12 (13.80), -25.22 (17.91) and -18.55 (19.12) at Month 12, Month 24, and last visit, respectively. For subjects ≥ 15 years old, the mean (SD) change from baseline was -19.39 (15.17), -24.17 (16.68) and -19.67 (17.18) at Month 12, Month 24, and last visit, respectively. Improvement was continued in all groups throughout the trial and no relevant differences were observed among subgroups.

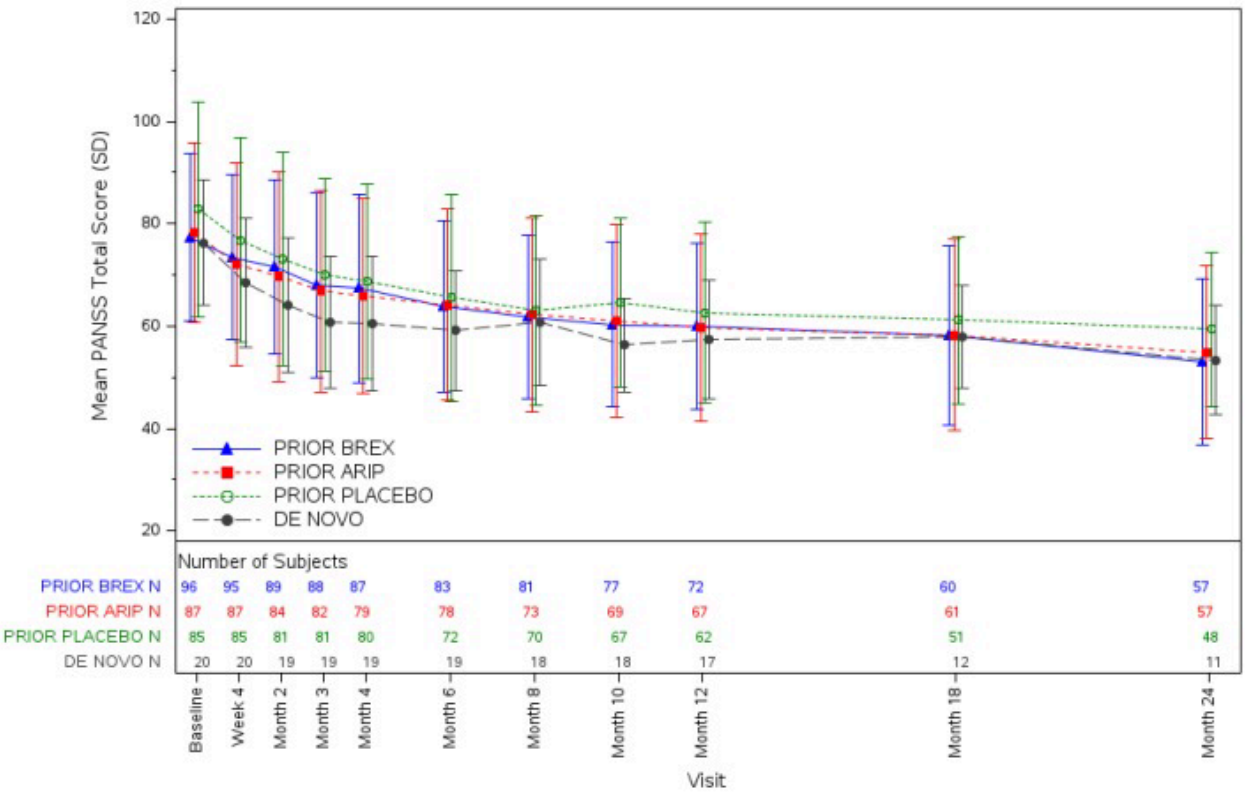

Figure 11.4.1.2.1-1 Mean PANSS Total Score by Visit (Efficacy Sample)

Arip = aripiprazole; Brex = brexpiprazole; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation. Bars are means +/- one standard deviation.

