30 January 2025
EMA/75373/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rxulti

International non-proprietary name: Brexpiprazole

Procedure No. EMEA/H/C/003841/II/0015

Note

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

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List of abbreviations

$5\text{-}HT_{1A}$	serotonin 5-hydroxytryptamine $_{1A}$
$5\text{-}HT_{2A}$	serotonin $5\text{-}HT_{2A}$
AIMS	Abnormal Involuntary Movement Scale
ASD	autism spectrum disorder
AUC_{T}	area under the concentration-time curve during the dosing interval at steady-state
$AUC_{tau,ss}$	area under the concentration-time curve during a dosing interval (τ) at steady-state
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CDP	clinical development program
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity of Illness Scale
$CL_{ss/F}$	maximal peak steady-state plasma concentration
$C_{max,ss}$	maximum (peak) steady-state plasma concentration
CPK	creatine phosphokinase
$C_{ss,min}$	minimum trough steady-state plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
$C_{trough,ss}$	trough concentration at steady-state
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
E_{max}	maximum brexpiprazole effect on PANSS Total Score
EPS	extrapyramidal symptoms
K-SADs-PL	Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version
LOCF	last observation carried forward
LS	least squares
LSMD	least squares mean difference
OC	observed case
PANSS	Positive and Negative Syndrome Scale
PCR	potentially clinically relevant
PIP	paediatric investigation plan
PSUR	periodic safety update report
QD	once daily
SAS	Simpson-Angus Scale
SD	standard deviation
SE	standard error
SOC	system organ class
$t_{1/2,z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
$t_{ss,max}$	time to maximal peak steady-state plasma concentration
ULN	upper limit of normal
VTE	venous thromboembolism
$V_{z,ss/F}$	apparent volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Pharmaceutical Netherlands B.V. submitted to the European Medicines Agency on 26 June 2024 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of schizophrenia in adolescent patients aged from 13 years to 17 years for RXULTI, based on results from the following clinical studies: one phase 1 dose-escalation trial (Trial 331-10-233) and two phase 3 clinical trials (Trial 331-10-234 and Trial 331-10-236). In addition, a paediatric extrapolation study was completed (Study 331-201-00185). These studies investigated the efficacy and safety of brexpiprazole in paediatric patients (13-17 years old) with schizophrenia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, and to bring the PI in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 EMEA-001185-PIP01-11-M08 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice on the development of brexpiprazole for the treatment of schizophrenia from the CHMP on 11/11/2021 (EMA/SA/0000053607). The Scientific Advice pertained to the following Clinical aspects:

- Acceptability of an extrapolation based on an exposure-response modelling approach from adults to adolescents for brexpiprazole similar to aripiprazole;

- Adequacy of a data package to support an adolescent indication for brexpiprazole comprising PK data and simulations from completed paediatric studies, ari- and brex-piprazole exposure-response modelling, existing adolescent long-term safety data and comparison of adult adolescent PANSS data from open-label trials.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 June 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	13 September 2024
PRAC Rapporteur Assessment Report	20 September 2024
PRAC members comments	25 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	8 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	2 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	29 January 2025 & 30 January 2025
Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

This type II variation has been submitted in order to seeks approval for the use of brexpiprazole for the treatment of schizophrenia in paediatric patients aged 13 to 17 years old.

The clinical development program consists of 3 trials: one phase 1 dose-escalation trial (Trial 331-10-233) and two phase 3 clinical trials (Trial 331 10 234 and ongoing Trial 331-10-236) to demonstrate a statistically significant improvement for brexpiprazole compared to placebo for the primary efficacy endpoint, mean change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score.

In addition, a paediatric extrapolation study was completed (Study 331-201-00185) to provide evidence of maintenance of efficacy of brexpiprazole monotherapy based on extrapolation of data from both adolescent and adult subjects with schizophrenia.

The safety profile of brexpiprazole in adolescents with schizophrenia was also presented.

2.1.1. Problem statement

Disease or condition

Schizophrenia is a life-long psychiatric disorder. The cardinal symptoms fall into 3 domains: positive symptoms such as delusions and hallucination, negative symptoms such as lack of drive and social withdrawal, and cognitive symptoms such as problems with attention and memory.

Childhood-onset psychotic disorders before the age of 13 years are rare, but there is a considerable increase in the prevalence during adolescence. Up to one-third of patients with schizophrenia develop the disease during adolescence.

State the claimed the therapeutic indication

The MAH seeks approval for the use of brexpiprazole for the treatment of schizophrenia in paediatric patients aged 13 to 17 years old.

Epidemiology and risk factors, screening tools/prevention

Schizophrenia is a chronic debilitating illness with an approximate prevalence of 1% worldwide, and up to one-third of patients with schizophrenia develop the disease during adolescence.

Biologic features, aetiology and pathogenesis

Biological theories of schizophrenia have focused on genetics and, structural and functional abnormalities in the brain. Family, twin and adoption studies indicate an important genetic contribution to the aetiology of schizophrenia.
Clinically, schizophrenia is heterogeneous, and this may point to heterogeneous aetiology. It seems that genetics, neurodevelopmental problems, neurochemistry and abnormal connectivity, as well as psychosocial stressors probably all contribute to developing the typical clinical pictures of schizophrenia. Abnormalities in neurotransmission have provided the basis for theories on the pathophysiology of schizophrenia. Most of these theories focus on either an excess or a deficiency of neurotransmitters including dopamine, serotonin, and glutamate. Other theories implicate aspartate, glycine, and gamma-aminobutyric acid (GABA) as part of the neurochemical imbalance of schizophrenia.

Clinical presentation, diagnosis and stage/prognosis

The diagnosis of schizophrenia in children and adolescents is made using the same diagnostic criteria in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as for adult-onset schizophrenia. Early-onset schizophrenia, defined as schizophrenia onset before 18 years of age, is phenomenologically continuous with schizophrenia in adulthood and has high diagnostic stability.

Data from phenomenological, cognitive, neuroimaging, and genetic studies suggest a similar profile of clinical and neurobiological abnormalities between early- and adult-onset patients. Though similar profiles, early onset patients tend to have more severe negative symptoms, cognitive impairment, impulsivity, frequent hospitalizations, and poor social functioning compared with adult-onset schizophrenia.

While a longer duration of untreated psychosis in adolescent schizophrenia patients was associated with a lower level of functioning, less functional improvement, and lower rates of clinical remission, there still remains limited availability of approved medications in the European Union (EU) for this patient population.

Management

There are high unmet needs for a wider availability of antipsychotics with fewer side effects (e.g., sedation, extrapyramidal symptoms [EPS], metabolic symptoms, prolactin changes, and suicidality), which may help lead to higher medication compliance in adolescents who may be more vulnerable and sensitive to antipsychotic side effects compared with adults.

Latuda (lurasidone) film-coated tablets, indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over, was approved in 2014 in adults and on 2020 variation II/29 was approved to extend indication in adolescents from 13 years of age.

2.1.2. About the product

Brexpiprazole is an atypical antipsychotic agent discovered by Otsuka and co-developed by Otsuka and H. Lundbeck A/S (Lundbeck) for several psychiatric indications. Brexpiprazole is a serotonin-dopamine activity modulator that combines partial agonist activity at serotonin 5-hydroxytryptophan receptor 1A (5-HT1A) and dopamine D2 receptors with antagonist activities at serotonin 5-hydroxytryptophan receptor 2A (5-HT2A) receptors with similar high affinities at all these receptors. Brexpiprazole also shows antagonist activity at noradrenergic α1B/2C receptors at similar potency.

Brexpiprazole is supplied as 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, and 4.0 mg tablets for oral use.

Brexpiprazole taken orally once daily was approved for the treatment of schizophrenia and as adjunctive treatment for major depressive disorder in adults (ages 18 to 65 years) by the United States Food and Drug Administration (FDA) in 2015. In the EU, brexpiprazole was approved for the treatment of schizophrenia in adults in 2018. Brexpiprazole has been registered and approved in more than 60 countries worldwide. Furthermore, based on the extrapolation of adult efficacy data to support a new indication, brexpiprazole was approved by the FDA for the treatment of schizophrenia in adolescents aged 13 years and older in 2021. In 2023, it was approved by the FDA for the treatment of agitation associated with dementia due to Alzheimer's disease.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The brexpiprazole paediatric schizophrenia clinical development program (CDP) includes the following trials:

- Trial 331-10-233: short-term, open-label, dose-escalation trial investigated the pharmacokinetic (PK), safety, and tolerability
- Trial 331-10-234: short-term, double-blind, controlled trial evaluating efficacy and safety
- Trial 331-10-236 (ongoing): long-term, open-label trial evaluating safety and tolerability
- Study 331-201-00185: data extrapolation study to assess the maintenance of efficacy in adolescent subjects with schizophrenia
- Study 331-24-201 (annex to Study 331-201-00185): population PK and exposure-efficacy analyses via external validation.

The EU schizophrenia paediatric investigation plan (PIP) was agreed upon in Jul 2012. In a PIP modification in Jul 2018 (EMEA-001185-PIP01-M05), Study 331-201-000185 was added to leverage phase 3 adolescent trials (Trials 331-10-234 and 331-10-236) in extrapolation of maintenance of efficacy from adult patient populations to paediatric patient populations. Consequently, the duration of Trial 331-10-234 was shortened to 6 weeks (previously 26 weeks). In the Scientific Advice meeting in Oct 2021, the European Medicines Agency (EMA) did not agree with extrapolation of short-term efficacy and still requested the clinical data for paediatric indication application (EMA/SA/0000053607; 2021).

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

No new non-clinical data in terms of PK, PD and toxicology have been submitted for this application of paediatric indication from 13-17 years of age, which is considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided the following justification for not updating the ERA of brexpiprazole as assessed for adult population at the time of the IMA and completed with the previous variation (phase II Tier A assessment for soil): “An increase in the environmental exposure is not expected because the calculation of PEC was not limited to adult patients. Therefore, it can be concluded that the calculated PEC covers all age groups. Furthermore, the calculated PEC sediment overestimated the environmental exposure because the PEC was calculated using the maximum daily dose of 4 mg/day (the same maximum daily dose proposed for adolescent schizophrenia).”

The justification of the MAH is endorsed, and the table below that was agreed in a previous variation procedure, is still valid for the present variation.

Table: Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): brexpiprazole					
CAS-number (if available): 913611-97-9					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD TG123	2.41, 4.27, 4.86 at pH 5, 7, 9 respectively			Potential PBT (Y)
PBT-assessment		Result			Conclusion
Bioaccumulation	log K_{ow}	See above			B
	BCF	10.875 L/kg fresh weight			B
Persistence	DT50 or ready biodegradability	DT50 whole systems, 12°C: > 10.000 plateau formation in water/sediment system (Not readily biodegradable)			P
Toxicity	NOEC	72 h= EC10 alga 0.011 mg/L			not T
PBT-statement:	The compound is considered as very Persistent and very Bioaccumulative (vPvB) but not toxic				
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.02	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	-	-			(Y/N)
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OPPTS TG 835.1110 OECD 106	Kd sludge: 6482 L/kg (the compound is immobile in soil) Kd soil (Bromsgrove): 5830 Kd soil (Drayton): 22200 Kd soil (Elmton): 6400 Kd,oc soil (Bromsgrove): 416000 Kd,oc soil (Drayton): 1060000 Kd,oc soil (Elmton): 145000			
Ready Biodegradability Test	OECD 301	Not biodegradable			Water/sediment study OECD 308 triggered
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ 12°C= > 10.000 plateau formation in water/sediment system (only marginal Co2 formation, 31%) % shifting to sediment > 10 at day 14 and any point in time thereafter			Very persistent in the acquatic environment. Sediment organism effect study required
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	Ca. 11	µg/L	Pseudokirchneriella subcapitata, geometric mean of initially

					measured value and ½ LOQ, degradation ca. 90% assumed to be photodegradation
Daphnia sp. Reproduction Test	OECD 211	NOEC	130	µg/L	Nominal concentration
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	56	µg/L	Danio rerio, arithmetic mean measured value, nominal 40 µg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	> 770 µg/L (i.e., the limit of water solubility)	µg/L	No Observed Effect Loading Rate (NOELR) ≥ 100 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	10.875 L/kg fresh weight	L/kg	% lipids: 5, low dose
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	140 4.7%		P
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	>1000	mg/ kg	Soil dry weight
Terrestrial Plants, Growth Test/Species: • Onion (Allium cepa, Alliaceae, Monocotyledonae) • Maize (Zea mays, Poaceae, Monocotyledonae) • Beetroot (Beta vulgaris, Chenopodiaceae, Dicotyledonae) • Tomato (Lycopersicon esculentum, Solanaceae, Dicotyledonae)	OECD 208	NOEC	> 1000	mg/ kg	Soil dry weight
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	> 1000	mg/ kg	Soil dry weight EC10 = 152 mg/kg
Collembola, Reproduction Test	ISO 11267	NOEC	250	mg/ kg	
Sediment dwelling organism	OECD 218	NOEC	41.67	mg/ kg	dry weight sediment, Chironomus riparius

2.2.2. Discussion on non-clinical aspects

No new non-clinical data in terms of PK, PD and toxicology have been submitted for this application of paediatric indication from 13-17 years of age, which is considered acceptable by the CHMP.

The MAH has provided the adequate justification for no update of the brexpiprazole ERA assessed for adult population at the time of the initial approval.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of brexpiprazole.

- Considering the above data, brexpiprazole should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

No new non-clinical data have been submitted which is considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Overview of Brexpiprazole Development Program for Paediatric Schizophrenia						
Protocol # Trial Location Trial Phase	**Trial Description (Treatment Duration)**	**IMP Dose and Regimen**	**# Subjects Enrolled/ (Randomized)/ Completed**	**Trial Population**	**Primary Endpoints**	**Trial Status, Date**
331-10-233 United States (Phase 1)	Multicenter, open-label, sequential cohort, open-label dose-escalation trial 2 weeks	Cohort 1 (0.5 mg): 0.5 mg QD for 14 days; Cohort 2 (1 mg): 0.5 mg on Days 1 - 2, followed by 1 mg QD for 14 days; Cohort 3 (2 mg): 0.5 mg on Days 1 - 2; 1 mg on Days 3 - 4; 1.5 mg on Days 5 - 6; followed by 2 mg QD for 14 days; Cohort 4 (3 mg): 1 mg on Days 1 - 2; 1.5 mg on Days 3 - 4; 2 mg on Days 5 - 6; 2.5 mg on Days 7 - 8; followed by 3	Total 43/(43)/37 Cohort 1: 8/(8)/7 Cohort 2: 8/(8)/7 Cohort 3: 9/(9)/7 Cohort 4: 9/(9)/8 Cohort 5: 9/(9)/8	Adolescent subjects (13 to 17 years of age) with a current primary schizophrenia spectrum diagnosis or other psychiatric disorder for which antipsychotic treatments are used in child and adolescent psychiatry clinical practice (ie, bipolar spectrum)	Primary PK: $C_{max,ss}$, $C_{min,ss}$, $t_{ss,max}$, AUC_{τ}, $t_{1/2,z}$, $CL_{ss/F}$, and $V_{z,ss/F}$ Primary Safety: Reported AEs, vital signs, body weight, ECGs, clinical laboratory tests, and physical examinations. The EPS rating scales including SAS, AIMS, BARS, and C-SSRS. Assessment of tolerability.	Completed 27 Jan 2017

Overview of Brexpiprazole Development Program for Paediatric Schizophrenia						
Protocol # Trial Location Trial Phase	**Trial Description (Treatment Duration)**	**IMP Dose and Regimen**	**# Subjects Enrolled/ (Randomized)/ Completed**	**Trial Population**	**Primary Endpoints**	**Trial Status, Date**
		mg QD for 14 days; Cohort 5 (4 mg): 1 mg on Days 1 - 2; 2 mg on Days 3 - 4; 2.5 mg on Days 5 - 6; 3 mg on Days 7 - 8; 3.5 mg on Days 9 - 10; followed by 4 mg QD for 14 days				
331-10-234 United States, Mexico, France, Italy, Poland, Romania, Serbia, Spain, Ukraine, and Russia (Phase 3)	Multicenter, randomized (1:1:1), double-blind, placebo- and active-controlled trial 6 weeks	Titrate up to brexpiprazole 2 mg daily (minimum dose) by Day 8; 2-3 mg daily by Day 15; dose may increase to 4 mg after Day 21 Aripiprazole 10 mg daily by Day 8; dose may increase in 5 mg increments weekly to a maximum of 20 mg after Day 21 Placebo	Total (316)/296 Brexpiprazole 2-4 mg/day: (110)/107 Aripiprazole 10-20 mg/day: (102)/97 Placebo: (104)/92	Adolescent subjects (13 to 17 years of age) with a DSM-5 diagnosis of schizophrenia confirmed by K-SADS-PL, a 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	Primary Endpoint: Change from baseline to Week 6 in PANSS Total Score Secondary Efficacy Endpoints: Mean change from baseline by visit in: PANSS Positive/Negative Subscale Score, CGI-S Score, and CGAS Score; CGI-I Score by Visit	Completed 03 Apr 2023

Overview of Brexpiprazole Development Program for Paediatric Schizophrenia						
Protocol # Trial Location Trial Phase	**Trial Description (Treatment Duration)**	**IMP Dose and Regimen**	**# Subjects Enrolled/ (Randomized)/ Completed**	**Trial Population**	**Primary Endpoints**	**Trial Status, Date**
331-10-236 United States, Mexico, France, Italy, Poland, Romania, Serbia, Spain, Ukraine, and Russia (Phase 3)	Long-term, multicenter, single-arm, open-label safety and tolerability rollover trial 24 months	Rollover subjects from Trial 331-10-234: Titrate up to brexpiprazole monotherapy at 1 mg/day (minimum dose) by Day 5, and optionally to 2 mg/day on Day 8. Dose titration is allowed at 1 mg increments up to a maximum of 4 mg/day anytime thereafter. De novo subjects: brexpiprazole tablet PO QD as needed to convert from other antipsychotic(s) to monotherapy with brexpiprazole (1 up to 4 mg/day)	Total 295/(294)/140 Rollover 275/(274)/129 De novo 20/(20)/11	Eligible adolescent subjects (13 to 17 years of age) with schizophrenia who completed double-blind Trial 331-10-234 (rollover subjects); and eligible de novo subjects	Primary Endpoint: Frequency and severity of AEs, serious TEAEs (clinical and laboratory), and discontinuation from trial due to AEs. Secondary Endpoints: Mean change from baseline by visit in: PANSS Total Score, PANSS Positive/Negative Subscale Score, CGI-S Score, and CGAS Score; CGI-I Score by Visit	Ongoing (data cutoff date: 10 Oct 2023)
331-201-00185 NA Efficacy Extrapolation (NA)	Extrapolation study to assess the long-term efficacy in adolescent (13 to 17 years of age) subjects with schizophrenia	NA	NA	Defined per Full Analysis Set	Change from baseline to Week 32 in PANSS Total Score for subjects treated with brexpiprazole 2 to 4 mg comparing adolescents from Trials 331-10-234 and 331-10-236 to adults from Trials 331-10-230, 331-10-231, and 331-10-237.	NA
331-24-201[a] NA Population PK Analysis	External validation and comparison of previously developed adult population PK and exposure-response models with PK and efficacy	NA	NA	Population PK: adolescents from Trials 331-10-233 and 331-10-234 and adults from 12 completed trials in healthy subjects and subjects with		NA

Overview of Brexpiprazole Development Program for Paediatric Schizophrenia						
Protocol # Trial Location Trial Phase	**Trial Description (Treatment Duration)**	**IMP Dose and Regimen**	**# Subjects Enrolled/ (Randomized)/ Completed**	**Trial Population**	**Primary Endpoints**	**Trial Status, Date**
	data collected from adolescents.			schizophrenia or MDD Exposure-efficacy: adolescents from Trial 331-10-234 and adults from Trials 331-07-203, 331-10-230, and 331-10-231		

AE = adverse event; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity of Illness scale; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition; E-R = exposure-response; F = female; IMP = investigational medicinal product; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version; LPI = last patient in; M = male; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PO = by mouth; QD = once daily; SD = standard deviation; TEAE = treatment-emergent adverse event.

[a]Disposition as of 10 Oct 2023 data cut-off date for ongoing Trial 331-10-236.

[b]Response rate = response defined as ≥ 30% improvement from baseline in PANSS Total Score or having a CGI-I Score of 1 or 2.

[c]Remission rate = remission 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).

[d]Study 331-201-00185 is an extrapolation study based on data from adult and pediatric brexpiprazole trials as well as literature to support the maintenance of the antipsychotic effect of brexpiprazole in adolescents with schizophrenia.

2.3.2. Pharmacokinetics

Brexpiprazole pharmacokinetics (PK) in adolescents (aged 13 to 17 years) has been evaluated in a clinical pharmacology trial 331-10-233 (see below).

To evaluate if drug exposure and the exposure-efficacy relationships were similar between adolescents and adults, external validations of the adult population PK model and exposure-efficacy model in Report 331-12-208 were performed on PK and efficacy (as measured by Positive and Negative Syndrome Scale [PANSS] Total Score) data collected from adolescents (data from Trials 331-10-233 and 331-10-234 for PK external validation, data from Trial 331-10-234 for exposure-efficacy external validation). Model simulations were conducted to compare brexpiprazole drug exposure between adolescents and adults following the same brexpiprazole daily dose and exposure-efficacy relationships were also compared between adolescent and adult subjects with schizophrenia.

Bioanalytical method

No additional biopharmaceutical studies have been conducted for this paediatric indication application.

The same bioanalytical method (Covance 6825-271 Final Amended Validation Report Number 5) developed for the quantification of brexpiprazole and its metabolites in plasma for trials submitted in the initial MAA was used to quantify brexpiprazole and DM-3411 concentrations for trials submitted in this application. OPC-34712 (brexpiprazole) and its metabolites (OPC-3952, OPC-54050, OPC-34835, DM-3404, DM-3411, DM-3412, MOP-54522, and SFO-34318) were determined in human plasma with sodium

heparin as an anticoagulant by high performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection. The lower limit of quantitation (LLOQ) for OPC-34712 and metabolites in human plasma was 0.300 ng/mL, with linearity demonstrable to 100 ng/mL (ULOQ). Stability for OPC-34712 and DM-3411 in human plasma was established for 632 days when stored in a freezer set to maintain -60 to -80ºC. The Addendum 6 of the validation report 6825-271 provides final results of the matrix frozen stability evaluation for OPC-34712 (brexpiprazole) and its metabolite DM-3411, at -60 to -80 °C for 1124 day. Dilution linearity was evaluated using six replicates of dilution QC [DQC (400 ng/mL)] samples, diluted ten-fold into the calibration range.

From Study 331-10-233, a total of 567 plasma samples were received by the bioanalytical laboratory (Covance Laboratories Inc. (Covance), Wisconsin, USA). Concentration results for brexpiprazole and DM-3411 were generated for 551 samples. The remaining 16 samples were backups (secondary aliquot) and were not analyzed. The HPLC-MS/MS method used for the determination of brexpiprazole and DM-3411 in plasma had adequate linearity, specificity, precision, and accuracy. The calibration coefficient of determination (R2) of the standard curve over the course of the trial was ≤ 0.9927 for all analytes. For each batch of samples processed, the calculated concentrations of at least 67% of the quality control samples were within 15% of nominal. Precision was evaluated via percent coefficient of variation over the duration of the trial. Interassay precision values of quality control samples obtained for brexpiprazole and DM-3411 were ≤ 7.0%. Interassay accuracy for all analytes ranged from −2.1% to 5.0% bias. The incurred sample reanalysis (ISR) experiment was performed by reanalysis of 56 plasma samples from 20 subjects for brexpiprazole and DM-3411. For each analyte, the acceptance criterion was 67% for the samples, the difference between the ISR sample results and the original value was to have been within 20% of the mean of the two. Brexpiprazole and DM-3411 passed the ISR assessment with 100% of the samples meeting the acceptance criteria. Based on the individual sample collection and extraction dates, samples were stored at a nominal temperature of −70°C ± 10°C for a maximum of 472 days, which was within the initial established stability of 632 days.

Chromatograms are from one analytical run and include a blank, a blank with internal standard, standards, QCs, and at least 5% of subject samples.

From Study 331-10-234, a total of 910 plasma samples were received by the bioanalytical laboratory (Labcorp Early Development Laboratories Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704, USA).

Concentration results for brexpiprazole and its metabolite, DM-3411, were generated for 406 samples. If every subject enrolled (316) donated a PK sample at every planned timepoint (3), there would be 948 PK samples. However, due to missed collections and subject discontinuations, not all PK samples were collected. Of the 910 samples received, 406 were analyzed, which included 3 samples per subject from those randomized to brexpiprazole and 1 sample (Week 4) per participant collected from those randomized to placebo, as available. The remaining samples were collected from subjects randomized to aripiprazole or placebo. The HPLC-MS/MS method used had adequate linearity, specificity, sensitivity, precision, and accuracy. Incurred sample reanalysis was performed on 19 samples for brexpiprazole, which is 4.7% of the total number of samples and 13 (68%) met acceptance criteria. Incurred sample reanalysis was performed on 15 samples for DM-3411, which is 8.7% of the total number of samples and 14 (93%) met acceptance criteria. According to the MAH, the incurred sample reanalysis met acceptance criteria.

Based on the individual sample collection and extraction dates, samples were stored at a nominal temperature of −70°C ± 10°C for a maximum of 1127 days. All samples were analyzed within the established storage stability period of 1124 days except for 1 sample. This sample was stored for 1127 days and was flagged and reported as “non reportable.”

For study 331-10-236 no drug concentration measurements are performed.

In the extrapolation 331-201-00185, in addition to studies 331-10-233 and 331-10-234, data from adult studies 331-10-230, 331-10-231 and 331-10-237 were used. Samples from studies 331-10-230 and 331-10-231 were analysed with the same method 6825-271. For Study 331-10-237 no PK determinations were performed.

Study 331-10-233 results

Study 331-10-233 was conducted to primarily evaluate the PK of brexpiprazole, and its major metabolite (DM-3411), in connection with a multiple oral dosing in adolescent subjects, and to assess the safety and tolerability of brexpiprazole used as a multiple-dose regimen in this population. The secondary aim was to assess the efficacy of brexpiprazole.

PK parameters were determined for Day 14 of the fixed dose period using a noncompartmental approach for each subject.

Selected PK parameters (Cmax, AUC, and CL/F) were further used in exploratory statistical analyses to assess PK dose proportionality (PK linearity), and PK in comparison with historical data in adults with schizophrenia.

This was a phase 1, multicenter, open-label, sequential cohort, dose-escalation trial that consisted of a screening period, a dose titration period, a fixed dose period, and a safety follow-up.

In the exploratory analyses for selected PK parameters, there were 2 populations: population 1 (PK population): all subjects with at least 1 observation for each of the reported PK parameters; population 2 (PK evaluable population): all subjects with at least 1 observation for each of the reported PK parameters and who had reached steady-state (24-hour trough concentration on Day 14 of the fixed dose period within 20% of the pre-dose concentration).

Subjects entered the dose titration period (except for Cohort 1) during which they received the investigational medicinal product (IMP) for 2 to 10 days based on their assigned titration schedule. Subjects in Cohorts 3 to 5 were dosed for 2 days at each titration dosing level. Following the dose titration period, subjects entered the fixed dose period and were administered the assigned dose for that cohort for 14 days.

Dosing began with Cohort 1 at a dose of 0.5 mg/day of the IMP. Cohort 1 did not have a dose titration period, but proceeded directly to the fixed dose period. The following target doses were planned: 0.5, 1, 2, 3, and 4 mg; based upon the previous cohort's safety and tolerability observations.

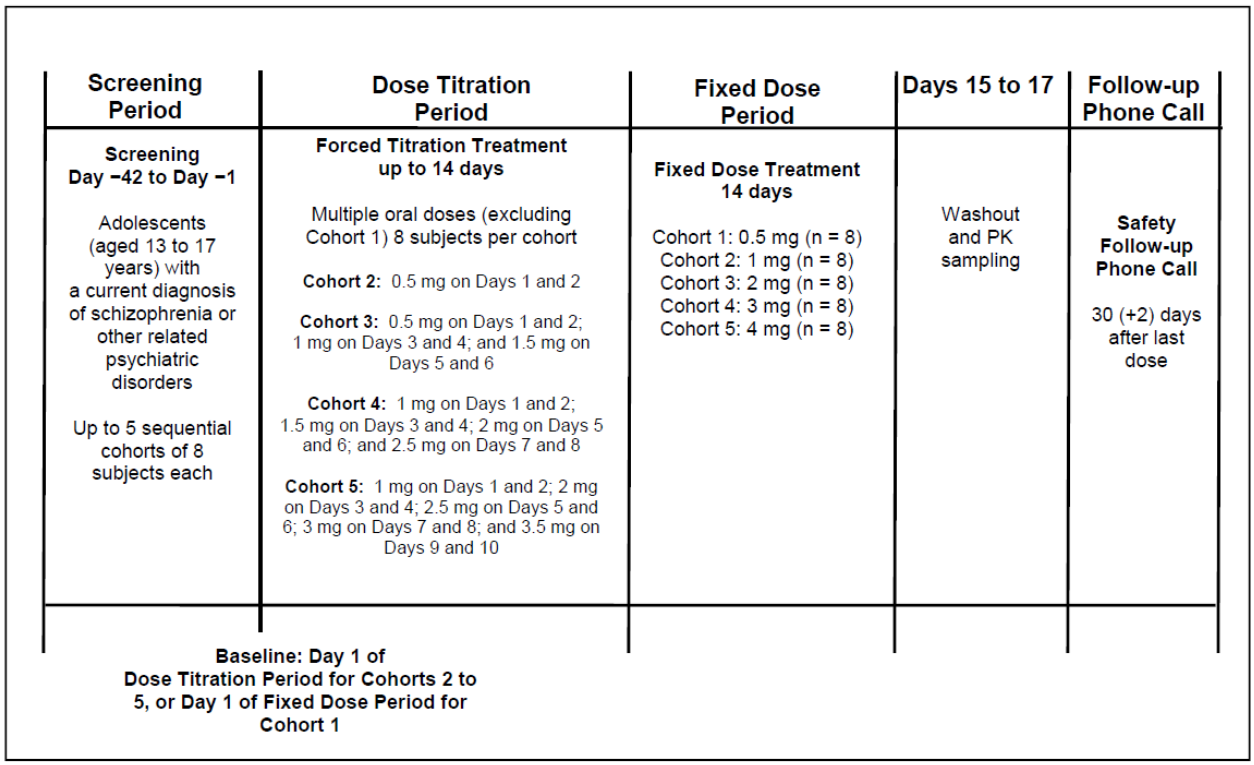
The planned dosing schedule for the dose titration and fixed dose periods was:

- Cohort 1 (0.5 mg; n = 8): 0.5 mg daily for 14 days
- Cohort 2 (1 mg; n = 8): 0.5 mg on Days 1 and 2, followed by 1 mg daily for 14 days
- Cohort 3 (2 mg; n = 8): 0.5 mg on Days 1 and 2; 1 mg on Days 3 and 4; and 1.5 mg on Days 5 and 6, followed by 2 mg daily for 14 days
- Cohort 4 (3 mg; n = 8): 1 mg on Days 1 and 2; 1.5 mg on Days 3 and 4; 2 mg on Days 5 and 6; and 2.5 mg on Days 7 and 8, followed by 3 mg daily for 14 days
- Cohort 5 (4 mg; n = 8): 1 mg on Days 1 and 2; 2 mg on Days 3 and 4; 2.5 mg on Days 5 and 6; 3 mg on Days 7 and 8; and 3.5 mg on Days 9 and 10, followed by 4 mg daily for 14 days

Dosing was conducted in a staggered fashion. For each cohort, 2 subjects were dosed initially. If there was acceptable tolerability 48 hours after the first 2 subjects received the first fixed dose of IMP, the other 6 subjects in the cohort began dosing. If dosing of the entire cohort was determined to be safe and tolerable, then dose escalation continued with the next cohort.

Subjects who did not tolerate the assigned dose in the fixed dose period had their dose reduced by 0.5 to 1 mg, based on the investigator's judgment. The dose titration period of the next cohort only started after safety and tolerability was established at the previous dose level.

A schematic of the trial design is shown in Figure below:



The doses used in this trial were determined based on results from trial in adult healthy subjects (Trial 331-07-202) and a completed phase 2 trial in adults with an acute relapse of schizophrenia (Trial 331-07-203).

Based on data from Trial 331-07-202 in adults with schizophrenia who received single doses of 0.25, 0.5, 1, 2, 4, 5, and 6 mg brexpiprazole and steady-state PK/pharmacodynamics (PD) modelling, it was predicted that the D2/D3 receptor occupancy after multiple daily dose administration of 1 to 2 mg and higher doses of brexpiprazole will result in at least 80% to 90% D2/D3 receptor occupancy in adults.

Based on the review of the safety data for Trial 331-07-203 in adults with acute schizophrenia (doses ranging from 0.25 to 6 mg daily) and evaluation of collective safety, efficacy, and receptor occupancy data, a maximum dose of 4 mg/day brexpiprazole was chosen for evaluation in adults with schizophrenia. As adults, children, and adolescent are expected to exhibit similar D2/D3 receptor binding, the same dose range was chosen for evaluation in adolescents with the initial dose of 0.5 mg which is 1/24 of the highest tolerated dose in adult subjects with schizophrenia.

Study 331-10-233 included male and female adolescents between 13 and 17 years of age, inclusive, at the time of consent/assent, with a primary schizophrenia spectrum diagnosis (schizophrenia, schizoaffective, or schizophreniform) confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL). Subjects with other psychiatric disorders for which antipsychotic treatments are used in child and adolescent psychiatry clinical practice, i.e., bipolar spectrum disorder (bipolar I, II, or NOS) were also enrolled. A total of 61 subjects were screened (excluding subjects that were re-screened) and 43 subjects were enrolled in the trial. Of the 43 enrolled subjects, 37 (86.0%) completed the trial and 6 subjects (14.0%) discontinued from the trial. The reasons for discontinuation included adverse events (AE, 1 [2.3%]), subject withdrawn from participation by the

investigator (2 [4.7%]), and subject withdrew consent to participate (3 [7.0%]). Discontinued subjects were replaced so that 8 subjects provided evaluable data for each cohort.

Overall, the subjects enrolled were predominantly black or African American (27 of 43 subjects [62.8%]) and ⩾ 15 years of age (24 of 43 subjects [55.8%]). Of the 43 subjects enrolled, 22 subjects (51.2%) were male and 21 subjects (48.8%) were female.

The mean age, height, and weight of the subjects was 14.7 years, 167.0 cm, and 69.0 kg, respectively.

At baseline, 12 subjects (27.9%) had a psychiatric history of schizophrenia and 31 subjects (72.1%) had a psychiatric history of bipolar disorder.

Table 11.2-1 Demographics and Baseline Characteristics

Demographic Characteristic	Cohort 1 0.5 mg (N = 8)	Cohort 2 1 mg (N = 8)	Cohort 3 2 mg (N = 9)	Cohort 4 3 mg (N = 9)	Cohort 5 4 mg (N = 9)	Total (N = 43)
Age (years)						
n	8	8	9	9	9	43
Mean	15.1	14.0	14.8	14.4	15.0	14.7
Median	15.5	13.5	15.0	15.0	15.0	15.0
SD	1.1	1.4	1.2	1.3	1.5	1.3
Min, max	13, 16	13, 17	13, 17	13, 17	13, 17	13, 17
Age Group [n (%)]						
< 15	2 (25.0%)	6 (75.0%)	4 (44.4%)	4 (44.4%)	3 (33.3%)	19 (44.2%)
≥ 15	6 (75.0%)	2 (25.0%)	5 (55.6%)	5 (55.6%)	6 (66.7%)	24 (55.8%)
Sex [n (%)]						
Male	3 (37.5%)	5 (62.5%)	3 (33.3%)	4 (44.4%)	7 (77.8%)	22 (51.2%)
Female	5 (62.5%)	3 (37.5%)	6 (66.7%)	5 (55.6%)	2 (22.2%)	21 (48.8%)
Race [n (%)]						
White	2 (25.0%)	2 (25.0%)	5 (55.6%)	4 (44.4%)	3 (33.3%)	16 (37.2%)
Black or African American	6 (75.0%)	6 (75.0%)	4 (44.4%)	5 (55.6%)	6 (66.7%)	27 (62.8%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity [n (%)]						
Hispanic or Latino	0 (0.0%)	3 (37.5%)	3 (33.3%)	1 (11.1%)	1 (11.1%)	8 (18.6%)
Not Hispanic or Latino	7 (87.5%)	5 (62.5%)	6 (66.7%)	8 (88.9%)	8 (88.9%)	34 (79.1%)
Unknown	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Height (cm)						
n	8	8	9	9	9	43
Mean	162.1	172.0	165.7	165.2	170.1	167.0
Median	165.0	170.0	164.0	164.0	172.0	166.0
SD	5.6	10.8	9.4	5.4	10.5	9.0
Min, max	152.0, 167.0	156.0, 189.0	154.0, 179.0	158.0, 172.0	154.0, 184.0	152.0, 189.0

Table 11.2-1 Demographics and Baseline Characteristics

Demographic Characteristic	Cohort 1 0.5 mg (N = 8)	Cohort 2 1 mg (N = 8)	Cohort 3 2 mg (N = 9)	Cohort 4 3 mg (N = 9)	Cohort 5 4 mg (N = 9)	Total (N = 43)
Weight (kg)						
n	8	8	9	9	9	43
Mean	71.0	73.3	64.6	63.1	73.9	69.0
Median	61.1	67.8	59.8	61.7	76.0	65.0
SD	20.7	21.8	18.6	11.7	15.4	17.6
Min, max	56.4, 109.2	44.8, 116.2	46.6, 108.5	43.4, 83.4	55.0, 107.8	43.4, 116.2

The number of subjects included in the PK analysis is presented in the table below:

Table 11.5.2.2-1 Number of Subjects Included in Each Cohort

Population	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
PK evaluable population[a]	2	5	4	6	7	24
PK population[a]	7	7	6	8	8	36

[a]The PK evaluable population includes subjects with at least 1 PK parameter and that reached steady-state; the PK population includes subjects with at least 1 PK parameter.

For Cohort 1, blood samples for the determination of brexpiprazole and its major metabolite, DM-3411, were collected during the fixed dose period on Day 1 predose and Day 14 predose, and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, and 72 hours postdose. The 24- and 30-hour samples were collected on Day 15 and the 72-hour sample was collected on Day 17.

For Cohorts 2 to 5, blood samples for the determination of brexpiprazole and its major metabolite, DM-3411, were collected on Day 1 (dose titration period) predose and during the fixed dose period on Day 1 predose and Day 14 predose, and 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, and 72 hours post dose. The 24- and 30-hour samples were collected on Day 15 and the 72-hour sample was collected on Day 17.

Median and mean brexpiprazole plasma concentration versus time profiles for the PK evaluable population on Day 14 of the fixed dose period following once-daily administration of 1, 2, 3, or 4 mg of brexpiprazole in adolescents with schizophrenia or other related psychiatric disorders are provided in the figures below:

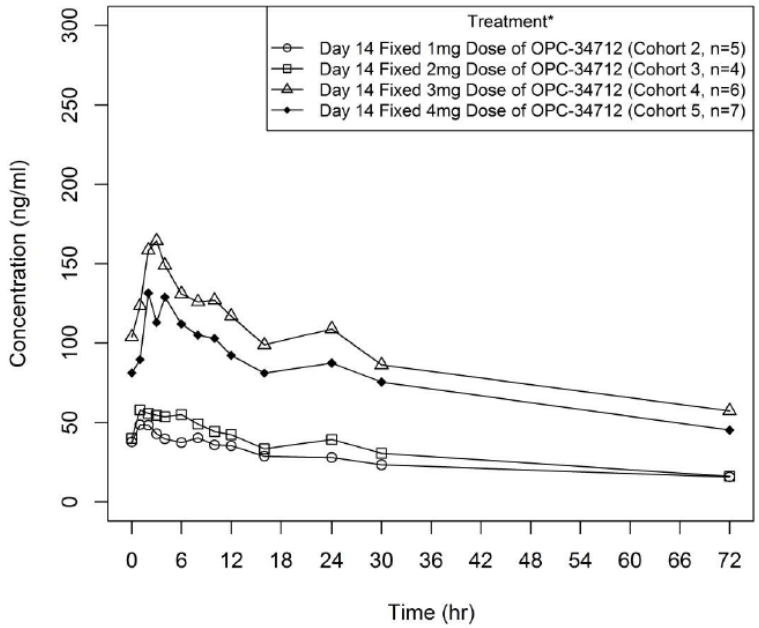
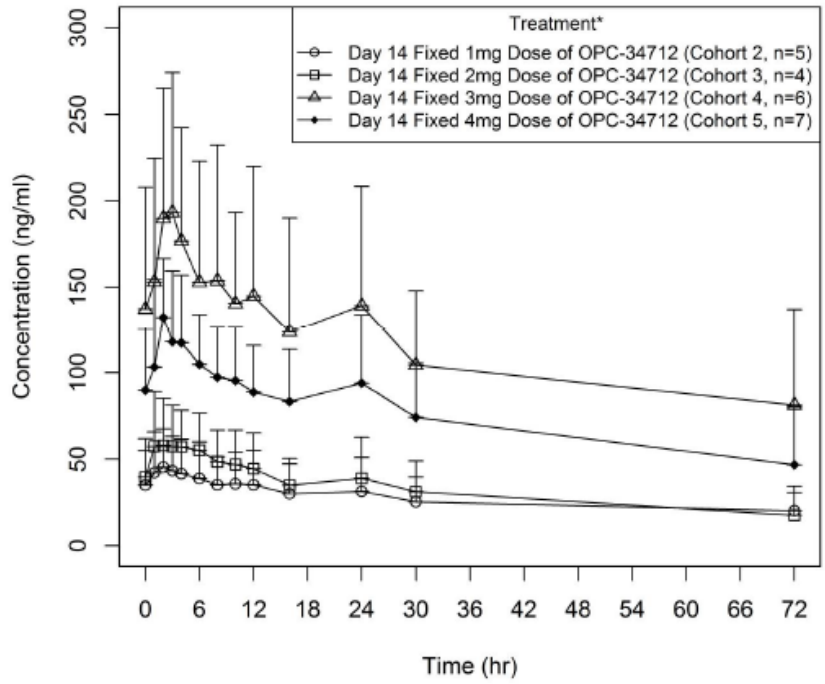


Figure 11.5.2.3.1-1 Median Brexpiprazole Plasma Concentration Versus Time Profiles on Day 14 of the Fixed Dose Period Following Once-Daily Administration of 1, 2, 3, or 4 mg Brexpiprazole in Adolescents with Schizophrenia or Other Related Psychiatric Disorders (PK Evaluable Population)

Note: Cohort 1 (0.5 mg) is not plotted due to the limited number of PK evaluable subjects (n = 2).
Lower limit of quantification: 0.3 ng/mL.
Source: Analysis dataset containing PK concentrations.

PKF-2 **Mean (SD) Brexpiprazole Plasma Concentration versus Time Profiles on Day 14 of the Fixed-Dose Period following Once-Daily Administration of 1mg, 2mg, 3mg, or 4mg Brexpiprazole in Adolescents with Schizophrenia or Other Related Psychiatric Disorders (PK Evaluable Population)**



*Cohort 1 (0.5mg) is not plotted due to limited number of PK evaluable subjects (n=2)
Lower Limit of Quantification: 0.3 ng/mL
Source: ADPC analysis dataset.

Table 11.5.2.4.1-1 Mean (SD) Brexpiprazole PK Parameters Following Once-Daily Administration of 0.5, 1, 2, 3, or 4 mg of Brexpiprazole in Adolescents with Schizophrenia or Other Related Psychiatric Disorders (PK Evaluable Population)

PK Parameter	0.5 mg (n = 2)	1mg (n = 5[a])	2 mg (n = 4[a])	3 mg (n = 6[b])	4 mg (n = 7[a])
$C_{max,ss}$ (ng/mL)	ND	46.4 (21.4)	63.0 (26.0)	197 (77.6)	129 (43.7)
$t_{max,ss}$ (h)[c]	ND	2.00 (1.00 - 4.00)	2.03 (1.00 - 4.00)	2.99 (2.00 - 3.05)	3.00 (1.00 - 6.00)
AUCτ (h·ng/mL)	ND	841 (455)	1080 (489)	3410 (1640)	2300 (793)
$C_{min,ss}$ (ng/mL)	ND	29.1 (17.3)	33.3 (17.4)	129 (64.7)	80.1 (31.0)
$t_{1/2,z}$ (h)	ND	81.6 (40.9)	ND	88.5 (83.1)	50.6 (23.6)
CL/F (mL/h)	ND	1550 (917)	2190 (999)	983 (431)	2070 (1210)

ND = not determined due to lack of data; only 2 out of 7 subjects in Cohort 1 (0.5 mg) reached steady-state; number of subjects having evaluable $t_{1/2,z}$ in Cohort 3 (2 mg) is not more than 50%.

[a] $t_{1/2,z}$ in Cohort 2 (1 mg), Cohort 3 (2 mg), and Cohort 5 (4 mg) has n = 4, n = 3, and n = 6, respectively due to λ_z calculation criteria.

[b] In Cohort 4 (3 mg), AUC_τ and CL/F has n = 5 as Subject had a protocol time deviation at the 24-hour postdose sample on Day 15.

[c] Median (minimum - maximum) is presented.