- **PANSS Positive and Negative Subscale Scores**: Overall, the mean (SD) decrease from baseline PANSS Positive Subscale Score was -5.07 (4.56), -6.36 (4.97), and -5.02 (5.27) at Month 12, Month 24, and last visit, respectively. Overall, the mean (SD) decrease from baseline PANSS Negative Subscale Score was -4.29 (4.67), -5.71 (5.20), and -4.73 (5.19) at Month 12, Month 24, and last visit, respectively.
- **CGAS Score**: Overall, subjects experienced continuous improvement in the CGAS Score. The mean (SD) change from baseline showed an increase of 13.11 (12.01), 18.33 (12.58), and 14.26 (13.70) at Month 12, Month 24, and last visit, respectively.
- **CGI-S and CGI-I Scores**: Overall, subjects exhibited a mean (SD) decrease from baseline CGI-Severity Score of -1.05 (0.99), -1.35 (1.10), -1.05 (1.18) at Month 12, Month 24, and last visit, respectively. The CGI-Improvement mean (SD) score was 2.1 (0.9), 1.7 (0.8), and 2.1 (1.1) at Month 12, Month 24, and last visit, respectively.
- **Response Rates**: Response was defined as ≥30% improvement from baseline in PANSS Total Score or having a CGI-Score of 1 or 2. The proportion of responders was initially, at Week 4, 110 of 286 (38.5%) subjects, and progressively increased to 153 to 252 (60.7%) at Month 6, 152 to 221 (68.8) at Month 12, 137 to 184 (74.5%) at Month 18, and 144 of 172 (83,7%) at Month 24. At last visit a total of 207 of 288 (71.9%) subjects were considered responders.

6.3. Discussion

The MAH proposed changes to the SmPC for Rxulti (brexpiprazole) limited to sections 4.8 and 5.1 of Annex 1 on the basis of the recently completed paediatric Trial 331-10-236. Within this variation the MAH also updated Package Leaflet related to drug interactions part to clarify that ketoconazole's co-administration refers to use in Cushing's syndrome.

Initially approved for the treatment of schizophrenia in adults, brexpiprazole received an extension of indication to include treatment of schizophrenia in adolescents aged from 13 to 17 years based on results from 3 clinical trials: one phase 1 dos-escalation trial (331-10-233) and two phase 3 clinical trials (331-10-234 and 331-10-236). Trial 331-10-236 was ongoing at the time of the paediatric marketing authorisation.

On that occasion, results from an interim analysis were reviewed (latest cut-off date of 13 September 2024) comprising a total of 288 (97.6%) subjects, of whom 168 subjects having completed the study and 12 subjects ongoing in the trial.

With this procedure, the MAH submitted the final study report of trial 331-10-236 (completion date 22 Apr 2025) involving 295 adolescents (ages 13 to 17) with diagnosis of schizophrenia treated with brexpiprazole 1 to 4 mg flexibly dosed. With the completion of trial 331-10-236, the MAH accomplishes all requirements of the agreed EU PIP (EMA/PE/0000183866).

Trial 331-10-236 was a long-term, multicenter, single-arm, open-label trial involving 295 adolescents (aged 13-17 years) with diagnosis of schizophrenia treated with brexpiprazole 1 to 4 mg flexibly dosed. This trial was designed to evaluate the long-term (24 months) safety and supportive efficacy of brexpiprazole monotherapy in adolescent patients with schizophrenia. The majority of included subjects (275) rolled over from the previous double blind, phase 3 efficacy Trial (99 subjects had prior brexpiprazole, 89 subjects had prior aripiprazole, 87 subjects had prior placebo), 20 subjects were de novo. A total of 178 of 295 subjects completed the full open label treatment period of the trial.

A total of 294 subjects (99.7%) were analysed for safety, and 288 (97.6%) of subjects were analysed for efficacy. Subgroup analyses were conducted by prior treatment (brexpiprazole, aripiprazole, placebe, de novo subjects). The **primary outcome** included safety endpoints, namely frequency and severity of treatment emergent adverse events (TEAEs), frequency of serious TEAEs and discontinuation from trial due to AEs. Additional safety aspects were analysed among **secondary outcomes**, such as clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose, insulin, serum prolactin, glycosylated hemoglobin HbA1C, creatine phosphokinase), body weight, height waist circumference and body mass index (BMI), vital signs, electrocardiogram parameters. AEs of special interest comprised extrapiramidal symptom-related TEAEs, suicidality, somnolence and weight gain. Efficacy was evaluated a secondary outcome and assessed using the PANNS Total score, PANSS Positive subscale, PANSS Negative subscale, and the CGI (Clinical Global Impression) S-score (severity) and I-score (improvement) over a period of 24 months.

Methods, timing, and clinical data appear appropriate for the population studied and for the pharmacological characteristics of brexpiprazole. **Sample size** was not determined by a formal computation to achieve a target power but derived from the sample size of the previous Trial 331-10-234, which is considered adequate for a long-term trial particularly focusing on safety. Compared with the prior reviewed interim analysis, the **SAP** was changed to include analysis of adverse events of special interest (metabolic parameters, effects on weight, extrapyramidal symptoms, prolactin, QT prolongation, somnolence, suicidality).