A summary of DM-3411 PK parameters in the PK evaluable population following once-daily administration of 0.5, 1, 2, 3, or 4 mg of brexpiprazole in adolescents with schizophrenia is provided in the table below:

Table 11.5.2.4.2-1 Mean (SD) DM-3411 PK Parameters Following Once-Daily Administration of 0.5, 1, 2, 3, or 4 mg of Brexpiprazole in Adolescents with Schizophrenia or Other Related Psychiatric Disorders (PK Evaluable Population)

PK Parameter	0.5 mg (n = 2)	1 mg (n = 5[a])	2 mg (n = 4[a])	3 mg (n = 6[a, b])	4 mg (n = 7[a])
$C_{max,ss}$ (ng/mL)	ND	14.7 (5.10)	36.9 (14.4)	56.7 (34.8)	53.4 (14.8)
$t_{max,ss}$ (h)[c]	ND	2.00 (0.00 - 4.00)	6.02 (3.00 - 10.00)	3.00 (2.00 - 4.03)	4.00 (2.00 - 24.02)
AUCτ (h·ng/mL)	ND	295 (113)	720 (333)	1180 (659)	998 (263)
$C_{min,ss}$ (ng/mL)	ND	10.5 (4.57)	22.7 (12.7)	40.1 (22.6)	34.6 (9.25)
$t_{1/2,z}$ (h)	ND	61.9 (31.3)	ND	ND	38.7 (18.0)

ND = not determined due to lack of data; only 2 out of 7 subjects in Cohort 1 (0.5 mg) reached steady-state; number of subjects having evaluable $t_{1/2,z}$ in Cohort 3 (2 mg) and Cohort 4 (3 mg) are not more than 50%.

[a] $t_{1/2,z}$ in Cohort 2 (1 mg), Cohort 3 (2 mg), Cohort 4 (3 mg) and Cohort 5 (4 mg) has n = 4, n = 3, n = 4, and n = 5, respectively due to λ_z calculation criteria.

[b] In Cohort 4 (3 mg), AUC_τ and CL/F has n = 5 as Subject had a protocol time deviation at the 24-hour postdose sample on Day 15.

[c] Median (minimum - maximum) is presented.

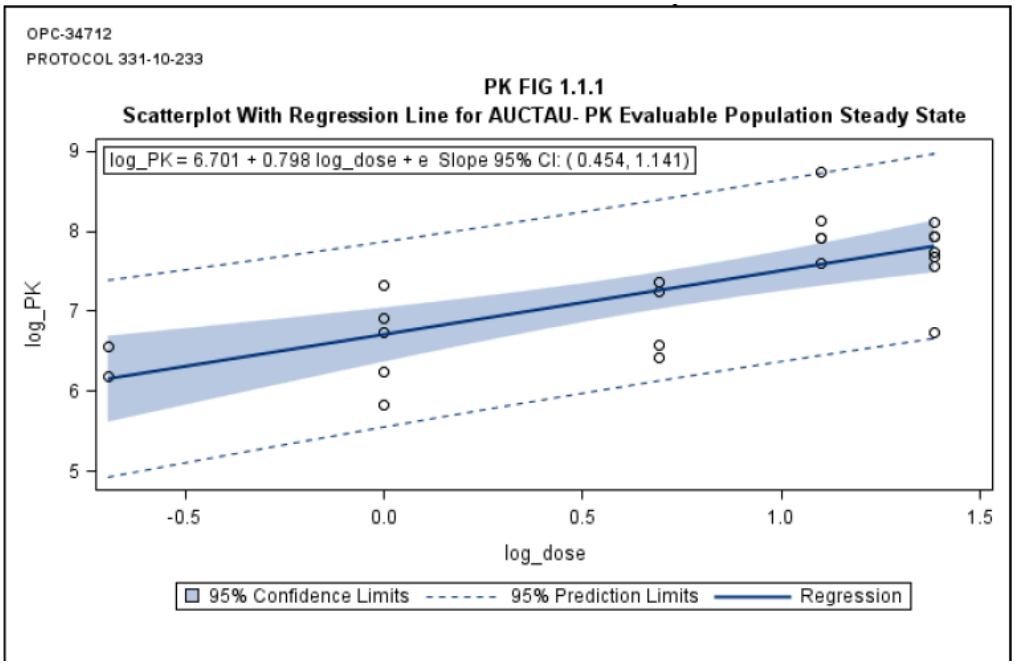
The dose proportionality analysis included 24 subjects for the PK evaluable population and 36 subjects for the PK population. The dose-proportionality was assessed using analysis of variance (ANOVA) on dose-normalized exposure (Cmax and AUC) and CL/F. In addition, a regression analysis (power model) was applied to test dose proportionality, using the equation below:

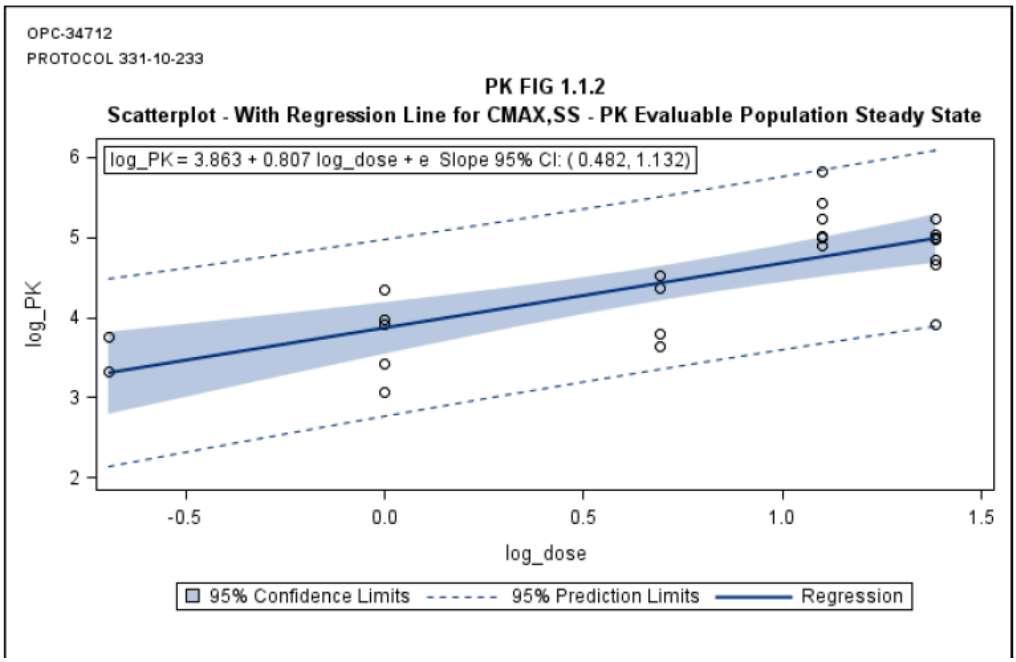
$$\ln(Y) = a + b \times \ln(Dose) + e$$

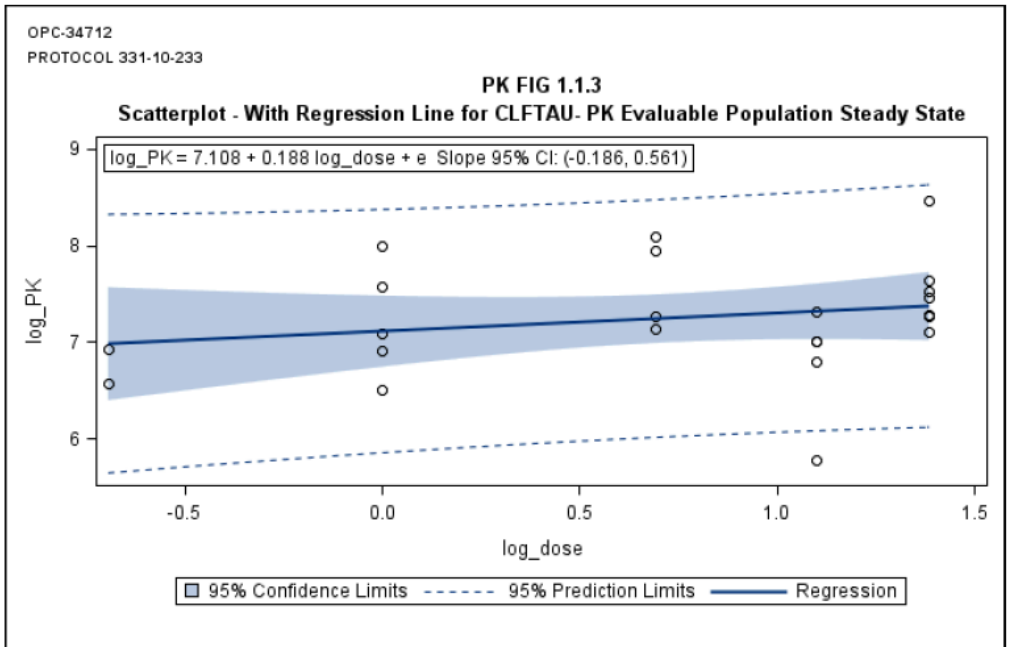
where Y represents PK parameter, b, the slope, measures the proportionality between dose and Y, *a* represents intercept of the regression line and *e* represents other variability. Dose proportionality could be claimed if the 95% confidence intervals (CIs) for b included 1 for the PK parameters mentioned above except for CL/F, where the 95% CIs for b including 0 indicated dose proportionality.

Dose proportionality was evaluated separately in Study 331-10-233 and in Study 331-08-205 (Phase I ascending dose in adults with schizophrenia in which doses from 1 to 12 mg were evaluated).

Dose proportionality was observed for the adolescent data based on ANOVA results. All p-values where >0.05 except for the dose-normalized Cmax in the PK population which had a p-value of 0.0489. In the power model, the dose proportionality was also established as the 95% CIs of the slopes included 1 for Cmax and AUC and the 95% CIs of the slopes included 0 for CL/F for both the PK population and PK evaluable population. Comparison of adolescent PK with adult PK showed no significant difference based on ANOVA test, but slightly higher systemic exposure and lower apparent clearance in adolescent subjects based on geometric mean ratios (GMRs) presented below.


OPC-34712
PROTOCOL 331-10-233
PK FIG 1.1.1
Scatterplot With Regression Line for AUCTAU- PK Evaluable Population Steady State
log_PK = 6.701 + 0.798 log_dose + e Slope 95% CI: (0.454, 1.141)
log_PK
log_dose
95% Confidence Limits
95% Prediction Limits
Regression


OPC-34712
PROTOCOL 331-10-233
PK FIG 1.1.2
Scatterplot - With Regression Line for CMAX,SS - PK Evaluable Population Steady State
log_PK = 3.863 + 0.807 log_dose + e Slope 95% CI: (0.482, 1.132)
log_PK
log_dose
95% Confidence Limits
95% Prediction Limits
Regression



According to the MAH, as dose proportionality was demonstrated in both adults (Trial 331-08-205, dose 1 - 4 mg) and adolescents (Trial 331-10-233, dose 1 mg-4 mg) separately, dose groups 1 to 4 mg from both trials were compared between the adult and adolescent populations.
Results from ANOVA test suggest no significant difference between adult and adolescent PK (all p-values are > 0.05). Geometric means ratios and 90% CIs for adolescent versus adult PK parameters are presented in the table below:

Table 11.5.2.5-1 Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole PK Parameters Following Administration of 1 to 4 mg Brexpiprazole in Adolescent With Schizophrenia or Other Related Psychiatric Disorders Versus Adults With Schizophrenia or Schizoaffective Disorder

Population	PK Parameter	n in Trial 331-08-205	n in Trial 331-10-233	GMR	90% CI
PK Evaluable Population[a]	AUC_τ/Dose ([h·ng/mL]/mg)	17	21	1.09	0.797 - 1.50
	$C_{max,ss}$/Dose ([ng/mL]/mg)	18	22	1.29	0.952 - 1.73
	CL/F (mL/h)	17	21	0.914	0.666 - 1.25
PK Population[a]	AUC_{0-24h}/Dose ([h·ng/mL]/mg)	23	28	0.948	0.720 - 1.25
	C_{max}/Dose ([ng/mL]/mg)	24	29	1.09	0.844 - 1.42

GMR = geometric means ratio.
[a]The PK evaluable population included subjects with at least 1 PK parameter and that reached steady-state; the PK population included subjects with at least 1 PK parameter.

In the PK evaluable populations, systemic exposure seems slightly higher (based on AUC_τ, GMR: 1.09, 90% CI: 0.797 - 1.50, and Cmax,ss, GMR: 1.29, 90% CI: 0.952 - 1.73) and apparent clearance seems slightly lower (GMR: 0.914, 90% CI: 0.666 - 1.25) in adolescent subjects compared with adult subjects. High variability due to limited number of PK evaluable subjects was observed which limits a robust estimation of differences between adolescent and adult subjects.

Study 331-10-234 PK results

This was a multicenter, randomized, double-blind, placebo- and active controlled trial designed to assess the efficacy and safety of brexpiprazole compared to placebo in adolescent subjects, ages 13 to 17 years.

Subjects were randomized 1:1:1 to 1 of 3 double-blind treatment arms in the 6-week treatment double-blind period. The brexpiprazole dose chosen for this study was: 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.

Brexpiprazole has been well tolerated at multiple oral doses up to 12 mg/day in adult subjects with schizophrenia or schizoaffective disorders. A dose range of 0.25 to 6 mg/day was investigated in a phase 2 trial in adults with schizophrenia. Based on results of pivotal safety and efficacy in adult patients with schizophrenia, a dose range of 2 to 4 mg is shown to be efficacious. A PK, safety, and tolerability trial in adolescent (13–17 years old) were assessed in Trial 331-10-233 in which brexpiprazole at doses of 0.5 mg/day, 1 mg/day, 2 mg/day, 3 mg/day, and 4 mg/day.

Based on the safety and PK data in Trial 331-10-233, no dose adjustment is deemed necessary in children and adolescents and thus a similar efficacious dose range of 2 to 4 mg is proposed for this trial.

In study 331-10-234, during the 6-week double-blind treatment phase, PK samples were collected on Day 1 (baseline) and at Week 4 (± 2 days) and Week 6 (± 2 days), and analysed from 101, 94, and 94 subjects, respectively. Samples collected at Week 4 and Week 6 were expected to have measurable brexpiprazole concentrations consistent with taking multiple doses of brexpiprazole (> 10 ng/mL).

For subjects randomized to placebo, PK samples were collected at Week 4 and analysed from 81 subjects. Overall, 2 subjects had measurable brexpiprazole plasma concentration levels at Week 4; however, both reported results were < 10 ng/mL.

No statistical analysis was planned or performed for PK data.

For Study 331-10-236 pharmacokinetics/pharmacodynamics/pharmacogenomic were not assessed.

2.3.3. Pharmacodynamics

Mechanism of action

Brexpiprazole is an atypical antipsychotic agent. The pharmacology of brexpiprazole is believed to be mediated by a modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5 HT1A and at dopaminergic D2 receptors with antagonist activity at serotonergic 5 HT2A receptors, with similar high affinities at all of these receptors (Ki: 0.1 nM to 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic α1B/2C receptors with affinity in the same sub nanomolar Ki range (Ki: 0.2 nM to 0.6 nM).

2.3.4. PK/PD modelling

Report 331-24-201

The aims of the population PK (PopPK) and exposure-response (E-R) - as measured by Positive and Negative Syndrome [PANSS] Total Score - analyses were to: 1) perform external validation of the adult PopPK and E-R models on data collected from adolescents with schizophrenia; and 2) conduct model simulation to compare brexpiprazole exposure and the E-R between adolescents and adults with schizophrenia. These analyses were divided into 4 steps:

Step 1) The adult PopPK model (331-12-208) was developed using PK data from 12 clinical trials, including 154 (6.5%) healthy subjects, 1033 (43.8%) subjects with major depressive disorder (MDD),

and 1170 (49.6%) subjects with schizophrenia. Age ranged from 18 to 81 years (median 42.0 years), about half (49.9%) were males; body weight (BW) ranged from 31.7 to 170.6 kg (78.2 kg). The cytochrome P450 (CYP) 2D6 metabolism status of the study population was 38.7% extensive metabolizers (EM), 24.0% intermediate metabolizers (IR), 3.0% poor metabolizers (PM), 1.4% ultra-rapid metabolizers (UM), and 33.0% unknown status. The structural model was a 2-compartment model with 1st-order absorption and elimination. The model included inter-individual variability on CL/F, V_c/F and k_a. The following covariate effects were also included in the model: a) the effects of age, sex, and BW on V_c/F and the effect of sex on CL/F; b) the effect of CYP2D6 metabolism status (PM, IM, and UM relative to EM) on CL/F, and c) the effects of adjunctive co-administration of strong CYP2D6 inhibitors (i.e., fluoxetine, paroxetine) and non-protocol mandated strong CYP2D6/3A4 inhibitors on CL/F.
The external validation of the adult PopPK model included 749 brexpiprazole concentrations from 144 adolescents (331-10-233 and 331-10-234). Summary statistics for continuous, categorial covariates and other baseline characteristics of subjects in the adolescent population PK dataset are presented in Table 4.1.1.2-1 and in Table 4.1.1.2-2.

Table 4.1.1.2-1 Summary Statistics for Continuous Covariates and Baseline Characteristics of Adolescents Included in the Brexpiprazole Population PK External Validation

Covariate	Mean (SD)	Median	Minimum	Maximum
Age (years)[a]	15.1 (1.48)	15.0	13.0	17.0
Body Weight (kg)[a]	65.8 (16.8)	62.0	30.0	115
BMI (kg/m^2)	23.7 (5.45)	22.5	15.3	46.6
GFR (mL/min/1.73 m^2)	130 (13.5)	133	83.2	158
ALT (IU/L)	18.8 (16.5)	14.0	6.00	121

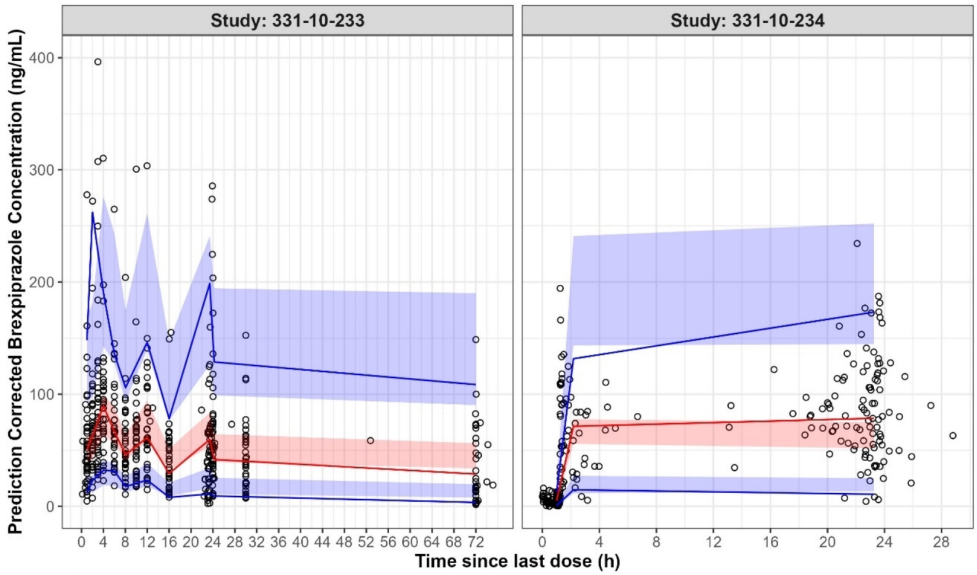
[a]Covariates retained in the adult population PK model and used in external validation.
Note: BMI = body mass index, GFR = glomerular filtration rate, ALT = alanine aminotransferase

Table 4.1.1.2-2 Summary Statistics for Categorical Covariates and Baseline Characteristics of Adolescents Included in the Brexpiprazole Population PK External Validation

Covariate	Category	Number of Subjects (% Total) [Total n = 144]
Sex[a]	Male	68 (47.2%)
	Female	76 (52.8%)
Race	White	81 (56.2%)
	Black	31 (21.5%)
	Asian	1 (0.7%)
	Other	31 (21.5%)
CYP2D6 metabolism status[a]	Normal	62 (43.1%)
	Poor	3 (2.1%)
	Intermediate	33 (22.9%)
	Ultra-rapid	1 (0.7%)
	Unknown	45 (31.2%)

[a]Covariates retained in the previous population PK model and used in external validation.

A Bayesian fit of the adult PopPK model to brexpiprazole concentrations collected from adolescents were performed. The adult PopPK model, with BW as a covariate on Vc/F but not CL/F, was sufficient to describe and predict brexpiprazole PK in adolescents as (see the Figure 4.1.3-2).



Circle represents observed data.
Red line represents the observed median.
Blue lines represent the 5th and 95th percentile of boserved data.
Shaded region represents the 90% CI of predicted percentiles.

One observation with prediction corrected concentration >400 ng/mL is not shown.
One observation with time since last dose at 69 h in Study 331-10-234 is not shown.

Figure 4.1.3-2 Prediction-Corrected Visual Predictive Check for External Validation of the Adult Population Pharmacokinetic Model with Adolescent Brexpiprazole Concentrations from Trials 331-10-233 and 331-10-234

Step 2) The adult E-R analysis (331-12-208) was performed using data from one phase 2 (331-07-203) and two phase 3 trials (331-10-230 and 331-10-231) in subjects with schizophrenia. A placebo model was developed with data from subjects in the placebo arm; then, the effect of brexpiprazole on PANSS Total Score response in subjects treated with brexpiprazole were modelled by fixing the placebo effect. A linear function was used to describe the placebo effect (Eq. 1), while an E_{max}-model with a time-delay function (i.e., with onset parameter Dk_{on}) was deemed adequate in describing the effect of brexpiprazole exposure on PANSS Total Score (Eq. 2).

$$PLC(t) = slope \times t \quad \text{(Eq. 1)}$$

$$Drug(t) = [E_{max} \times C_{trough} / (EC_{50} + C_{trough})] \times [1 - \exp(-Dk_{on} \times t)] \quad \text{(Eq. 2)}$$

Where $PLC(t)$ represents the improvement in PANSS Total Score overtime by placebo, *slope* is the rate of placebo effect, $Drug(t)$ represents the improvement in PANSS Total Score overtime by brexpiprazole, E_{max} is the maximum brexpiprazole effect on PANSS Total Score, C_{trough} is the trough concentration at each time of PANSS Total Score assessment, EC_{50} is the C_{trough} needed to achieve half of E_{max}, and Dk_{on} is the brexpiprazole effect onset rate constant. The overall equations describing PANSS Total Score in placebo arm and brexpiprazole arm are shown below in Eq. 3 and 4, respectively:

$$\text{PANSS total score(t)} = Base - PLC(t) \quad \text{(Eq. 3)}$$

$$\text{PANSS total score(t)} = Base - PLC(t) - Drug(t) \quad \text{(Eq. 4)}$$

Where *Base* is modelled baseline PANSS Total Score.
None of tested covariates (age, sex, BW and observed baseline PANSS Total Score on the *slope* parameter in the placebo model, and on E_{max} of the brexpiprazole E-R model) was statistically significant and retained in the final exposure-PANSS response model.

The final external validation of the adult E-R model included a total of 1392 PANSS Total Score from 207 adolescents from (331-10-234). Only subjects treated with either brexpiprazole (n=104) or placebo (n=103) were included in the analysis and subjects must have the baseline and at least 1 post-baseline PANSS Total Score to be included in this analysis (see Table 4.2.1.1-1).

Table 4.2.1.1-1 Breakdown of Exposure-Efficacy Data by Treatment Arm

Arm	Number of Subjects	Number of PANSS Total Score
Placebo	103	684
Brexpiprazole	104	708
Total	207	1392

Summary statistics of potential covariates of interest in the E-R analysis are shown in Table 4.2.1.2-1.