As regards the **study conduct**, a total of four protocol amendments were introduced to the original version. Overall, the rate of reported major protocol deviations was particularly high (66.4%) although it is acknowledged that the majority of cases were to be ascribed to Covid-related protocol deviations (41%). The remaining deviations mainly concerned dosing errors and the use of prohibited medications.

Results

With a total of 178 subjects (60.3%) completing the full 24-month treatment period and 216 (73.5%) receiving more than 12 months of treatment, the **exposure** reached in the trial sufficiently enables a long-term safety profiling. The study population comprised subjects aged ≥15 (74.2%) and <15 years (25.8%), equally distributed between female (51.9%) and male (48.1%) sex, who rolled over from prior brexpiprazole (n=99), aripiprazole (n=89), placebo (n=87) treatments or were de novo subjects (n=20). **Discontinuation** included a total of 117 (39.7%) participants overall with no relevant differences among subgroups. Only a minority of subjects (3.1%) discontinued due to an AE or lack of efficacy (2.4%). Given that the discontinuation rate of antipsychotics in early-onset schizophrenia is a significant concern, related to the complex adherence issues generally observed in these patients, the observed rates are considered acceptable.

Primary safety endpoints

Overall, 188 of 294 subjects (63.9%) experienced at least a **TEAE**. The most commonly reported TEAEs (>5% overall) were weight increased, somnolence, headache, nasopharyngitis and akathisia, for which a casual relationshihp with the IMP was reported in the 31.3% of cases. The most common TEAEs potentially related to the IMP were somnolence (27 subjects, 9.2%), weight increased (23 subjects, 7.3%), and akathisia (15 subjects, 5.1%). Expectedly, the incidence of IMP-related TEAEs was higher in the placebo group (40.2%) and de novo subjects (45%) compared with the brexpiprazole (25.5%) and aripiprazole (25.8%) groups. The overall incidence of TEAEs was 60.3% in

males and 67.3% in females, with a similar rate of TEAEs across subgroups when presented by gender, race, region, and age group (66.7% and 63.9% for <15 and >15 years, respectively).

A total of 9 (3.1%) subjects experienced at least one **serious TEAEs**, including schizophrenia (1%), psychotic disorder (0.7%) and suicide attempt (0.7%). All reported SAEs occurred in rollover subjects. None of the serious AEs was causally related to the IMP.

No deaths were registered during the trial.

Overall, the observed events were consistent with the previously described toxicity profile of Rxulti in the paediatric age in terms of both frequency and nature of adverse reactions. Clinically important finding for any of the **safety topics of special interest** were also consistent with the previous paediatric trial data.

In particular, **EPS-related TEAEs** were reported for 31 (10.5%) subjects with the most relevant EPS-related AEs being akathisia (15 subjects, 5.1%) and muscle rigidity (6 subjects, 2.0%). EPS are a known ADR and the incidence of these extrapyramidal symptoms in the adolescent population was consistent with adult schizophrenia trials. The mean changes in SAS, AIMS and BARS scores were considered not clinically significative.

Metabolic changes have been associated with antipsychotic treatment and **weight gain** has been observed with brexpiprazole. Mean (SD) change in body weight was 3.9 (6.5) kg, overall. To adjust for the natural growth of paediatric patients, z-scores were derived. The mean change in z-score of body weight at Month 24 was -0.04 SD and at last visit 0.00 SD. One TEAE of weight increased resulted in the discontinuation of IMP. None of the findings about mean changes over time in metabolics parameters were considered clinically meaningful.

TEAEs of blood prolactin increased (6 subjects, 2.0%) and **hyperprolactinaemia** (2 subjects, 0.7%) were reported in Trial 331-10-236. All of these prolactin-related TEAES were considered nonserious, mild in severity and related to IMP. All subjects continued treatment. Hyperprolactinaemia is a well-known side effect of many antipsychotic medications and a common adverse event of brexpiprazole.

The emergence of **suicidal ideation** measured with C-SSRS was reported in 15 subjects (5.1%). TEAEs associated with suicidality were reported for 9 subjects (3,1%). All events related to suicidality were considered not related to IMP. Risk of suicidal behaviour is, moreover, intrinsic to psychotic disorders and the frequency of suicidal events observed appears to be in line with what already known in adolescent population. The suicide related safety profile observed in the adolescent population was previous considered to be similar to that observed in the adult population.