Table 4.2.1.2-1 Summary Statistics of Potential Covariates of Interest in Exposure-Efficacy Analysis

Continuous Covariate					
Covariate	**Treatment**	**Mean (SD)**	**Median**	**Minimum**	**Maximum**
Age (years)	Placebo	15.3 (1.44)	15.0	13	18[a]
	Brexpiprazole	15.3 (1.51)	15.5	13	17
Body Weight (kg)	Placebo	68.2 (17.7)	66.2	39.1	119
	Brexpiprazole	64.1 (16.4)	60.7	30.0	113
Baseline PANSS Total Score	Placebo	102 (16)	97	81	152
	Brexpiprazole	101 (15)	98	80	150

Categorical Covariate			
Covariate	**Covariate Category**	**Covariate n (%)**	
		Placebo	**Brexpiprazole**
Sex	Male	53 (51.5%)	48 (46.2%)
	Female	50 (48.5%)	56 (53.8%)
Race	Caucasian	67 (65.0%)	65 (62.5%)
	Black	6 (5.8%)	7 (6.7%)
	Asian	0 (0.0%)	1 (1.0%)
	Other	30 (29.1%)	31 (29.8%)

[a]One subject was 18 years old, all other subjects are ≤ 17 years old.

Bayesian fit of the adult placebo model was performed in adolescents in the placebo group. There was slight, but constant underprediction of the population prediction in the diagnostic plot. However, such underprediction was not present when baseline PANSS Total Score and slope were estimated for the adolescent data; model predicted baseline PANSS in the adolescent data from the placebo arm in Trial 331-12-234 was slightly higher than that in the adult placebo model (100 *vs* 94), while model predicted slope in adolescents was close to that in the adult placebo model (2.93/week vs 3.16/week), as shown in the Table 4.2.3.1-1.

Table 4.2.3.1-1 Parameter Estimation of the Final Placebo-Efficacy Model in Adolescents with Schizophrenia

Parameter	Parameter Description (Units)	Estimate (%RSE)	Shrinkage
Base	Baseline PANSS Total Score	100 (2%)	-
Slope	Placebo Effect Rate (1/week)	2.93 (8%)	-
IIV_Base	Inter-individual Variability in Baseline PANSS Total Score (CV%)	17.2% (16%)	2%
σ_add	Additive Residual Error (SD)	7 (11%)	5%

Note: RSE = relative standard error, CV = coefficient of variation, SD = standard deviation.

According to the MAH, the diagnostic plots of the placebo model with estimated baseline and slope (Figure 9-3) showed close agreement between observed and population predicted, as well as individual predicted PANSS Total Score; the conditional weighted residual errors were evenly distributed along the horizontal line of zero; suggesting adequate model fitting.

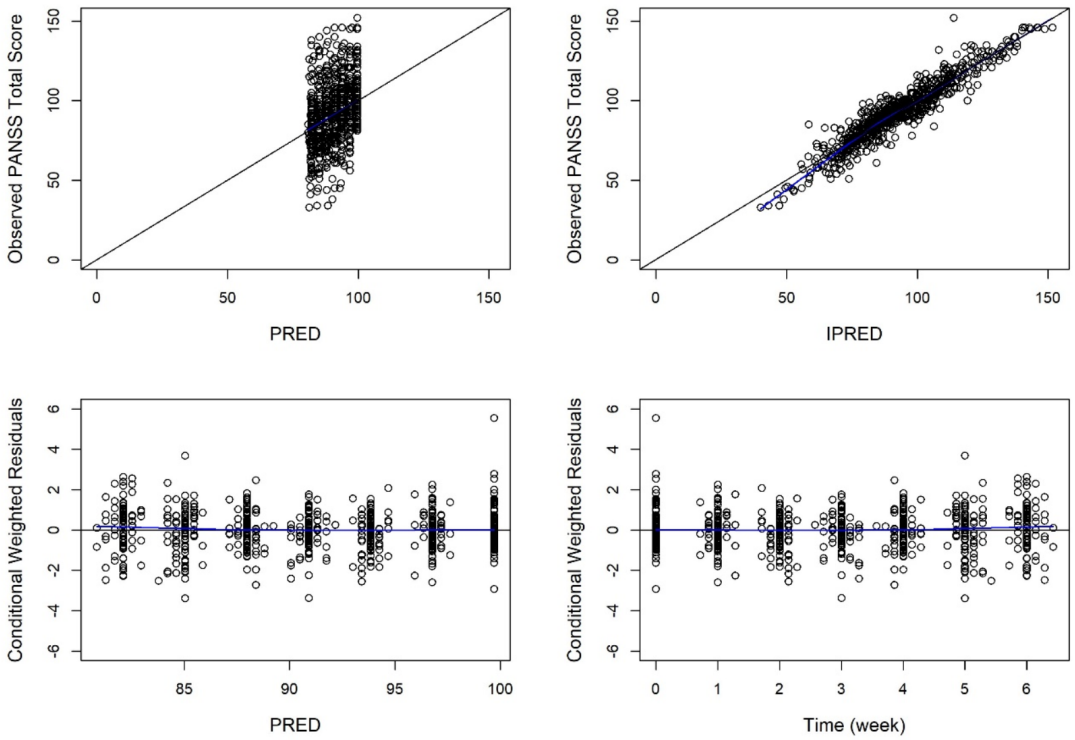
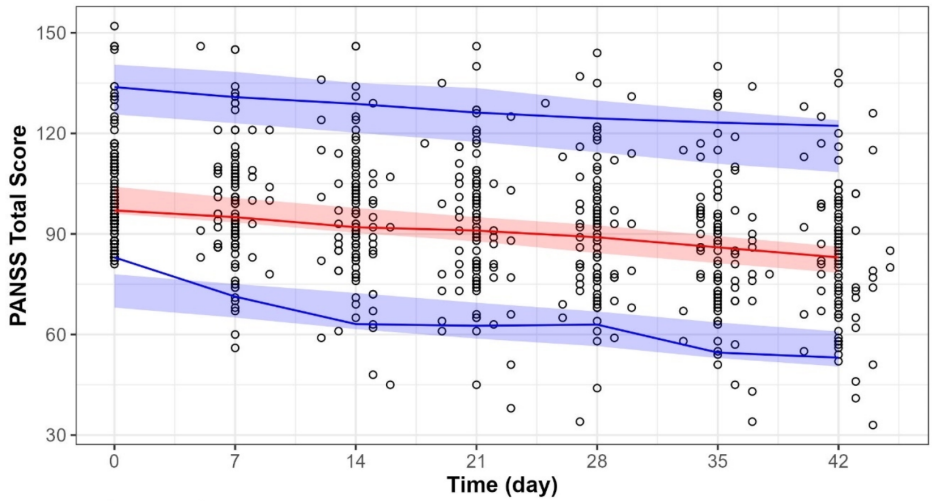


Figure 9-3 Diagnostic Plots of the Final Placebo-Effect Model for Adolescent

Note: Circle represents observed data; the black line is the line of unity (upper panels) and a horizontal line with intercept at zero (lower panels); and the blue line represents the trend line; PRED = population prediction, and IPRED = individual prediction.

According to the MAH, the relationship between brexpiprazole exposure and the efficacy response, as measured by PANSS Total Score, in adolescents with schizophrenia was adequately described by the E-R model for adults as suggested by VPC plot presented in Figure 9-4.



Circle represents observed data.
Red line represents the observed median.
Blue lines represent the 5th and 95th percentile of boserved data.
Shaded region represents the 90% CI of predicted percentiles.

Figure 9-4 **Visual Predictive Check of the Final Placebo-Effect Model for Adolescents**

External validation of the adult drug effect model was performed with adolescent data in the brexpiprazole treatment arm of Trial 331-10-234. All parameters relevant to the drug effect were fixed to the estimated values of the final adult E-R model. Slope for placebo effect was fixed to the value estimated for adolescents (2.93/week). Similar to the external validation of the placebo effect model, typical value of the baseline PANSS Total Score was estimated for adolescents because similar underprediction in population prediction was observed when the typical value of the baseline PANSS Total Score was fixed to the estimation from the adult exposure-efficacy model (95.8). Parameter estimation of the updated exposure efficacy model for adolescents is presented in Table 4.2.3.2-1.

Table 4.2.3.2-1 **Parameter Estimation of the Final Exposure-Efficacy Model in Adolescents with Schizophrenia**

Parameter	Parameter Description (Units)	Estimate (%RSE)	Shrinkage
Base	Baseline PANSS Total Score	101 (1.3%)	-
Slope	Placebo Effect Rate (1/week)	2.93 Fixed	-
DKon	Brexpiprazole Effect Onset Rate Constant (1/week)	0.336 Fixed	-
Emax	Maximum Drug Effect	4.37 Fixed	-
EC50	Brexpiprazole Concentration to achieve 50% of maximum effect (ng/mL)	10.1 Fixed	-
IIV_Base	Inter-individual Variability in Baseline PANSS Total Score (CV%)	17.2% Fixed	4%
IIV_Emax	Inter-individual Variability in Emax (CV%)	145% Fixed	25%
σ_add	Additive Residual Error (SD)	7 Fixed	13%

Note: RSE = relative standard error, CV = coefficient of variation, SD = standard deviation.

Diagnostic plots of the final E-R model in adolescents with schizophrenia is presented in Figure 4.2.3.2-1 below.

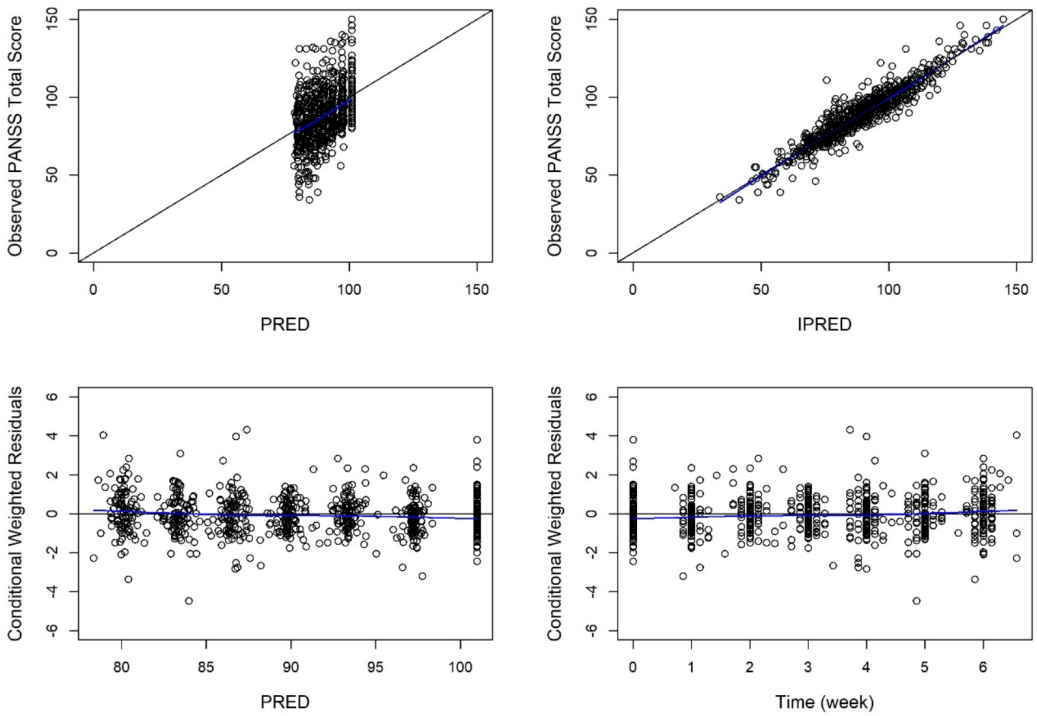
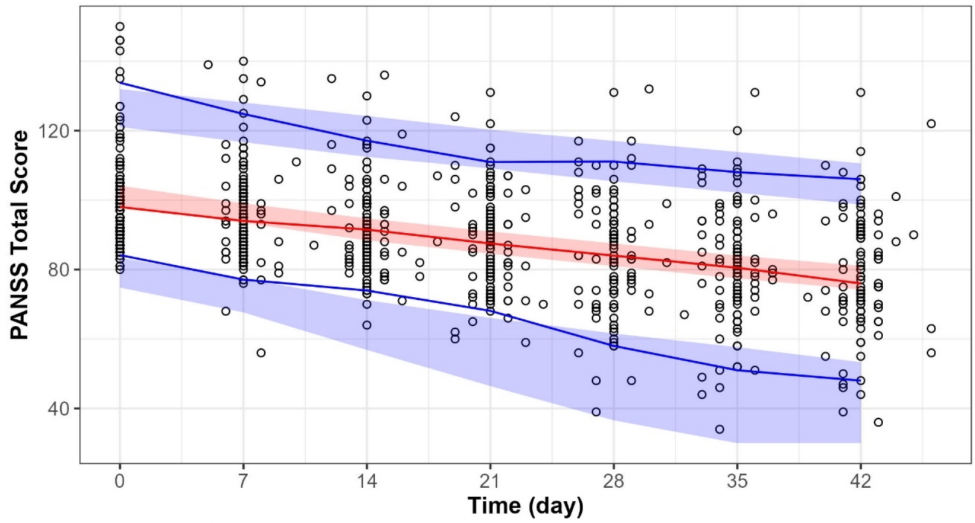


Figure 4.2.3.2-1 Diagnostic Plots of the Final Exposure-Efficacy Model for Adolescent

Note: Circle represents observed data in adolescents; the black line is the line of unity (upper panels) and a horizontal line with intercept at zero (lower panels); and the blue line represents the trend line; PRED = population prediction, and IPRED = individual prediction.

According to the MAH, there was close agreement the observed and the population predicted, as well as individual predicted PANSS Total Scores; and the CWRES are evenly distributed along the horizontal line of zero, suggesting an adequate fit overall. VPC plot presented in Figure 4.2.3.2-2 also demonstrated that the E-R model with slope and baseline PANSS Total Score estimated for adolescents were able to predict the PANSS Total Score well in adolescents with schizophrenia.



Circle represents observed data.
Red line represents the observed median.
Blue lines represent the 5th and 95th percentile of boserved data.
Shaded region represents the 90% CI of predicted percentiles.

Figure 4.2.3.2-2 Visual Predictive Check of the Final Exposure-Efficacy Model for Adolescents

Step 3) Population simulation was conducted using the PopPK model to compare brexpiprazole exposures between adolescents and adults following the same brexpiprazole daily dose. A total of 1000 virtual subjects for each of the adolescent and adult groups were generated by resampling individuals with covariate information (i.e., age, sex and BW) in the adolescent and adult phase 3 trials, respectively. All subjects were assigned extensive metabolism (EM) status of CYP2D6, without influence of concomitant medication that were moderate or strong CYP2D6 or CYP3A4 inhibitors. Exposure parameters, including $C_{trough,ss}$, $C_{max,ss}$, $AUC_{tau,ss}$, and $C_{avg,ss}$, were derived from the simulated individual PK profiles using non-compartmental analysis (NCA), and compared between adolescents and adults. Observed and simulated change from baseline (CFB) in PANSS Total Score at Week 6 were compared between adolescents and adults. Boxplots of simulated $C_{trough,ss}$, $C_{max,ss}$, $AUC_{tau,ss}$, and $C_{avg,ss}$ in adolescents and adults following a daily dose of 2 mg brexpiprazole are presented in Figure below.

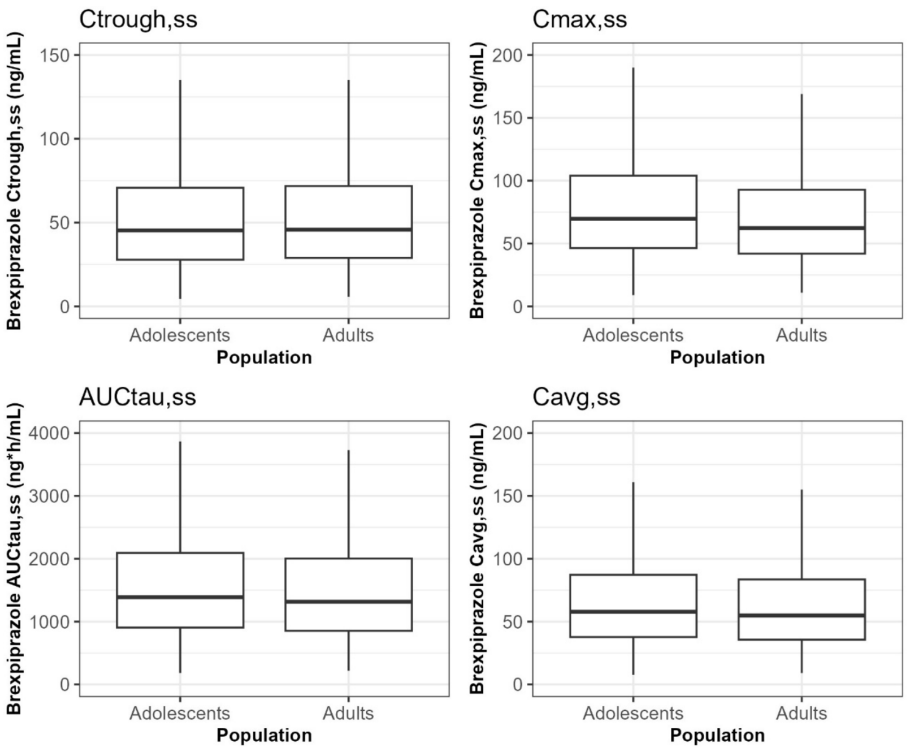


Figure 4.3-1 **Simulated Brexpiprazole Exposure in Adolescents and Adults with Schizophrenia following Administration of Brexpiprazole 2 mg/day**

Results suggest that, following the same daily dose of brexpiprazole, simulated brexpiprazole exposures were overall comparable between adolescents and adults with schizophrenia; although the median $C_{max,ss}$ was slightly higher in adolescents, the overall distribution was comparable to that of adults. A similar figure was generated by stratifying the adolescents into two groups: <15 years old, and ≥15 years old.

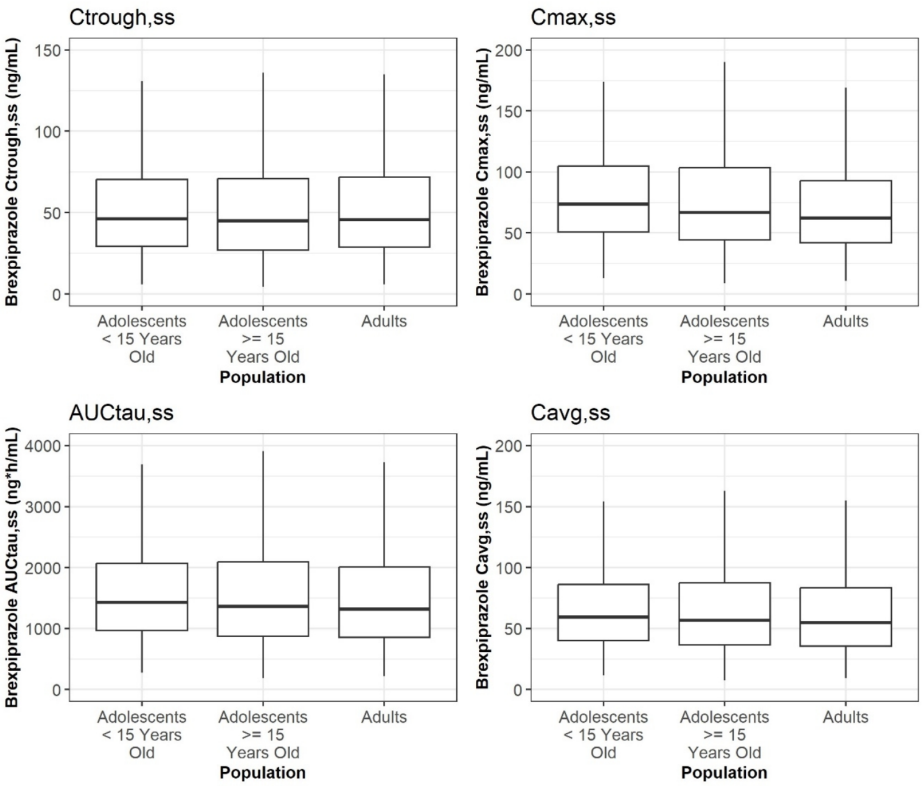


Figure 9-5 **Brexpiprazole Exposure in Adolescents (< 15 Years Old, and ≥ 15 Years Old) and Adults with Schizophrenia following Administration of Brexpiprazole 2 mg/day**

According to the MAH, the differences in simulated brexpiprazole exposures between these two adolescent groups were negligible; and the brexpiprazole exposures of the two adolescent groups were comparable to those of the adult group.

Step 4) Observed and simulated change from baseline (CFB) in PANSS Total Score at Week 6 were compared between adolescents and adults. The mean and 95% confidence intervals (CIs) of the observed and model predicted CFB in PANSS Total Score at Week 6 in adolescents and adults are presented in the Figure 4.4-1.

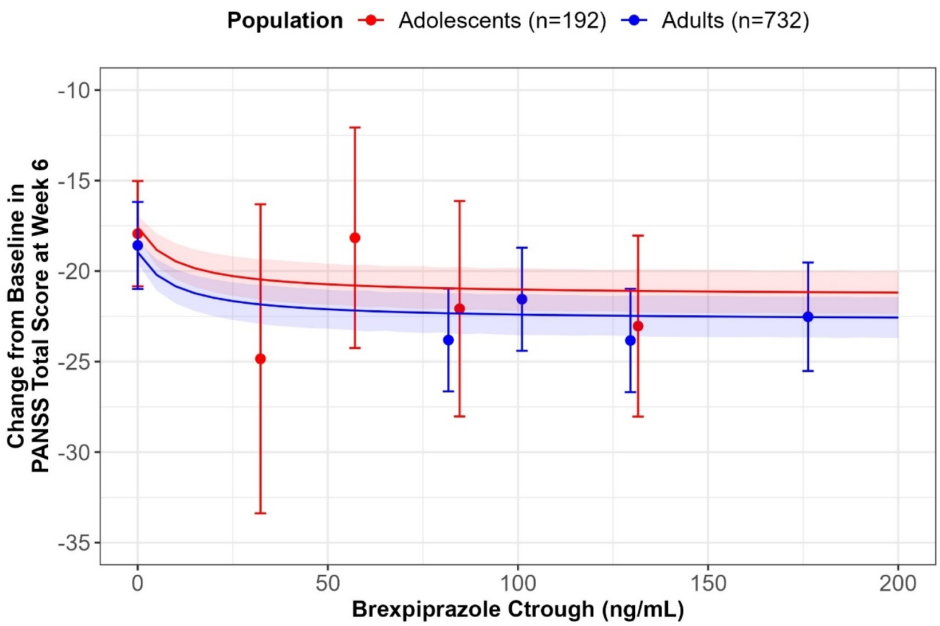


Figure 4.4-1 **Observed and Model Predicted Mean and 95% Confidence Intervals of Change from Baseline in PANSS Total Score at Week 6 versus Predicted Brexpiprazole C_{trough} in Adolescents and Adults with Schizophrenia in Phase 3 Trials**

Note: C_{trough} = trough concentration at time of efficacy assessment.
Points and error bars represent mean and 95% confidence intervals of the observed change from baseline in PANSS Total Score at Week 6 by placebo treatment group and brexpiprazole C_{trough} quartiles. The solid line and shaded region represent mean and 95% confidence intervals of the model predicted change from baseline in PANSS Total Score at Week 6.

For the observed data, CFB in PANSS Total Score was summarized by placebo group (C_{trough} = 0 ng/mL) and C_{trough} quartiles in the brexpiprazole treatment group. As stated by the MAH, while distributions of C_{trough} were different between adolescents and adults because of the variation in brexpiprazole dose received, the overall E-R relationship was comparable between adolescents and adults based on observed data; and such relationship was adequately predicted by the exposure-efficacy model. The slight difference in model predicted CFB in PANSS Total Scores between adolescents and adults was due to the slight difference in placebo effect parameters. A similar plot with adolescents stratified by age groups (< 15 years old and ≥ 15 years old) were also generated.

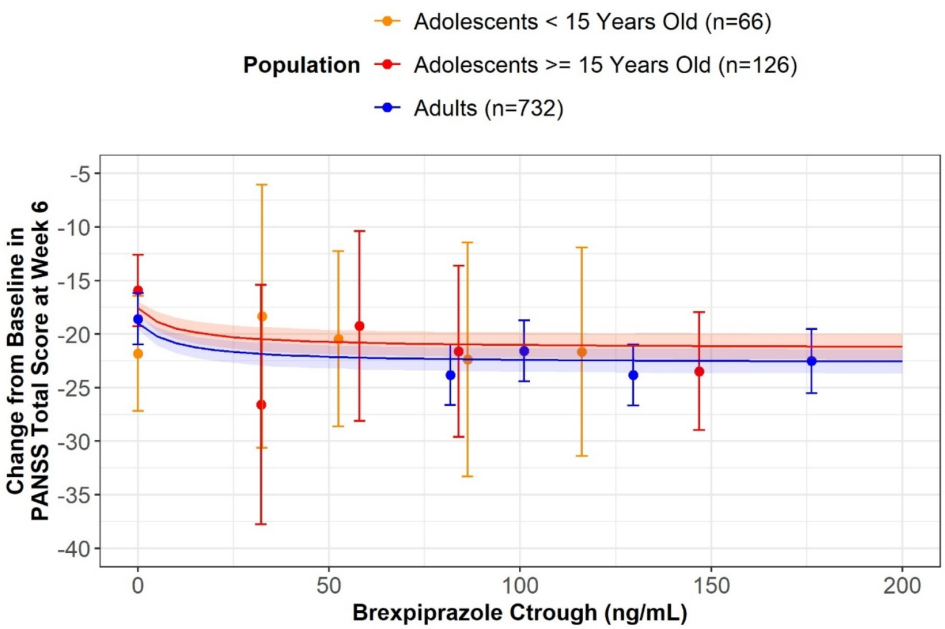


Figure 9-6 **Observed and Model Predicted Mean and 95% Confidence Interval of Change from Baseline in PANSS Total Score at Week 6 Overlaid with Predicted Brexpiprazole C_{trough} in Adolescents < 15 Years Old, Adolescents ≥ 15 Years Old, and Adults with Schizophrenia in Phase 3 Trials**

Note: C_{trough} = trough concentration at time of efficacy assessment.
Points and error bars represent mean and 95% confidence intervals of the observed change from baseline in PANSS Total Score at Week 6 by placebo treatment group and brexpiprazole C_{trough} quartiles. The solid line and shaded region represent mean and 95% confidence intervals of the model predicted change from baseline in PANSS Total Score at Week 6.

The overall E-R relationships were consistent among adolescents < 15 years old, adolescents ≥ 15 years old, and the adult group.

One additional figure comparing simulated brexpiprazole effect on PANSS Total Score (on top of placebo effect) between adolescents and adults are presented in Figure 9-7. As parameters that are relevant to the drug effect in the exposure-efficacy model for adolescents were fixed to the estimates of the final adult exposure-efficacy model, the simulated mean drug effect, as well as derived EC_{50} (10.1 ng/mL), EC_{80} (40.4 ng/mL), and EC_{90} (90.9 ng/mL) in adolescents are the same as those in adults.

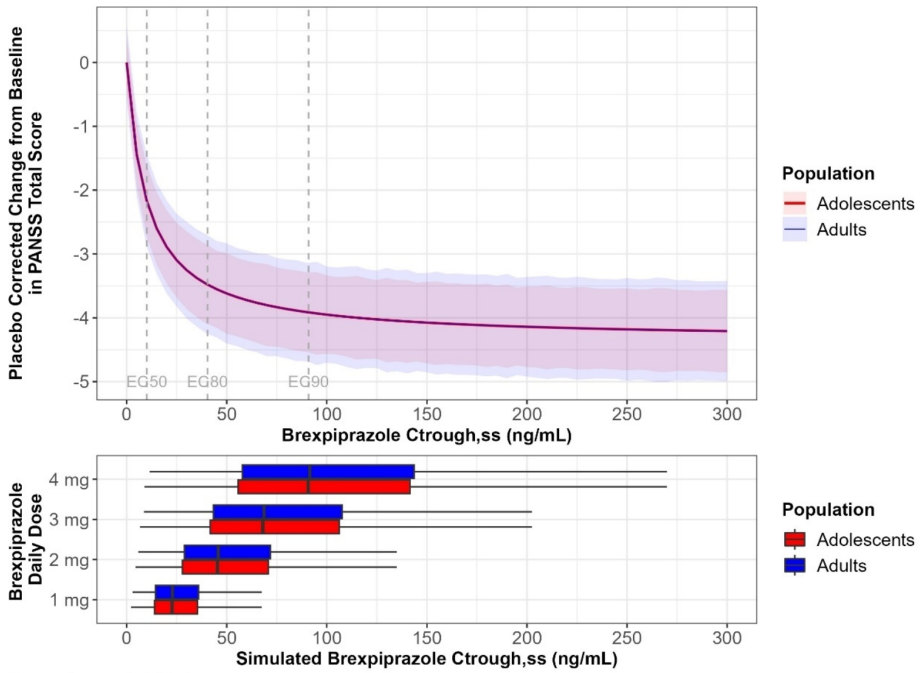


Figure 9-7 **Predicted Mean and 95% Confidence Interval of the Effect of Brexpiprazole Exposure (on Top of the Placebo Effect) on Change from Baseline in PANSS Total Score Overlaid with Simulated Brexpiprazole Exposures in Adolescents and Adults with Schizophrenia**

Note: EC50 = brexpiprazole concentration to achieve 50% of maximum drug effect, EC80 = brexpiprazole concentration to achieve 80% of maximum drug effect, EC90 = brexpiprazole concentration to achieve 90% of maximum drug effect.

2.3.5. Discussion on clinical pharmacology

Brexpiprazole PK in adolescents (aged 13 to 17 years) has been evaluated in a clinical pharmacology trial 331-10-233 (Phase 1). PK samples were also collected from Study 331-10-234, designed to assess the efficacy and safety of brexpiprazole compared to placebo in adolescent subjects, ages 13 to 17 years (Phase 2).

Samples from studies 331-10-233 and 331-10-234 were analysed according to the same validated method 6825-271. This method was submitted within the initial MAA as final version 5 dated 2014 and the validated LTS for OPC-34712 (brexpiprazole) and DM-3411 was 632 days at -60 to -80ºC. The Addendum 6 of the validation report 6825-271 provides final results of the matrix frozen stability evaluation for OPC-34712 (brexpiprazole) and its metabolite DM-3411, at -60 to -80 °C for 1124 day. Samples from study 331-10-233 and study 331-10-234 were stored within the validated LTS.

Study 331-10-233 was conducted to evaluate the PK in adolescent patients. The protocol, methodology and results of the study are clearly described. Based on data provided, PK results for 3 mg seems to be not perfectly in line with the proportional model, however due to the limited sample size and variability, no clear conclusion can be drawn. To note, linearity in adults was demonstrated after a single dose (from 0.2 mg to 8 mg) and multiple dose (from 0.5 mg to 4 mg; once daily administration), as reported in the approved SmPC. The dose range (0.5 mg to 4 mg) selected for the study 331-10-233 was considered adequate to study the PK profile of the proposed posology.

However, also in the light of the main purpose of the procedure, it was asked to the MAH to better clarify to what extent the observed exposure in adolescent volunteers overlaps with that in adults. In this

regard, the MAH has provided the requested data: 1) the percentage overlap of the distribution of the exposure parameters obtained for adolescent and adult subjects; 2) a comparison of observed PK profile of adults vs adolescents observed, e.g. concentration-versus-time plot. The requested analysis has been presented also for age range, i.e. <15 and ≥ 15 yrs vs adult data.

There was 90.5% overlap in dose normalized AUC_T, 88.3% overlap in dose normalized $C_{trough,ss}$ and 83.1% overlap in dose normalized $C_{max,ss}$ between adolescents and adults (331-08-205).
Therefore, submitted data shows that for all the exposure parameters a large (≥80%) overlap in the distributions exists when comparing adolescent and adult values.
In addition, comparing adults to adolescents concentration-time profiles, a wide overlap has been reported. However, some adolescent patients could reach higher brexpiprazole plasma concentrations than adults. Moreover, analysing data by age groups, <15-year-old and ≥15-year-old vs adults, it could be noted that adolescent ≥15 years could reach higher brexpiprazole plasma concentration than subjects in the other age groups. Overall, these results show that brexpiprazole plasma concentrations are usually comparable between adults and adolescents. However, in some adolescents, particularly those aged >15 years, unexpectedly high concentrations were measured compared with other age groups. To investigate the impact of body weight, significant covariate impacting exposure (Report 331-24-201) a linear regression on weight normalized exposures (AUC_T, $C_{trough,ss}$, $C_{max,ss}$) in adolescents was submitted and results can be considered in line with ANOVA results submitted in the initial MA dossier.
The MAH provided a supportive extrapolation study 331-201-00185 aiming to assess the maintenance of efficacy in adolescent patients with schizophrenia based on the efficacy data from trials conducted in both adolescent and adult patients. The main assumptions of this extrapolation exercise was the similarity in exposure and E-R relationship in adults and adolescents, supported from the present analysis (Report 331-24-201). In particular, to ascertain whether drug exposure and the E-R relationships were similar between adolescents and adults, external validations of the adult popPK model and E-R model in Report 331-12-208 were performed on PK and efficacy data collected from adolescents (data from Trials 331-10-233 and 331-10-234 for PK external validation, data from Trial 331-10-234 for E-R validation).

Simulations were conducted to compare brexpiprazole drug exposure between adolescents and adults following the same brexpiprazole daily dose and E-R relationships were also compared between adolescent and adult subjects with schizophrenia. These analyses were carried out using an appropriate methodological approach and results are clearly described. Overall, there are no significant critical elements in this analysis.
For the simulation, 1000 virtual subjects for each of the adolescent and adult groups were generated by resampling individuals with covariate information (i.e., age, sex, and body weight) in the adolescent and adult phase 3 trials. The distribution between the phase 3 and simulated populations are comparable.

In general, simulated brexpiprazole exposure were comparable between adolescents and adults, although the median Cmax,ss was slightly higher in adolescents. In line, results were observed in the subgroup analysis in adolescents <15 years old and ≥15 years old.

The E-R relationship in adolescents and adults at Week 6 results were comparable, with a slight difference in model-predicted CFB in PANSS Total scores due to the difference in placebo effect that was higher in adolescents. A subgroup analysis (<15 years and ≥15 years) was also submitted showing similar E-R relationship observed in the general adolescent population.
In figure (4.4-1) comparing observed and simulated CFB in PANSS Total Score at Week 6 in adolescents and adults vs predicted brexpiprazole Ctrough. Some data points representing the mean observed change in CFB PANSS are outside the model prediction 95%CI for the lower concentrations. This Figure looks better when subpopulations (<15 years and ≥15 years) are considered, even if the very low concentrations are still out of model prediction 95%CI. This could be due to both the low number of

observations and the high variability in the data points. Given the above, the predicted PK/PD relationship could catch the central tendency of observed data, supporting the analysis. However, the analysis of real clinical data remains pivotal.
Results of the E-R models in adolescents and adults with schizophrenia (331-24-201) only compare observed and model-predicted mean of change from baseline in PANSS Total Score versus Predicted Brexpiprazole Ctrough in Adolescents and Adults with Schizophrenia in Phase 3 Trials at Week 6, hence a comparison of short-term scenario for which data from clinical trial were available.
All the above considered, the present PK/PD analysis could be considered with just a supportive role for the present variation; thus, the analysis of real clinical data remains pivotal.

2.3.6. Conclusions on clinical pharmacology

Brexpiprazole PK in adolescents (aged 13 to 17 years) has been characterised. The MAH provided a supportive extrapolation study 331-201-00185 including analysis of similarity in exposure and E-R relationship in adults and adolescents to support maintenance effect. However, in light of the limitation identified, it has been considered only as a supportive PK/PD analysis.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

A phase 1 study 331-10-233 has been conducted in paediatric population (13-17 years old), in which doses from 0.5 mg to a maximum of 4 mg with 0.5 mg increments has been administered. This is in line with the dose range approved in adults. In the two phase 3 studies in adolescents a similar posology to that in adults, except for the starting dose of 0.5 mg instead of the approved initial dose of 1 mg of adults, has been used. The comparison of exposure between adolescents and adults has been carried out in the extrapolation study 331-201-00185.

2.4.2. Main study(ies)

The brexpiprazole pediatric schizophrenia clinical development program for efficacy includes two phase 3 clinical trials (1 completed short-term controlled trial and 1 ongoing long-term, open-label trial) and 1 completed paediatric extrapolation study:

- Trial 331-10-234: a multicenter, randomized, double-blind, placebo and active-controlled trial designed to evaluate the short-term efficacy of brexpiprazole monotherapy for the treatment in adolescents with schizophrenia. Subjects were randomized to 1 of 3 treatment groups: brexpiprazole 2 to 4 mg/day, aripiprazole 10 to 20 mg/day, or placebo.

- Trial 331-10-236: an ongoing long-term (24-month), multicenter, open-label trial designed to evaluate the safety, tolerability, and efficacy of flexible dose brexpiprazole 1 to 4 mg/day as maintenance treatment in adolescents with schizophrenia.

- Study 331-201-00185: designed to assess the maintenance of efficacy in adolescent subjects with schizophrenia by extrapolation of data from trials conducted in both adolescent and adult subjects with schizophrenia.

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.

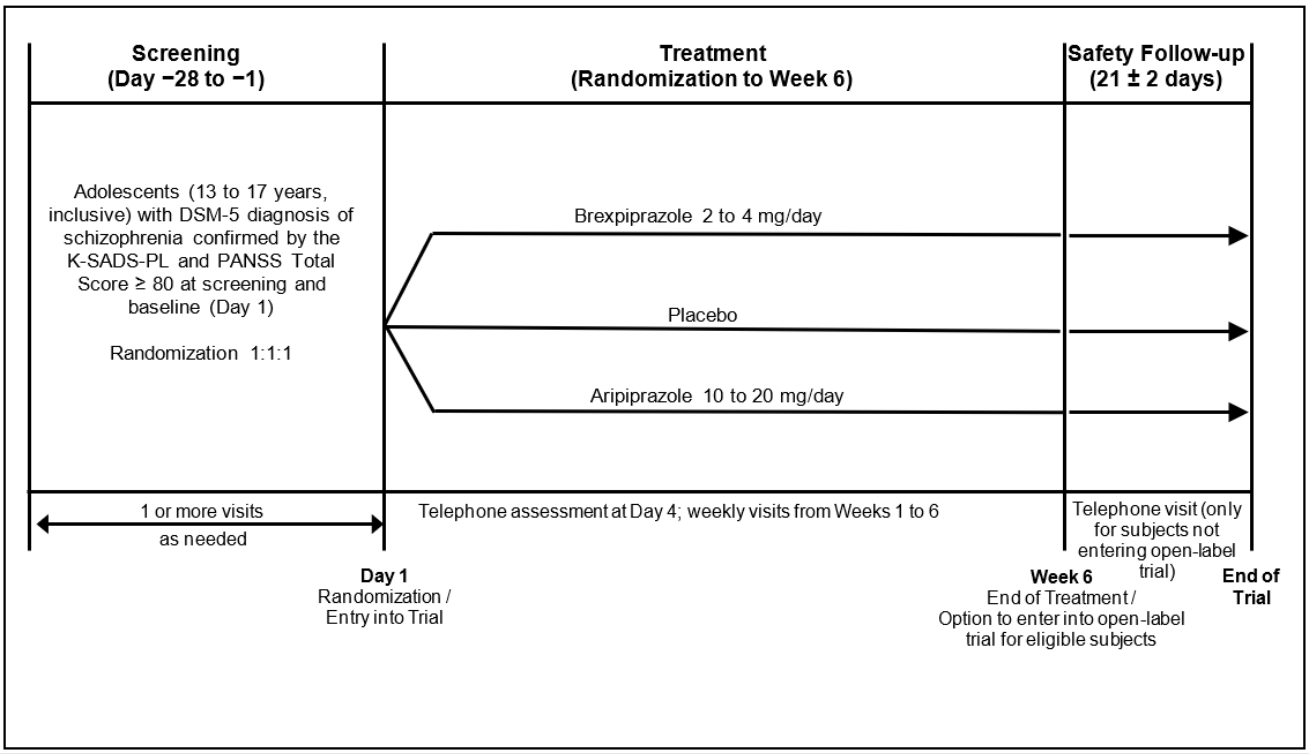
Methods

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.

Study participants

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.

Objectives

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 behaviour (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)

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.

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 (i.e., drug dispensed = drug returned or no IMP dispensed). If a subject was dispensed IMP and was lost to follow up, he/she was 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 used in the primary analysis of efficacy endpoints.

Handling of missing data: missing data 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.

Primary endpoint: 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, baseline by visit interaction as covariates).Percentage of subjects achieving response and remission (with relative risk and 95% CI), and CGI-I (difference and 95% CI) were 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 analysed. 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 analysed. Percentage of subjects with clinically significant changes in weight, BMI, and waist circumference were also analysed.

Results

Participant flow

Subject disposition for the randomized sample is presented in Error! Reference source not found..

Table 01 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%]).

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 0-2.

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%)
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)
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
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

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.

Numbers 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 analysed for safety. Of the 316 subjects, 314 subjects (99.4%) were analysed 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.

Outcomes and estimation

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 0-4 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).

Discussion on the study 331-10-234

The 331-10-234 study design is compliant with EMA Guidelines (EMA/CHMP/40072/2010/Rev1) clearly stating that the preferred design for demonstrating short term efficacy is a 6 week clinical trial; this is because so far for first- and second generation antipsychotics, a reasonable stability of effect has been observed as well as some effect on negative symptoms often only after 6 weeks of treatment.

The cut-off lower age at 13 years reflects the waiver granted by PDCO as well as CHMP relevant GL.

The endpoints are adequate for the aim of the study. The primary endpoint is a validated measure used in schizophrenia studies (PANSS - Positive and Negative Symptom Scale).

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.

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. Pre-specification of these methods is seen as important in view of potential issues with adherence to therapy.

In the SAP no pre-specified analysis is reported regarding the comparative arm with aripiprazole hence this will be descriptive.

In total, a low percentage of subjects discontinued the trial with a higher percentage, as expected, in the PLB arm.

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 with 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.

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 trials in adults. The brexpiprazole group showed a statistically significant improvement compared with the placebo group in PANSS at week 6: LS Mean (SE) Change at Week 6 of –22.75, -23.95 and –17.42 for Brex, Apri and PLB, respectively; the LS mean difference between Brex and PLB = −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 difference between these two arms. Thus, the results highlight that the impact of brexpiprazole short treatment on PANSS is of limited effect size over PLB response.

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), noting that results are consistent between brexpiprazole and aripiprazole arms. 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.

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). Overall, results from secondary endpoints at week 6 show some positive impact of the treatment on symptoms (excluding negative symptoms) and minimal impact on the Clinical Global Impression-Severity of Illness Scale (CGI-S, MMRN) scores.

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). Subgroups analysis of the primary outcome by age range (cut-off ≥15-year and < 15-year) doesn't suggest consistent results between groups: the mean difference (brexpiprazole group vs placebo group) at Week 6 in the PANSS Total Score showed significant and clinically relevant 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 as in brexpiprazole arm is seen when the primary endpoint is analysed by the two age cut-offs 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 was observed 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 and its consistency when considering aripiprazole results, likely suggests 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.

Study 331-10-236

Title: A 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.

Methods

Ongoing long-term, open-label trial designed to evaluate the long-term safety, tolerability, and measurements of efficacy of brexpiprazole in adolescent subjects, ages 13 to 17 years, with a DSM5 diagnosis of schizophrenia.

The trial consists of up to a 24-month open-label treatment period and is being conducted on an outpatient basis.

The trial population includes 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 consists of a 24-month open-label treatment period and a 21 (± 2) day follow-up period. (scheme below)

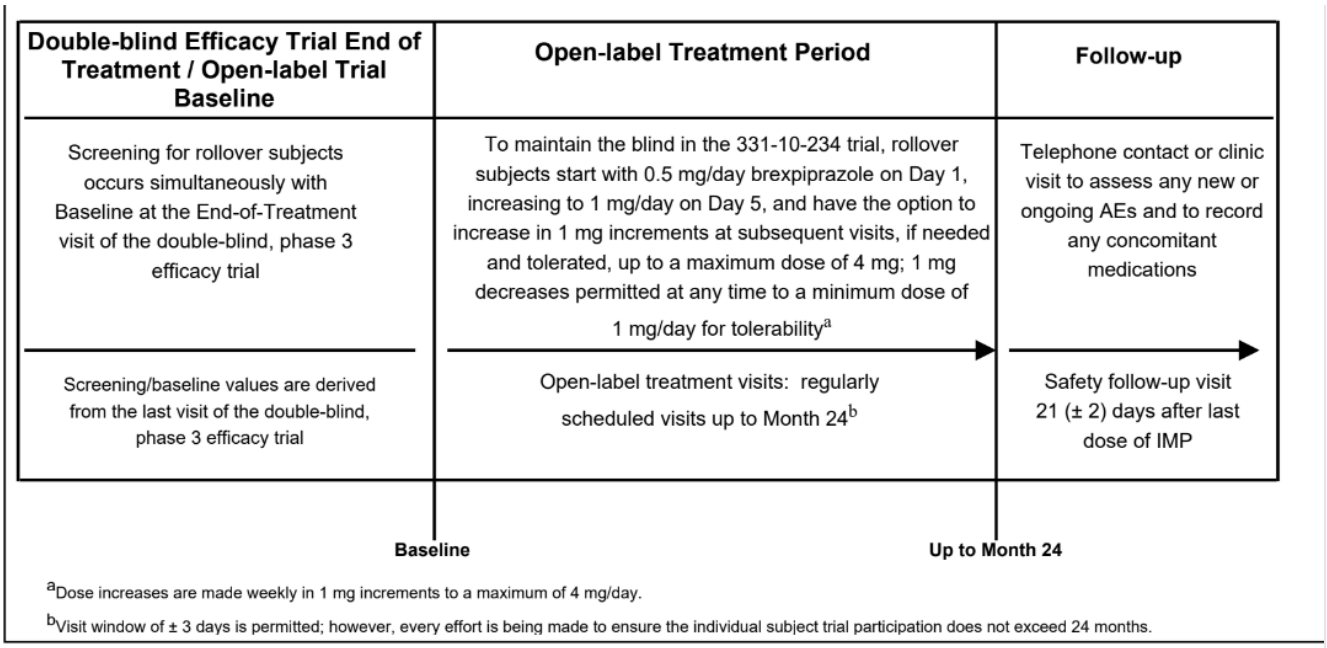


Figure 9.1-1 Trial Design Schematic - Rollover Subjects from Trial 331-10-234

For *de novo* subjects, Trial 331-10-236 consists 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.