Mean changes from baseline in **ECG parameters** were minimal and not considered clinically meaningful. There were no clinically important findings related to QT prolongation.

A total of 37 (12.6%) subjects had **somnolence**-related TEAEs (hypersomnia 0.7%, sedation 1.4%, somnolence 11.2%), the majority of events being casually related to the IMP and mild or moderate in severity. A total of 14 TEAEs of somnolence and 2 TEAEs of sedation resulted in a dose reduction of IMP. A total of 2 TEAEs of somnolence resulted in a dose increase.

The analysis of additional events of clinical relevance showed no clinically meaningful changes in **Laboratory tests and vital signs**. The incidence of **salivary hypersecretion** in Trial 331-10-236 was 3.1% (9 subjects). In the adult schizophrenia trials, the incidence of salivary hypersecretion was 0.5% in the long-term trials. On the other hand, no subjects were withdrawn due to salivary hypersecretion and all events resolved (9 out of 10 without changes in brexpiprazole dose). Concerning **Psychiatric symptoms,** the total incidence of **anxiety** was 4.1% (12 subjects, 16 total

events). All events were assessed as nonserious and either mild or moderate in severity. In the short-term trial (331-10-224) the incidence of anxiety was 0.0% and in the long-term adult schizophrenia trials the incidence of anxiety was 2.8%, slightly lower than reported in the paediatric population. Nonetheless, anxiety symptoms are highly prevalent in schizophrenia. The total incidence of **insomnia** (4.8%), was significantly lower than in the long-term adult schizophrenia trials (8.3%). The total incidence of **irritability** was 2.0% (6 subjects), higher than in the long-term adult schizophrenia trials (0.8%). However, all of the events were assessed as non-serious and either mild or moderate in severity and only 3 of the events of irritability were reported as related to brexpiprazole.

Overall, no new safety signals emerged and no clinically relevant trends in abnormalities were observed in any of clinical laboratory results, vital signs, ECG or suicidality. The safety results were consistent with the known tolerability and safety profile of brexpiprazole.

Efficacy

In the Trial 331-10-236 efficacy were measured **secondary efficacy outcomes**, assessed using the PANNS score (Total, Positive and negative subscales), and the CGI S-score and I-score. Each of these variables were evaluated at baseline and at different endpoints through 24 months.

A total of 288 (97.6%) of subjects were analysed for efficacy.

No data about exacerbations (positive and negative symptoms) were provided as schizophrenia exacerbations were not formally defined in the 331-10-236 trial protocol.

Improvement in PANSS Total score, PANSS Positive and Negative Subscales scores and CGI scores were continued in all groups throughout the 24-month period of treatment, and no relevant differences were observed among subgroups by prior treatment (around -24 points from baseline at Month 24 in PANSS total, -19 points from baseline at last visit). The proportion of responders as defined by a 30% reduction in PANSS total score progressively increased throughout the trial reaching a 71.9% of responders at last visit. Discontinuation due to lack of efficacy was 2.3% in the overall population. Subjects maintained improvement in symptoms from baseline through Month 24 and last visit on all mean efficacy measures and response rates. There was no meaningful difference in PANSS Total Score across age groups (subjects <15 years old and ≥15 years old with a change in PANSS total score at Month 24 of -25.22 and -24.17 points in the groups, respectively).

The effect of the treatment, measured through different scales, appears to be maximum during the initial months to plateaued around month 12 and be maintained over time, in cases where discontinuation did not occur. The measures used in the trial for efficacy evaluation appear appropriate and the improvement described is consistent across the different assessment scales adopted. The clinical significance of the observed effect is further confirmed by the progressively increasing percentage of responders throughout the treatment period up to 24 months. The generalizability and external validity of the result is limited by the lack of a comparator due to the open-label long-term design of the trial. However, the overall efficacy data from Trial 331-10-236 supports the maintenance of treatment effect of brexpiprazole when flexibly dosed 1 to 4 mg/day in adolescent subjects with schizophrenia.

7. PRAC advice

No specific PRAC advice was requested for this variation; the update concerned minor numeric updates to the SmPC section 4.8 and does not raise new safety concerns requiring PRAC review.

8. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are updated to reflect final results from study 331-10-236. The Package Leaflet (PL) is updated related to drug interactions part to clarify ketoconazole co-administration. In addition, the list of local representatives in the PL was revised.