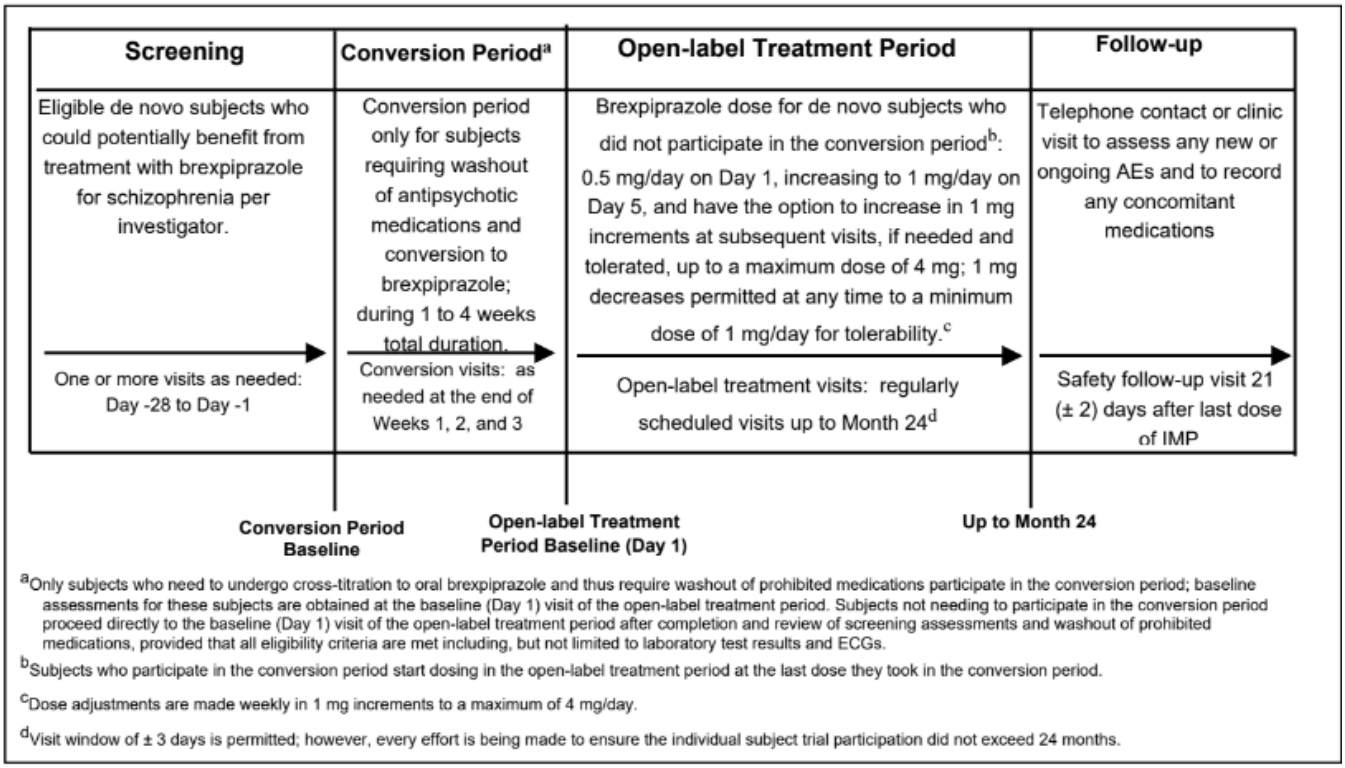


Figure 9.1-2 Trial Design Schematic - De Novo Subjects

AE = adverse event; IMP = investigational medicinal product.

Study participants

Main Inclusion Criteria:

- Male & female subjects 13-17 years of age, inclusive.
- Subjects who turn 18 during trial 331-10-234 are permitted in this trial.
- Subjects with a current primary diagnosis of schizophrenia, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and confirmed by the K-SADS-PL completed at time of entry into Trial 331-10-234. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia must be made and documented, and the diagnosis confirmed by the K-SADS-PL at screening.
- Subjects who, in the investigator's judgment, require 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 is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (e.g., medication, illicit drug use).
- History of failure of clozapine treatment or response to clozapine treatment only.
- History of neuroleptic malignant syndrome

Treatments

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

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 is not appropriate for de novo subjects, in the opinion of the investigator, the subjects must enter a conversion period to cross-titrate from their current antipsychotic treatment(s) to brexpiprazole monotherapy and washout from prohibited medications.

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.

All other de novo subjects enter the trial at the baseline (Day 1) visit of the open-label treatment period after completion and review of screening assessments, provided that all eligibility criteria are met (ie, laboratory test results, ECGs), and follow the dosing strategy for rollover subjects

Following the initial titration to 1, 2, or 3 mg/day (by Day 21 for rollover subjects or by Day 7 for de novo subjects following conversion), subjects may maintain the same dose, or have the option to increase or decrease the dose by 1 mg/day in 1-week increments (minimum dose 1 mg/day and maximum dose 4 mg/day). The dose of brexpiprazole may be decreased at any time based on the investigator's judgment after the start of the open-label treatment period, with the frequency of the 1 mg decreases based upon tolerability. Those unable to tolerate the minimum 1 mg daily dose of brexpiprazole are to be withdrawn from the trial. Rechallenge with higher doses of brexpiprazole (in 1 mg/day increments) is permitted following dose decreases if clinically warranted based on the investigator's judgment.

Objectives

The objective of the trial is to characterize the long-term safety and tolerability of brexpiprazole in adolescents with schizophrenia.

Outcomes/endpoints

Primary endpoints were safety.

Secondary Endpoints (Efficacy)

Change from baseline in the PANSS Total Score and the Positive and Negative Subscale Scores

Change from baseline in the CGAS Score
Change from baseline in the CGI-S scale
CGI-I scale at endpoint

Sample size

Based on interim analysis, the majority of subjects who completed Trial 331-10-234 continued into Trial 331-10-236 (295 of 296 subjects); 288 of the 295 (97.6%) subjects enrolled in the open-label trial have been analyzed for efficacy as of the data cutoff date of 10 Oct 2023.

This trial is currently ongoing and anticipated to be completed in April 2025.

A more recent update of efficacy data has been provided with a cutoff date on 13 Sept 2024. A total of 168 subjects have completed the study, including 28 additional subjects since the previous 10 Oct 2023 data cutoff date, and 12 subjects are currently ongoing in Trial 331-10-236. The total number of subjects analysed for efficacy remains 288 (97.6%).

Disposition

Table 2.2-2 Subject Disposition for Subjects Enrolled into the Open-Label Treatment Period (Trial 331-10-236 - 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	56 (56.6)	57 (64.0)	44 (50.6)	11 (55.0)	168 (56.9)
Discontinued	40 (40.4)	29 (32.6)	36 (41.4)	9 (45.0)	114 (38.6)
Ongoing	2 (2.0)	3 (3.4)	7 (8.0)	0 (0.0)	12 (4.1)
Analyzed For Efficacy[c]	96 (97.0)	87 (97.8)	85 (97.7)	20 (100.0)	288 (97.6)

Arip = aripiprazole; Brex = brexpiprazole.

[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]All treated subjects who had a baseline assessment and at least one post-baseline assessment of the PANSS total score.
Based on 13-Sep-2024 data cutoff.

Discontinuations included a total of 114 (38.6%) subjects overall (40 [40.4%] subjects that had prior brexpiprazole, 29 [32.6%] subjects that had prior aripiprazole, 36 [41.4%] subjects that had prior placebo, and 9 [45.0%] de novo subjects). Primary reasons for discontinuations included withdrawal by subject (35 [11.9%] 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. There were no deaths in the trial.

Treatment compliance: in the open-label treatment period, 281 (95.6%) subjects were ≥ 90% compliant with IMP: 92 (93.9%) subjects that had prior brexpiprazole, 85 (95.5%) subjects that had prior aripiprazole, 84 (96.6%) subjects that had prior placebo, and all 20 (100.0%) de novo subjects.

Protocol deviations

Overall, 182 (61.7%) subjects had at least one major protocol deviation. Of these subjects, a majority (121 [41.0%] subjects) had at least one COVID-related protocol deviation. Protocol deviations related to COVID-19 were mainly due to remote assessments.

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	61 (61.6)	53 (59.6)	53 (60.9)	15 (75.0)	182 (61.7)
Entry Criteria	2 (2.0)	3 (3.4)	4 (4.6)	0 (0.0)	9 (3.1)
Procedural Deviations	50 (50.5)	44 (49.4)	40 (46.0)	10 (50.0)	144 (48.8)
Dosing	8 (8.1)	11 (12.4)	13 (14.9)	3 (15.0)	35 (11.9)
Prohibited Medications	15 (15.2)	14 (15.7)	13 (14.9)	3 (15.0)	45 (15.3)
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.

Protocol deviations lead to discontinuation in 2 (2.3%) patients previously treated with placebo (n=87) (Table 10.1-3).

Demographics and baseline characteristics

Demographics and baseline characteristics are presented by rollover category (prior brexpiprazole, prior aripiprazole, or prior placebo) and de novo.

A total of 153 (51.9%) subjects were female and 142 (48.1%) subjects were male. Overall, the mean (SD) age of subjects was 15.5 (1.5) years with 76 (25.8%) subjects that were < 15 years old and 219 (74.2%) subjects that were ≥ 15 years old. The overall mean (SD) weight was 66.0 kg (16.2). The overall mean (SD) BMI of subjects was 23.5 (5.0) kg/m2, with a minimum BMI of 14.4 kg/m2 and a maximum BMI of 47.3 kg/m2. The majority of subjects who entered this trial were White (205 [69.5%] subjects) and not Hispanic or Latino (207 [70.2%] subjects). The next most frequently represented race category was Other (23.1%), followed by Black or African American, American Indian or Alaska Native, and Asian (4.1%, 2.4%, and 0.7%, respectively).

De novo subjects entering the conversion period were equally divided male and female (7 subjects each, respectively). Overall, the mean (SD) age of subjects was 15.4 (1.2) years with a mean (SD) weight of 72.9 kg (15.6). The overall mean (SD) BMI of subjects who entered the conversion period was 24.7 kg/m2 (5.3), with a minimum BMI of 17.8 kg/m2 and a maximum BMI of 35.7 kg/m2. The majority of subjects who entered the conversion period were White (13 [92.9%] subjects) and not Hispanic or Latino (13 [92.9%] subjects) followed by Other (1 [7.1%] subject). Overall, the demographic characteristics of subjects who entered the conversion and open-label treatment periods were similar.

Statistical methods

- The enrolled sample consists of all consented/assented subjects who were screened for eligibility and deemed eligible.

- The safety sample consists of all enrolled subjects who received at least one dose of IMP. Subjects were excluded from this population only if there was documented evidence that the subject did not take any IMP (i.e., number of tablets dispensed = number of tablets returned or no IMP dispensed).

The efficacy sample consists of all subjects in the safety sample who had a baseline assessment and at least one postbaseline assessment of the PANSS Total Score.

All efficacy analyses specified in this section were performed on the Efficacy Sample.

Methods for secondary efficacy outcome analyses: changes from baseline for each of the continuous variables (except the CGI-I Score) were summarized using descriptive statistics.

Results

Efficacy results for Trial 331-10-236 as of the data cutoff date of 10 Oct 2023. Upon request a more recent update of efficacy data has been provided with a cut-off date of 13 Sept 2024. The final analysis will be performed upon completion of the trial. Moreover, the DMC open session minutes and the DMC recommendation of the most recent DMC meeting (25 July 2024) have been provided by the MAH. Efficacy data were presented for the ongoing Trial 331-10-236 based on the data cut-off date of 15 May 2024. The DMC unanimously concluded that the trial could continue without modification based on the most recent data presentation. The response is considered adequate.

Outcomes and estimation

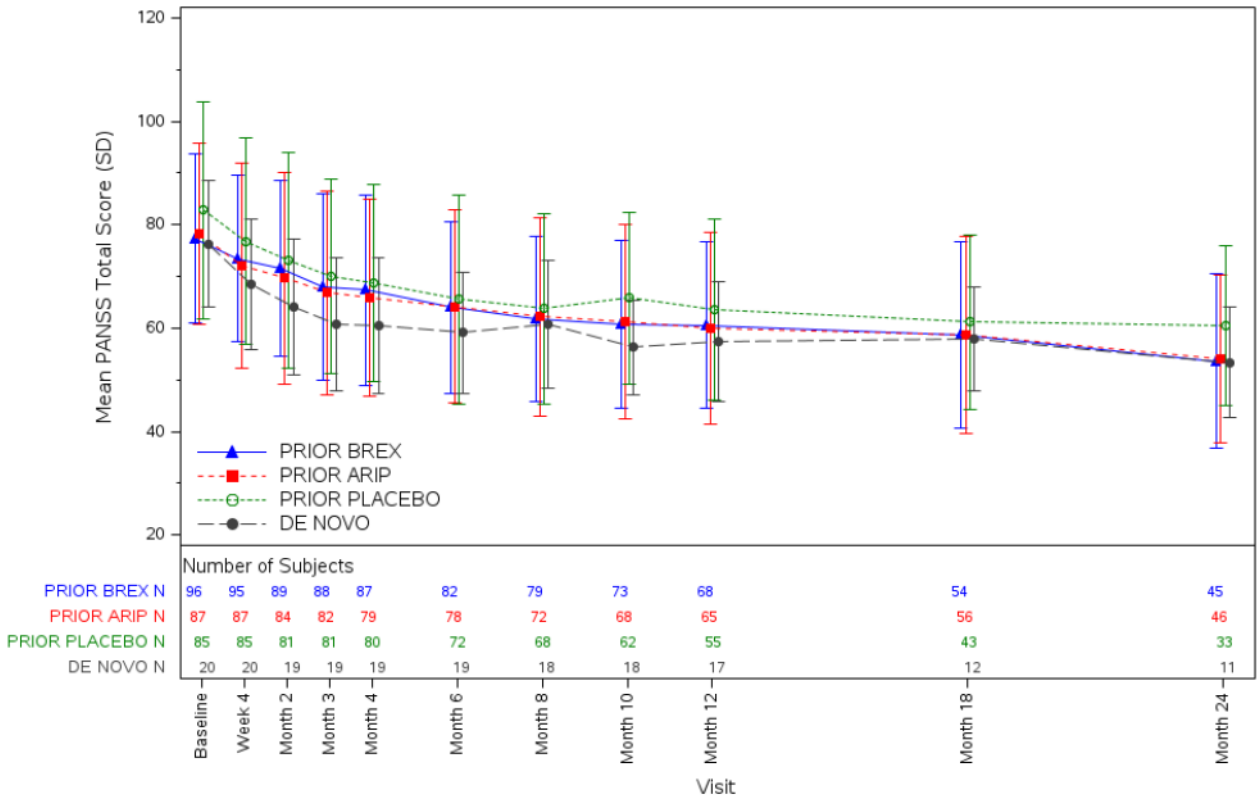
Primary endpoint: safety.

Secondary efficacy endpoints:

Mean Change from Baseline in PANSS Total Score

Overall, subjects had a decrease in the mean (SD) change of −19.18 (15.10), −25.87 (17.39), and −19.12 (17.61) from baseline in PANSS Total Score at Month 12, Month 24, and last visit, respectively. Both rollover subjects and de novo subjects had a decrease in the mean (SD) change from baseline in PANSS Total Score at last visit (−17.83 [17.46], −20.00 [17.46], and −19.69 [18.91] for subjects that had prior brexpiprazole, aripiprazole, or placebo, respectively and −19.00 [13.61] for de novo subjects).

Mean PANSS Total Score by Visit - Trial 331-10-236 (Efficacy Sample)



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

Results from the subgroup analysis of mean change from baseline in PANSS Total Score by age: the mean (SD) change from baseline in PANSS Total Score was summarized by age group. For subjects < 15 years old, the mean (SD) change from baseline was −18.11 (14.11), −25.97 (18.84), and −18.01 (18.87) at Month 12, Month 24, and last visit, respectively. For subjects ≥ 15 years old, the mean (SD) change was −19.56 (15.47), −25.83 (17.02), and −19.49 (17.19) at Month 12, Month 24, and last visit, respectively (CT-5.1.4).

The open-label paediatric extension trial (331-10-236) demonstrates to date (13 Sep 2024) continued symptom improvement and no change in brexpiprazole safety Profile. These findings are similar to what was observed in the adult open-label extension study for brexpiprazole (CSR 331-10-237) as well as lurasidone (the only EMA approved treatment for ≥ 13-year-old patients with schizophrenia).

-Change from baseline in the PANSS Total Score and the Positive and Negative Subscale Scores

An erratum has been provided by the MAH to correct the results shown in tables 11.4.1.2.2.1 and 11.4.1.2.2.2. A table title error (inversion of correct titles) was identified in the initial source CTs for the mean change from baseline in PANSS Positive and Negative Subscale scores for Trial 331-10-236 as originally presented in iCSR 331-10-236 Table 11.4.1.2.2-1 and Table 11.4.1.2.2-2 respectively.

The mean (SD) decrease from baseline PANSS Positive Subscale Score was −5.16 (4.66), −6.81 (5.04), and −4.97 (5.22) at Month 12, Month 24, and Last Visit, respectively.

Table 11.4.1.2.2-~~2~~1 Mean Change from Baseline in PANSS ~~Negative~~Positive Subscale Score (Efficacy Sample)							
Parameter (Units)	**Visit**	**Statistic**	**Prior Brex**	**Prior Arip**	**Prior Placebo**	**De Novo**	**All**
PANSS ~~Negative~~ Positive Subscale Score	Baseline	n	96	87	85	20	288
		Mean (SD)	17.32 (4.70)	17.51 (4.53)	18.47 (6.12)	17.55 (5.04)	17.73 (5.14)
	Week 4	n	95	87	85	20	287
		Mean (SD)	-0.94 (3.04)	-1.80 (3.08)	-1.89 (3.71)	-2.55 (2.68)	-1.60 (3.27)
	Month 6	n	82	78	72	19	251
		Mean (SD)	-3.51 (3.87)	-3.54 (4.35)	-4.89 (4.62)	-5.47 (4.72)	-4.06 (4.34)
	Month 12	n	68	65	55	17	205
		Mean (SD)	-4.49 (4.12)	-4.94 (4.46)	-6.15 (5.44)	-5.47 (4.57)	-5.16 (4.66)
	Month 18	n	54	56	43	12	165
		Mean (SD)	-5.13 (4.64)	-5.54 (4.76)	-6.33 (5.39)	-6.75 (4.69)	-5.70 (4.88)
	Month 24	n	45	46	33	11	135
		Mean (SD)	-6.56 (5.10)	-6.76 (3.96)	-6.88 (6.39)	-7.82 (4.81)	-6.81 (5.04)
	Change at Last Visit	n	96	87	85	20	288
		Mean (SD)	-4.52 (5.09)	-5.16 (4.95)	-5.24 (5.73)	-5.15 (4.97)	-4.97 (5.22)

Arip = aripiprazole; Brex = brexpiprazole; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

The mean (SD) change from baseline in PANSS Negative Subscale Score was −4.28 (4.74), −6.26 (5.25), and −4.70 (5.20) at Month 12, Month 24, and last visit, respectively.

Table 11.4.1.2.2-~~1~~2 Mean Change from Baseline in PANSS ~~Positive~~Negative Subscale Score (Efficacy Sample)							
Parameter (Units)	**Visit**	**Statistic**	**Prior Brex**	**Prior Arip**	**Prior Placebo**	**De Novo**	**All**
PANSS ~~Positive~~ Negative Subscale Score	Baseline	n	96	87	85	20	288
		Mean (SD)	20.84 (5.35)	20.83 (5.93)	21.65 (5.82)	20.70 (5.22)	21.07 (5.64)
	Week 4	n	95	87	85	20	287
		Mean (SD)	-0.92 (2.92)	-1.23 (2.74)	-1.08 (3.05)	-1.60 (2.46)	-1.11 (2.87)
	Month 6	n	82	78	72	19	251
		Mean (SD)	-3.44 (3.88)	-3.23 (4.27)	-3.78 (4.92)	-2.79 (4.04)	-3.42 (4.32)
	Month 12	n	68	65	55	17	205
		Mean (SD)	-3.76 (4.75)	-4.62 (4.11)	-4.73 (5.30)	-3.59 (5.15)	-4.28 (4.74)
	Month 18	n	54	56	43	12	165
		Mean (SD)	-5.02 (5.76)	-5.45 (4.35)	-4.84 (4.56)	-5.00 (4.26)	-5.12 (4.87)
	Month 24	n	45	46	33	11	135
		Mean (SD)	-6.98 (5.65)	-6.11 (4.96)	-5.36 (5.64)	-6.64 (3.41)	-6.26 (5.25)
	Change at Last Visit	n	96	87	85	20	288
		Mean (SD)	-4.61 (5.57)	-4.94 (4.88)	-4.61 (5.36)	-4.40 (4.11)	-4.70 (5.20)

Arip = aripiprazole; Brex = brexpiprazole; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

-Change from baseline in the CGAS Score: Overall, subjects experienced continuous improvement in psychological, social, and school functioning as evaluated by the CGAS. The mean (SD) change from baseline showed an increase in the CGAS Score of 13.32 (12.18), 19.07 (12.33), and 14.04 (13.66) at Month 12, Month 24, and Last Visit, respectively.

The baseline CGAS Score was lower for de novo subjects compared with the other prior treatment groups; however, the de novo group exhibited notable improvement and achieved a mean CGAS Score similar to the other prior groups by Month 3 and continued through Last Visit.

Table 11.4.1.2.3-1 Mean Change from Baseline in CGAS Score (Efficacy Sample)							
Parameter (Units)	**Visit**	**Statistic**	**Prior Brex**	**Prior Arip**	**Prior Placebo**	**De Novo**	**All**
CGAS Score	Baseline	n	96	87	85	20	288
		Mean (SD)	58.76 (12.78)	59.64 (14.64)	57.06 (15.84)	50.00 (8.77)	57.92 (14.23)
	Week 4	n	96	87	84	20	287
		Mean (SD)	1.88 (7.74)	4.52 (8.20)	3.54 (9.90)	8.25 (7.05)	3.61 (8.64)
	Month 6	n	82	78	73	19	252
		Mean (SD)	8.98 (10.75)	9.63 (13.20)	10.42 (10.70)	16.42 (8.84)	10.16 (11.52)
	Month 12	n	71	65	55	17	208
		Mean (SD)	11.55 (10.73)	12.77 (14.14)	14.71 (11.82)	18.29 (9.87)	13.32 (12.18)
	Month 18	n	56	57	44	12	169
		Mean (SD)	13.48 (11.29)	16.19 (13.95)	16.48 (11.72)	22.42 (11.09)	15.81 (12.45)
	Month 24	n	47	46	33	11	137
		Mean (SD)	17.91 (11.97)	19.48 (13.06)	17.15 (11.63)	28.00 (10.09)	19.07 (12.33)
	Change at Last Visit	n	96	87	85	20	288
		Mean (SD)	13.68 (13.23)	14.18 (14.04)	12.18 (13.34)	23.05 (12.80)	14.04 (13.66)

Arip = aripiprazole; Brex = brexpiprazole; CGAS = Children's Global Assessment Scale; SD = standard deviation.

- Change from baseline in the CGI-S scale: Improvement in the severity of illness was observed based on change from baseline to last visit on the CGI-S Score for both rollover and de novo subjects. Overall, subjects exhibited a mean (SD) decrease from baseline of −1.06 (1.00), −1.40 (1.12), −1.02 (1.19) at Month 12, Month 24, and Last Visit, respectively.

The efficacy of brexpiprazole in the treatment of schizophrenia was rated for each subject using the CGII. Subjects exhibited a mean (SD) in CGI-I Score of 2.10 (0.90), 1.70 (0.80), and 2.10 (1.10) at Month 12, Month 24, and last visit, respectively.

Overall, 68.8%, 83.6%, and 70.8% of subjects had 'much' or 'very much' improvement on the CGI-I (scores of 1 or 2) during the open-label treatment period at Month 12, Month 24, and Last Visit, respectively.

Table 11.4.1.2.4-1 Mean Change from Baseline in CGI-S Score (Efficacy Sample)							
Parameter (Units)	**Visit**	**Statistic**	**Prior Brex**	**Prior Arip**	**Prior Placebo**	**De Novo**	**All**
CGI-S Score	Baseline	n	96	87	85	20	288
		Mean (SD)	3.81 (0.90)	3.83 (1.01)	3.87 (1.03)	4.05 (0.89)	3.85 (0.97)
	Week 4	n	96	87	85	20	288
		Mean (SD)	-0.24 (0.71)	-0.39 (0.69)	-0.29 (0.63)	-0.60 (0.75)	-0.33 (0.69)
	Month 6	n	82	78	73	19	252
		Mean (SD)	-0.74 (0.84)	-0.81 (0.97)	-0.86 (0.96)	-1.21 (0.79)	-0.83 (0.92)
	Month 12	n	71	65	55	17	208
		Mean (SD)	-1.03 (0.96)	-1.08 (1.05)	-1.02 (0.99)	-1.29 (1.05)	-1.06 (1.00)
	Month 18	n	54	56	43	12	165
		Mean (SD)	-1.09 (1.07)	-1.25 (1.13)	-1.00 (1.11)	-1.58 (0.90)	-1.16 (1.09)
	Month 24	n	45	46	33	11	135
		Mean (SD)	-1.42 (1.20)	-1.48 (0.98)	-1.15 (1.25)	-1.73 (0.90)	-1.40 (1.12)
	Change at Last Visit	n	96	87	85	20	288
		Mean (SD)	-1.03 (1.18)	-1.13 (1.21)	-0.84 (1.19)	-1.30 (1.08)	-1.02 (1.19)

Arip = aripiprazole; Brex = brexpiprazole; CGI-S = Clinical Global Impression Severity; SD = standard deviation.

- CGI-I scale at endpoint: Overall, subjects exhibited a mean (SD) in CGI-I Score of 2.10 (0.90), 1.70 (0.80), and 2.10 (1.10) at Month 12, Month 24, and last visit, respectively. The CGI-I Scores indicate general improvement among all subjects.

During the trial, the mean CGI-I Scores were observed to be low and in the range of 1.6 to 2.8 with the median ranging from 1.0 to 3.0.

Overall, 68.8%, 83.6%, and 70.8% of subjects had much or very much improvement on the CGI-I (scores of 1 or 2) during the open-label treatment period at Month 12, Month 24, and last visit, respectively.

Table 11.4.1.2.5-1 Summary of Clinical Global Impression - Improvement (Efficacy Sample)							
Parameter (Units)	**Visit**	**Statistic**	**Prior Brex**	**Prior Arip**	**Prior Placebo**	**De Novo**	**All**
CGI-I Score	Week 4	n	96	87	84	20	287
		Mean (SD)	2.80 (1.00)	2.60 (0.90)	2.80 (0.90)	2.60 (0.90)	2.70 (0.90)
	Month 6	n	82	77	73	19	251
		Mean (SD)	2.40 (0.90)	2.20 (0.90)	2.50 (1.10)	1.90 (0.90)	2.30 (1.00)
	Month 12	n	71	65	55	17	208
		Mean (SD)	2.20 (0.90)	2.00 (0.90)	2.20 (1.00)	1.90 (1.10)	2.10 (0.90)
	Month 18	n	54	56	43	12	165
		Mean (SD)	2.00 (1.00)	1.90 (0.90)	2.00 (1.00)	1.70 (0.80)	2.00 (0.90)
	Month 24	n	44	46	33	11	134
		Mean (SD)	1.70 (0.80)	1.70 (0.70)	2.00 (0.80)	1.60 (0.80)	1.70 (0.80)
	Last Visit	n	96	87	85	20	288
		Mean (SD)	2.10 (1.10)	2.10 (1.10)	2.30 (1.10)	1.90 (1.10)	2.10 (1.10)

Arip = aripiprazole; Brex = brexpiprazole; CGI-I = Clinical Global Impression Improvement; SD = standard deviation.

Response Rates

Response was defined as ≥ 30% improvement from baseline in PANSS Total Score or having a CGI-I Score of 1 or 2.

At Week 4, 110 (38.5%) subjects were considered responders. This percentage progressively increased to 150 (59.8%) subjects at Month 6, 140 (67.3%) subjects at Month 12, 125 (75.8%) subjects at Month 18, and 112 (83.6%) subjects at Month 24. At Last Visit, a total of 204 (70.8%) subjects were considered responders.

Updated results

Since the data cutoff date is 10 Oct 2023, the MAH has been requested to provide updated data on efficacy (A more recent update of efficacy data has been provided with a cut-off date of 13 September 2024. A total of 168 subjects have completed the study, including 28 additional subjects since the previous 10 October 2023 data cut-off date, and 12 subjects are currently ongoing in Trial 331-10-236. A total of 288 (97.6%) subjects have been analysed for efficacy.

The updated efficacy data (data cut-off 13 September 2024) are consistent with the previously presented data, showing continuous improvement in symptoms from baseline through Month 24.

Moreover, the DMC open session minutes and the DMC recommendation of the most recent DMC meeting (25 July 2024) have been provided by the MAH. Efficacy data were presented for the ongoing Trial 331-10-236 based on the data cut-off date of 15 May 2024. The DMC unanimously concluded that the trial could continue without modification based on the most recent data presentation. The response is considered adequate.

Ancillary analyses

Not applicable

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Study 331-10-234: a summary of Efficacy Results at week 6 is presented in Table 0-4.

Table 0-5 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.

aLS mean difference = difference in LS mean change.

bDerived 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.
cCMH Row Mean Scores Differ test controlling for study center.
dCMH General Association test controlling for study center.

Study 331-10-236: a summary of mean change from Baseline in PANSS Total Score is provided in table below.

Table 2.7.3.2.2.2-1 Summary of Mean Change from Baseline in PANSS Total Score - Trial 331-10-236 (Efficacy Sample)

Parameter	Visit	Statistic	Prior Brex	Prior Arip	Prior Placebo	De Novo	All
PANSS Total Score	Baseline	n	96	87	85	20	288
		Mean (SD)	77.35 (16.41)	78.25 (17.47)	82.87 (21.00)	76.25 (12.21)	79.18 (18.04)
	Week 4	n	95	87	85	20	287
		Mean (SD)	-3.73 (9.16)	-6.22 (9.61)	-6.06 (10.55)	-7.80 (6.09)	-5.46 (9.60)
	Month 6	n	82	78	72	19	251
		Mean (SD)	-12.93 (11.55)	-14.28 (14.92)	-18.07 (16.11)	-16.53 (9.16)	-15.10 (14.00)
	Month 12	n	68	65	55	17	205
		Mean (SD)	-16.63 (13.72)	-19.28 (14.95)	-22.42 (17.21)	-18.47 (12.68)	-19.18 (15.10)
	Month 18	n	54	56	43	12	165
		Mean (SD)	-19.50 (17.09)	-21.61 (15.89)	-23.47 (16.36)	-22.25 (7.14)	-21.45 (15.92)
	Month 24	n	45	46	33	11	135
		Mean (SD)	-25.84 (17.80)	-25.83 (16.20)	-25.39 (21.04)	-27.55 (7.62)	-25.87 (17.39)
	Change at Last Visit	n	96	87	85	20	288
		Mean (SD)	-17.83 (17.46)	-20.00 (17.46)	-19.69 (18.91)	-19.00 (13.61)	-19.12 (17.61)

Discussion on the study 331-10-236

Overall, the baseline characteristics of patients are consistent with those of the short-term parent trial (Trial 331-10-234).

Since the data cutoff date is 10 Oct 2023, the MAH has been requested to provide updated data on efficacy. A more recent update of efficacy data has been provided with a cut-off date of 13 September 2024. A total of 168 subjects have completed the study, including 28 additional subjects since the previous 10 October 2023 data cut-off date, and 12 subjects are currently ongoing in Trial 331-10-236. A total of 288 (97.6%) subjects have been analysed for efficacy.

The updated efficacy data (data cut-off 13 September 2024) are consistent with the previously presented data, showing continuous improvement in symptoms from baseline through Month 24. Subjects enrolled in 331-10-236 trial (both rollover and de novo subjects) showed continuous improvement in symptoms from baseline through Month 24 and last visit on PANSS Total Score showing a decrease in the mean (SD) change of −19.18 (15.10), −25.87 (17.39), and −19.12 (17.61) from baseline in PANSS Total Score at Month 12, Month 24, and last visit, respectively.

Results from subgroup analysis by age cut-off obtained in the long-term trial, showed similar improvements in PANSS total score across the two different subgroups with a mean change of PANSS score of roughly 19-20 at last visit noting de novo subgroup showing a better change.

In the older subgroup (aged 15 to 17), a similar short-term response as in adults was observed (PANSS: -8.05 [-13.3, -2.80]). This is not unexpected since they are closer to the adult population. Therefore, to establish maintenance of effect, and considering that PK data for the different age groups are as would be expected, data may be extrapolated from adults to adolescents as of the age of 15 years, per EMA guidance (EMA/CHMP/40072/2010 Rev.1)
Regarding the subgroup 13-14 years, treatment effect is difficult to obtain since early onset schizophrenia is usually associated with a more severe course and a more prolonged treatment period would be required to achieve response. However, the observed placebo response in the subgroup of patients 13-14 years of age would be also compatible with a lack of efficacy of brexpiprazole.
Considering that short-term effects in children below 15 years of age are not yet substantiated, and extrapolation of long-term effects from adults to children below 15 years of age is not straightforward, the MAH has been requested to further justify the clinical benefit in adolescents below 15 years.

The MAH's response included considerations on recognition of the disease in adolescents <15 years of age with available diagnostic criteria, unmet medical need, efficacy results from both the short-term trial (331-10-234) and the ongoing 2-year open-label paediatric extension trial (331-10-236), including updated data from Trial 331-10-236 (data cutoff date 13 September 2024) and similarity of safety profile based on observed TEAEs in adult vs younger adolescent population (< 15 years of age).

Change from baseline in PANSS total score observed in the younger age group (13-14 years old subjects) compared with the older age group (15-17 years old subjects) in the short-term trial (331-10-234) is consistent with the results observed for the aripiprazole arm of this trial and the separate short-term adolescent trial for lurasidone.
Subjects enrolled in 331-10-236 trial showed continuous improvement in symptoms from baseline through Month 24 and last visit on PANSS Positive and Negative Score, the mean change form baseline has a similar trend in negative or positive subscales.

Subjects experienced continuous improvement in psychological, social, and school functioning as evaluated by the CGAS, especially in the de novo group.

Severity of illness, as measured by CGI-S, and improved from baseline to last visit for both rollover and de novo subjects. Response was defined as ≥ 30% improvement from baseline in PANSS Total Score or having a CGI-I Score of 1 or 2, corresponding as per the relevant EMA GL to criteria of clinical meaningfulness.

At Week 4, 110 (38.5%) subjects were considered responders. This percentage progressively increased to 150 (59.8%) subjects at Month 6, 140 (67.3%) subjects at Month 12, 125 (75.8%) subjects at Month 18, and 112 (83.6%) subjects at Month 24. At Last Visit, a total of 204 (70.8%) subjects were considered responders.

A high percentage of subjects (68.8%, 83.6%, and 70.8%) scored ‘much’ or ‘very much’ improvement on the CGI-I (scores of 1 or 2) during the open-label treatment period at Month 12, Month 24, and Last Visit. Moreover, the improvement was sustained through the study, with lower scores in the last months of treatment.

Throughout the open-label treatment period, the proportion of responders demonstrated consistent improvement across all subgroups. Thus, these results should be seen as clinically relevant.

Analysis performed across trials (pooled analyses and meta-analysis)

Study 331-201-00185
Title: Extrapolation Study Based on Data From Brexpiprazole Adult and Paediatric Trials and Literature to Support the Maintenance of the Antipsychotic Effects of Brexpiprazole in Adolescents with Schizophrenia

The 331-201-00185 study has as main aim to provide supportive evidence of maintenance of efficacy of brexpiprazole monotherapy based on extrapolation of data from trials conducted in both adolescent and adult subjects with schizophrenia.Rationale: The diagnosis of schizophrenia in adolescents is made using the same diagnostic criteria used for adult onset schizophrenia (AOS) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).1,4 Early-onset schizophrenia (EOS) is defined as illness onset before the age of 18 years.

Childhood-onset schizophrenia (COS) before the age of 13 years is rare, but there is a considerable increase in the prevalence during adolescence7,8,9 with an estimated prevalence of 0.5% among adolescents aged 13 to17 years. Early-onset schizophrenia patients tend to have more severe negative symptoms, cognitive impairment, impulsivity, frequent hospitalizations, and poor social functioning10 compared with AOS. COS (previously very early onset schizophrenia) defined as illness onset before 13 years of age, is phenomenologically continuous with schizophrenia in adolescents and adulthood and has high diagnostic stability. Additionally, data from phenomenological, cognitive, neuroimaging, and genetic studies suggest a similar profile of clinical and neurobiological abnormalities between early- and adult-onset patients.

Despite evidence that a long duration of untreated psychosis (DUP) in adolescent schizophrenia patients is associated with poor outcomes and lower rates of clinical remission, there remains limited availability of approved medications for this patient population. There are high unmet needs for a wider availability of antipsychotics with fewer side effects (e.g., sedation, extrapyramidal symptoms, metabolic symptoms, prolactin changes, and suicidality) which may help lead to higher compliance with medication in adolescents who may be more vulnerable and sensitive to antipsychotic side effects compared with adults.

A large body of data exists regarding the use of brexpiprazole in treating adult subjects with schizophrenia, including short-term efficacy trials (331-10-230, 331-10-231, 14644A, and 331-10-002), maintenance of efficacy in the relapse-prevention trial (331-10-232), and in open-label extension trials (Trials 331-10-237 and 14644B). Brexpiprazole also demonstrates clinically meaningful efficacy for adolescent schizophrenia with a favourable safety and tolerability profile in the short-term (6-weeks) Trial 331-10-234, and in an ongoing long-term (24 months) open-label Trial 331-10-236.

The use of “paediatric extrapolation” which is defined as “an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric and reference (adult or other paediatric) population.

Methods

The data sources for extrapolation were based on the following components:

-Evaluation of brexpiprazole pharmacokinetics (PK) in children and adolescents in one clinical pharmacology trial: phase 1 dose-escalation trial in adolescents (aged 13 - 17 years old) (Trial 331-10-233) showed that brexpiprazole concentrations were comparable in paediatric and adult subjects.

Since the recommended target dosage, i.e., 2 to 4 mg/day were the same in adults and adolescents with comparable PK exposure, a starting dose of 0.5 mg/day was proposed in Trial 331-10-234.

-Literature to support the appropriateness of extrapolation from adults to adolescents with schizophrenia (based on available knowledge of similarity of disease in adolescents and adults),

-Similarity of the exposure and E-R relationship in adults and adolescents (Study 331-24-201; see section 2.3.4. PK/PD modeling),

-Efficacy results from the short-term Trial 331-10-234 and open-label extension Trial 331-10-236 in adolescents, and, most relevant to this submission,

-Similarity of maintenance of efficacy in adolescents (up to 32 weeks following the start of treatment), based on data from Trial 331-10-234 and Trial 331-10-236 in adolescents and similar trials in adults (short-term Trials 331-10-230 and 33110-231, and long-term Trial 331-10-237). Maintenance of the improvement in PANSS Total Score (observed at Week 6) in the longer term up to 32 weeks was assessed, as well as its similarity with the improvement observed in adult trials.

Table 3.2.2-1 Description of Trials Included in 331-201-00185

Adult Trials			
Trial	**Type**	**Population**	**Inclusion of Doses**
331-10-230	Short-term (6 weeks) phase 3 randomized to brexpiprazole 4 mg, 2 mg, 1 mg or placebo	Adult subjects with a diagnosis of schizophrenia	Brexpiprazole (2 mg, 4 mg arms)[a]
331-10-231	Short-term (6 weeks) phase 3 randomized to brexpiprazole 4 mg, 2 mg, 0.25 mg or placebo	Adult subjects with a diagnosis of schizophrenia	Brexpiprazole (2 mg, 4 mg arms)[a]
331-10-237	Long-term (26 weeks) phase 3 open-label with brexpiprazole 1 to 4 mg (flexible)	Adult subjects rolling over from Trials 331-10-230, 331-10-231 or 331-10-232, or de novo	Brexpiprazole (2 or 4 mg arms)[a]
Adolescent Trials			
Trial	**Type**	**Population**	**Inclusion of Doses**
331-10-234	Short-term (6 weeks) phase 3 randomized to brexpiprazole 2 to 4 mg, aripiprazole 10 to 20 mg, or placebo	Adolescent (13-17 years) subjects with a diagnosis of schizophrenia	Subjects randomized to brexpiprazole and who rolled over to Trial 331-10-236
331-10-236	Long-term (2 years) phase 3 open-label with brexpiprazole 1 to 4 mg (flexible)	Adolescent subjects rolling over from Trial 331-10-234, or de novo	Subjects from Trial 331-10-234 who received brexpiprazole (2 mg and 4 mg) rolling over

[a]Subjects who rolled over from 2 mg and 4 mg arms of Trials 331-10-230 and 331-10-231 were randomized to brexpiprazole 2 or 4 mg in Trial 331-10-237.

Data from adolescent subjects who completed Trial 331-10-234 and rolled over to Trial 331-10-236 and adult subjects who completed Trial 331-10-230 or Trial 331-10-231 and rolled over to Trial 331-10-237 were compared based on the Full Analysis Set (FAS), as defined below:

Subjects from Trial 331-10-234 randomized to brexpiprazole who rolled over to Trial 331-10-236 with at least one observation for the PANSS Total Score in Trial 331-10-236.

Subjects from Trials 331-10-230 and 331-10-231 randomized to brexpiprazole 2 or 4 mg/day who continued into Trial 331-10-237 (regardless of whether subjects had a PANSS Total Score observation in Trial 331-10-237).

Based on the FAS, 96 subjects were identified for the adolescent population and 346 subjects were identified for the adult population. De novo subjects from Trials 331-10-236 and 331-10-237 were not included.

De novo subjects from Trials 331-10-236 (adolescents) and 33110237 (adults) were not included.

Study participants

The adolescent trial population in Trials 331-10-234 and 331-10-236 included male and female subjects between 13 and 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1), with a confirmed DSM-5 diagnosis of schizophrenia and a PANSS Total Score ≥ 80 at screening and at baseline (for Trial 331-10-234 only).

The adult trial population in Trials 331-10-230, 331-10-231, and 331-10-237 included males and females between 18 to 65 years of age, inclusive, with a DSM-4, Text Revision, diagnosis of schizophrenia, a PANSS Total Score ≥ 80 at screening and at baseline, and who would benefit from hospitalization or continued hospitalization for the treatment of a current acute relapse of schizophrenia (for Trials 331-10-230 and 331-10-231 only).

Objectives

The objectives of this extrapolation report were:

- To assess the maintenance of efficacy in adolescent (13 to 17 years of age) subjects with schizophrenia by extrapolating data from trials completed in both adolescent and adult subjects with schizophrenia.

-To compare adolescent subjects from Trial 331-10-234 brexpiprazole treatment arm who rolled over to Trial 331-10-236 with adult subjects from Trials 331-10-230 and 331-10-231 (brexpiprazole 2 mg and 4 mg) who rolled over to Trial 331-10-237, with the notion of having overlapping confidence intervals (CI) between adolescents and adults.

Outcomes/endpoints

The study endpoints of this extrapolation report were:

-Primary: To assess the change from baseline to Week 32 in PANSS total score (ie, short-term efficacy in 6 weeks and long-term maintenance of efficacy in 26 weeks), using the Trial 331-10-234 study baseline as the baseline value in the study, and compare adolescents from Trials 331-10-234 and 331-10-236 to adults from Trials 331-10-230, 331-10-231 and 331-10-237.

-Other: To compare the following endpoints between adult and adolescent subjects with schizophrenia: – Overall discontinuation rates – Discontinuation rates due to lack of efficacy – Percent of subjects with treatment response (≥ 30% decrease in PANSS Total Score or Clinical Global Impression-Improvement [CGI] Score of 1 or 2) by visit for the first 32 weeks of treatment with brexpiprazole (OC and LOCF).

Sample size

A total of 96 subjects were evaluated in the adolescent full analysis set and 346 subjects were included in the adult full analysis set.

Statistical methods

The FAS included:

-Subjects from Trial 331-10-234 randomized to brexpiprazole who rolled over to Trial 331-10-236 with at least one observation for the PANSS Total Score in Trial 331-10-236.

-Subjects from Trials 331-10-230 and 331-10-231 randomized to brexpiprazole 2 mg or 4 mg who continued into Trial 331-10-237 (regardless of whether subjects had a PANSS Total Score observation in Trial 331-10-237).

To evaluate the similarity of efficacy in adolescents to that of adults, the similarity of the long-term efficacy was established based on the similarity of 32-week trajectories for the change from baseline in the PANSS Total Score during the first 32 weeks of treatment with brexpiprazole 2 to 4 mg/day. The trajectories for the change from baseline in PANSS Total Score in adolescents and adults will be compared for the Full Analysis Set (FAS) population. Descriptive statistics will be provided for the PANSS Total Score and for the change from baseline in PANSS Total Score. In addition, 95% CIs associated with the change from baseline in PANSS Total Score will be provided for each visit up to 32 weeks.

If the majority of the 95% CIs associated with the change from baseline in PANSS Total Score over 32 weeks in Trials 331-10-234 and 331-10-236 in adolescents are overlapping with the 95% CIs observed in Trials 331-10-230/331-10-231/331-10-237 in adults, then similarity of efficacy between those populations will be established. In case the 95% CIs do not overlap but show better efficacy for adolescents, this will still be considered as a success for extrapolation.

Other efficacy endpoints: the FAS for adolescents and adults. Descriptive statistics (percentages) will be provided, and the 95% CI will be provided for response.

The definition of response in the statistical analysis plan (SAP) was aligned with the schizophrenia trials definition. In order to alleviate the fact that the CGI-I score is based on the new baseline for the roll-over trials, additional analysis was performed based on the criteria of a ≥ 30% decrease in PANSS Total Score only.

The primary analysis was based on the LOCF.

Sensitivity Analysis

The Observed Cases (OC) analysis was provided as sensitivity.

Mixed models for repeated measures were used as a sensitivity analysis based on all available data (OC dataset). The model will include fixed-effect factors of category (adolescents/adults), visit, category by visit interaction, and fixed effect covariates of baseline and baseline by visit interaction. The least squares mean differences between adolescents and adults in change from baseline at each common time point was provided with the 95% CI.

In addition, analysis using a population in adults using the same definition as for adolescents, i.e., for adults the population were subjects from Trials 331-10-230 and 331-10-231 who received brexpiprazole 2 mg or 4 mg and rolled over to Trial 331-10-237 with at least one observation for the PANSS Total Score in Trial 331-10-237 (Modified Analysis Set).

Handling of missing data: the main analysis was based on descriptive statistics for the LOCF approach. In addition, efficacy analyses were presented based on the OC. The OC dataset consisted of the actual observations recorded at each visit. The LOCF dataset included data recorded at a scheduled visit, i.e., all OC data, or, if no observation is recorded at that visit, data carried forward from the

previously scheduled visit. Baseline data (from Trials 331-10-230, 331-10-231, and 331-10-234) was not carried forward to impute missing values for the LOCF dataset. In addition, analysis by MMRM was performed.

Results

Participant flow

The overall discontinuation rate up to 32 weeks was lower in the adolescent population (14.6%) compared with the adult population (48.8%). The most frequently reported reason for discontinuation (≥ 5% of subjects) from the adolescent trial was withdrawal of consent (7.3%). The most frequently reported reasons for discontinuation (≥ 5% of subjects) from the adult trial were adverse events (18.8%), withdrawal of consent (16.5%), and subject met protocol-specified withdrawal criteria (5.8%).

Discontinuation rates due to lack of efficacy were similar between the adolescent and adult populations (2.1% vs 3.2%, respectively).

Baseline data

A total of 442 subjects, including 96 adolescents and 346 adults, were included in the FAS (Trial 331-10-236). Of the 96 adolescents that were treated, 44 were males (45.8%) and 52 were females (54.2%). The mean age, height, weight, and body mass index (BMI) of the subjects in the adolescent group was 15.3 years, 166.7 cm, 65.4 kg, and 23.4 kg/m^2, respectively. Of the 346 adults that were treated, 208 were males (60.1%) and 138 were Females (39.9%). The mean age, height, weight, and BMI of the subjects in the adult group was 38.6 years, 170.5 cm, 78.6 kg, and 27.0 kg/m^2, respectively. In terms of race, there were a higher number of subjects who were either Black or African American or Asian, and fewer subjects who were Hispanic or Latino in the adult population compared with the adolescent population.

Baseline disease characteristics: the baseline disease characteristics were similar for all parameters (comparison of mean [SD] for adolescents and adults, respectively): PANSS Total Score (100.6 [14.4] vs 95.8 [13.4]), PANSS Positive Subscale Score (24.1 [5.1] vs 24.9 [4.4]), PANSS Negative Subscale Score (25.8 [5.6] vs 23.8 [5.2]), and CGI-S score (4.7 [0.6] vs 4.9 [0.6]).

Outcomes and estimation

Primary Endpoint: Mean Change from Baseline in Positive and Negative Syndrome Scale Total Score

Table 2.7.3.3.1.2.1-1 Summary of Mean Change from Baseline in PANSS Total Score in Study 331-201-00185 - LOCF (Full Analysis Set)

Visit	Group	Change from Baseline					95% CI for Mean	
		N[a]	Mean	SD	Min	Max	Lower	Upper
Week 6	Adolescents	96	-23.29	16.54	-83.00	11.00	-26.64	-19.94
	Adults	346	-26.14	15.78	-88.00	22.00	-27.81	-24.48
Week 7	Adults	346	-26.64	16.50	-88.00	27.00	-28.39	-24.90
Week 8	Adults	346	-27.21	16.71	-88.00	23.00	-28.97	-25.44
Week 10	Adolescents	96	-26.98	17.00	-84.00	2.00	-30.42	-23.53
	Adults	346	-28.13	16.77	-88.00	23.00	-29.91	-26.36
Week 14	Adolescents	96	-28.75	17.70	-91.00	14.00	-32.34	-25.16
	Adults	346	-27.97	17.57	-88.00	23.00	-29.82	-26.11
Week 20	Adolescents	96	-31.99	19.39	-100.00	14.00	-35.92	-28.06
	Adults	346	-28.68	17.99	-88.00	23.00	-30.59	-26.78
Week 26	Adolescents	96	-32.70	20.33	-99.00	18.00	-36.82	-28.58
	Adults	346	-28.56	18.55	-88.00	23.00	-30.52	-26.60
Week 32	Adolescents	96	-34.07	20.17	-99.00	18.00	-38.16	-29.99
	Adults	346	-28.11	19.10	-87.00	23.00	-30.13	-26.09

CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

[a]Total number of treated subjects with both baseline and evaluation at the specific visit.

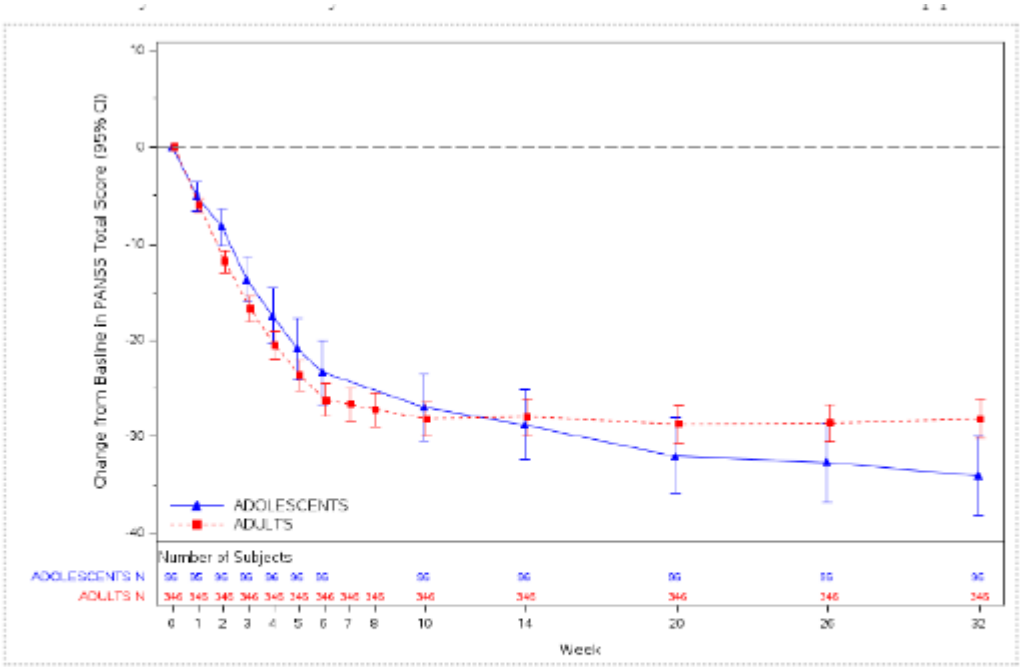


Figure 2.7.3.3.1.2.11 Mean Change from Baseline in PANSS Total Score by Visit in Study 331-201-00185 - LOCF (Full Analysis Set)

CI = confidence interval; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale.
Bars represent 95% confidence intervals.

The main analysis was conducted based on descriptive statistics for the LOCF approach as planned in the clinical protocol, however, the high rate of early termination in adult studies could affect the long-term efficacy. Therefore, additional analyses based on OC and mixed model repeated measures (MMRM) were performed.

Sensitivity Analyses:

Similar to the primary efficacy results, sensitivity analysis of mean change from baseline in PANSS Total Score based on OC by visit through Week 32 also showed overlapping CIs, with the exception of Week 2 for adolescents and adults.

Given that the longer-term data are from single-arm open-label trials, there are no long-term placebo data available to enable the placebo-based multiple imputation. In addition, in the long-term Trials 331-10-237 and 331-10- 236 subjects discontinuing the treatment discontinued from the trial without further efficacy assessments after the early termination visit. Consequently, the retrieved dropout multiple imputation method is not feasible.

In order to assess the impact of missing value on the outcome, a sensitivity analysis based on multiple imputation with a delta (shift) method was performed. In this sensitivity analysis, multiple imputation of missing values was performed by imputing progressively increasing delta values for the missing data points post discontinuation. The initial value of delta is 0 (simple multiple imputation), then increases by increments of 5 points until the 95% confidence interval for the difference between adults and adolescents excludes 0, for the MMRM mean changes through the entire follow-up period (32 weeks).

Additional analyses for the separate short-term and long-term follow-up were performed, including increasing delta to 15 points.

Results from multiple imputation on the entire follow-up period (32 weeks) shows that results are stable until adding a penalty of 12 points to the imputed value for the missing values on the PANSS total score scale, which would then provide results showing better outcome in the adolescents at Week 32. Of note,

the worst observed change from baseline at Week 32 was an increase of 11 points in adults and 7 points in adolescents, so the shift of 12 points is higher than the highest observed value.

Results from short-term follow-up (0 to 10 weeks) and a long-term follow-up (10 to 32 weeks): Given the small number of missing values in the early visits, the short-term model is similar to the main MMRM analysis provided in the CSR, showing larger improvement for adults up to Week 10. For the long-term analysis, results are similar to the main MMRM analysis provided in the CSR, showing a reduction of the difference between adults and adolescents over time with no difference at Week 32.

In addition, the multiple imputation as described for the entire follow-up period above was performed separately on the short-term and long-term follow-up periods, adding penalty delta shift to imputed missing values after dropout.
Given the small amount of missing data, the results for the short-term analysis are similar to the analysis taking into account the entire follow-up period.
For the long-term analysis, the results show better improvement for the adults versus adolescents for Week 10 and Week 14. The 95% confidence interval for the difference in change from baseline in PANSS total score contains 0 as of Week 20 for all delta (ranging from 0 to 15 points). At Week 32 with a delta of 15 points, the difference between adolescents and adults was −3.28 (95% CI: −8.20, 1.64), with better improvement for the adolescents.

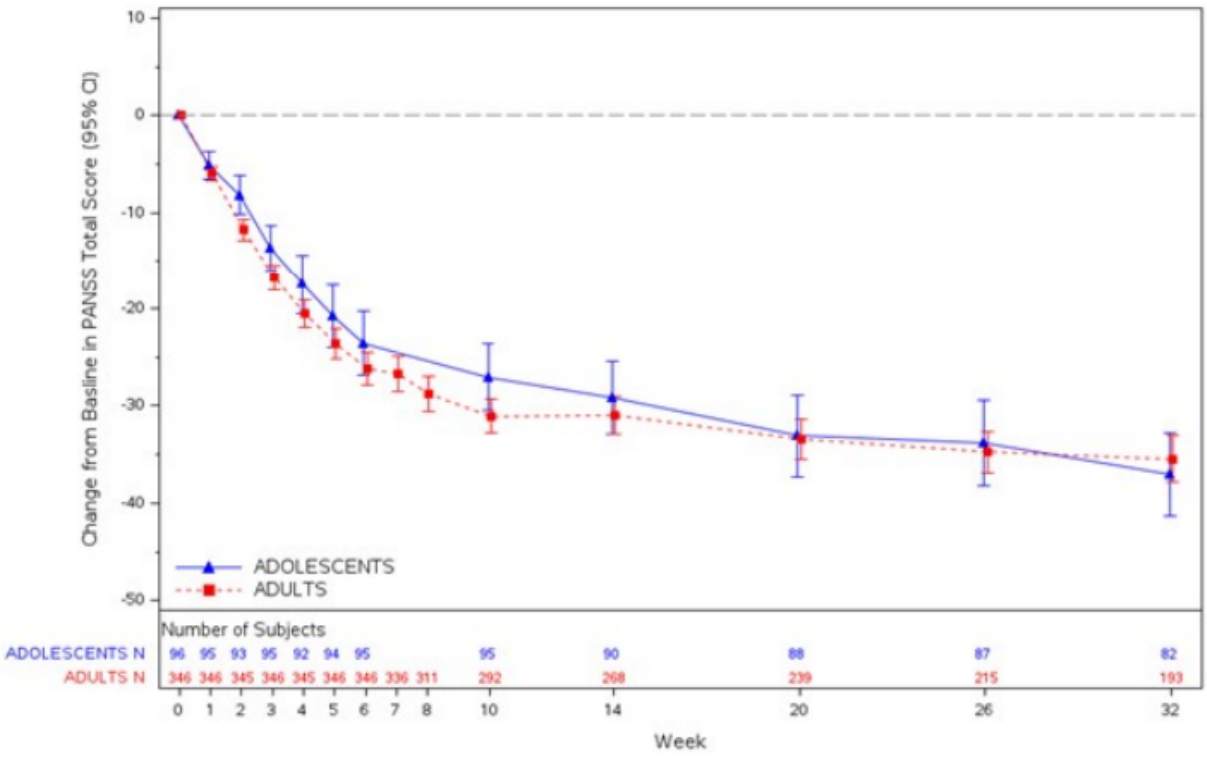


Figure 5.4.1.2-1 Mean Change from Baseline in PANSS Total Score by visit - Observed Cases (Full Analysis Set)

CI = confidence interval; LOCF = last observation carried forward; PANSS = positive and negative syndrome scale.
The bars represent 95% CI.

In terms of the change in PANSS Total Score for LOCF based on modified analysis set in which 9 subjects (2.6%) were excluded due to having no PANSS assessment in the adult rollover trial, results were similar to the primary analysis and do not change the overall conclusion.

Mixed models for repeated measures (MMRM) was also used as a sensitivity analysis based on all available data (OC dataset). Results indicate overlap of CIs between the adolescents and adults from

Week 10 to Week 32, indicating that the efficacy between the 2 populations is similar in the longer term (up to Week 32).

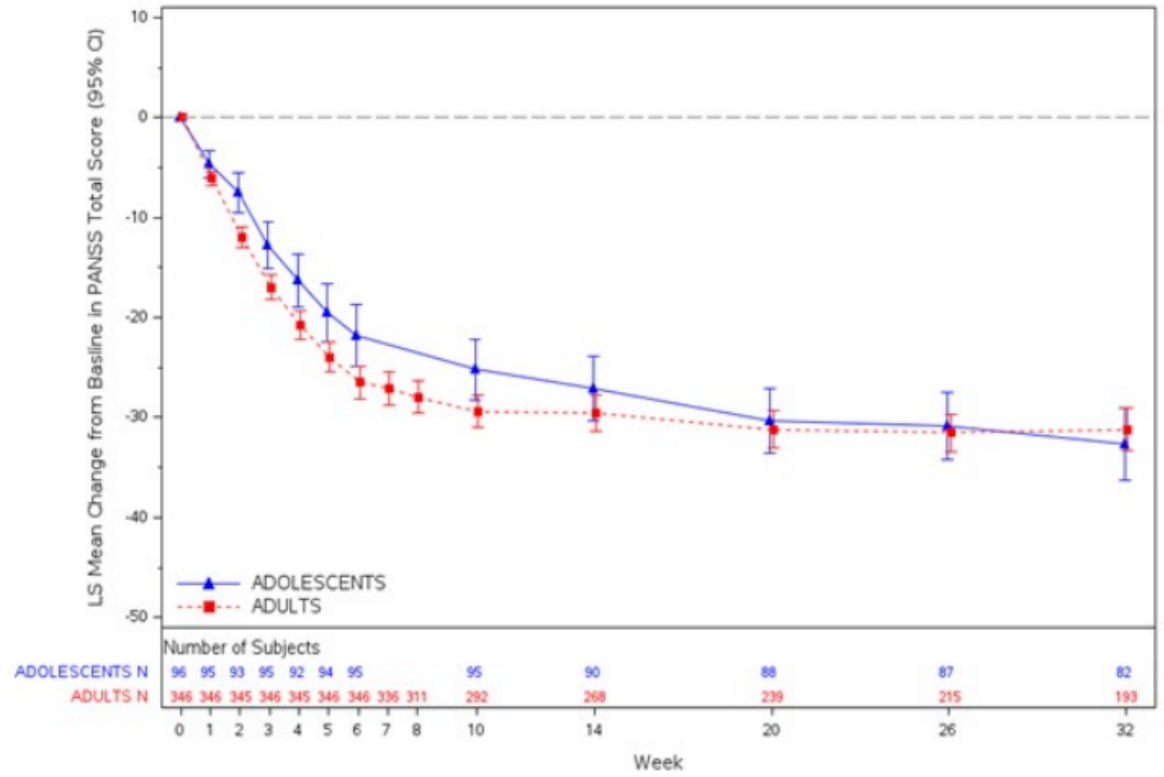


Figure 5.4.1.2-2 Least-Square Mean Change from Baseline in PANSS Total Score by visit - MMRM (Full Analysis Set)

CI = confidence interval; MMRM = mixed model repeated measures; PANSS = positive and negative syndrome scale.
The bars represent 95% CI. Derived from MMRM analysis with fixed effect of group (adolescent or adults), visit, group by visit interaction, Baseline, and baseline by visit interaction as covariate, and with an unstructured variance-covariance matrix structure.

SENSITIVITY ANALYSIS

A multiple imputation using direct Bernoulli sampling approach was used, imputing a response rate to the missing information from 0% to 100% in a stepwise manner. The response rate in adults, largely driven by the imputation, decreases to 41.0% (95% CI: 35.9%, 46.2%) at Week 32, while the response rate in adolescents continues to increase to 63.5% (95% CI: 53.9%, 73.2%) (Table 2.2-7).

As the imputed rate increases, the difference between adults and adolescents' groups gets smaller and the 95% confidence intervals overlap at Week 32 with an imputed response rate of 30%, which is yet much lower than the observed response rate at Week 32 in the adults (observed cases: 73.6%).

As expected, with an imputation rate of 70% (close to the observed cases results), the results are very similar for both groups with 73.7% (95% CI: 64.3%, 83.2%) for the adolescents and 72.1% (95% CI: 66.5%, 77.8%) for adults.

Other efficacy endpoints

-Overall discontinuation rates up to 32 weeks:

A total of 442 subjects, including 96 adolescents and 346 adults, were included in the FAS from Trial 331-10-236 and Trial 331-10-237, respectively.

The overall discontinuation rate up to 32 weeks was lower in the adolescent population (14.6%) compared with the adult population (48.8%).

-Discontinuation rates due to lack of efficacy up to 32 weeks.

Table 5.4.2.1-1 Reason for Discontinuation Up To 32 Weeks (Full Analysis Set)

	Adolescents (N = 96)	Adults (N = 346)	Total (N = 442)
Number of Subjects	**n (%)**	**n (%)**	**n (%)**
Treated	96 (100.0)	346 (100.0)	442 (100.0)
Ongoing[a]	81 (84.4)	177 (51.2)	258 (58.4)
Discontinued	14 (14.6)	169 (48.8)	183 (41.4)
Adverse Events	1 (1.0)	65 (18.8)	66 (14.9)
Lack Of Efficacy	2 (2.1)	11 (3.2)	13 (2.9)
Lost To Follow-Up	1 (1.0)	12 (3.5)	13 (2.9)
Non-Compliance With Study Drug [b]	1 (1.0)	0 (0.0)	1 (0.2)
Pregnancy [b]	1 (1.0)	0 (0.0)	1 (0.2)
Withdrawal of Consent	7 (7.3)	57 (16.5)	64 (14.5)
Physician Decision	0 (0.0)	4 (1.2)	4 (0.9)
Subject Met Protocol Specified Withdrawal Criteria[c]	0 (0.0)	20 (5.8)	20 (4.5)
Other[b]	1 (1.0)	0 (0.0)	1 (0.2)

Adolescent subjects: ongoing open-label phase 3 Trial 331-10-236.
Adult subjects: completed open-label phase 3 Trial 331-10-237.

[a]Includes the number of subjects who received at least 32 Weeks of treatment (6 Weeks of blinded IMP plus 26 Weeks of open-label brexpiprazole) as of the data cutoff date of 10 Oct 2023 in ongoing Trial 331-10-236 (adolescents) or completed Trial 331-10-237 (adults).

[b]Category only available for trial 331-10-236.

[c]Category only available for trial 331-10-237.

-Percent of subjects with treatment response (≥ 30% decrease in PANSS Total Score or CGI-I score of 1 or 2) by visit for the first 32 weeks of treatment with brexpiprazole (OC and LOCF).

Table 2.7.3.3.1.2.2.2-1 Summary of Proportion of Subjects with Response in Study 331201-00185 - LOCF (Full Analysis Set)

Visit	Group	N	n[a]	%	95% CI
Week 1	Adolescents	95	4	4.2	(1.2, 10.4)
	Adults	346	17	4.9	(2.9, 7.8)
Week 2	Adolescents	96	9	9.4	(4.4, 17.1)
	Adults	346	65	18.8	(14.8, 23.3)
Week 3	Adolescents	96	16	16.7	(9.8, 25.6)
	Adults	346	125	36.1	(31.1, 41.4)
Week 4	Adolescents	96	24	25.0	(16.7, 34.9)
	Adults	346	168	48.6	(43.2, 54.0)
Week 5	Adolescents	96	34	35.4	(25.9, 45.8)
	Adults	346	206	59.5	(54.2, 64.8)
Week 6	Adolescents	96	45	46.9	(36.6, 57.3)
	Adults	346	237	68.5	(63.3, 73.4)
Week 7	Adults	346	175	50.6	(45.2, 56.0)
Week 8	Adults	346	173	50.0	(44.6, 55.4)
Week 10	Adolescents	96	45	46.9	(36.6, 57.3)
	Adults	346	191	55.2	(49.8, 60.5)
Week 14	Adolescents	96	50	52.1	(41.6, 62.4)
	Adults	346	201	58.1	(52.7, 63.3)
Week 20	Adolescents	96	58	60.4	(49.9, 70.3)
	Adults	346	204	59.0	(53.6, 64.2)
Week 26	Adolescents	96	61	63.5	(53.1, 73.1)
	Adults	346	207	59.8	(54.5, 65.0)
Week 32	Adolescents	96	65	67.7	(57.4, 76.9)
	Adults	346	195	56.4	(51.0, 61.7)

CI = confidence interval; CGI-I = Clinical Global Impression-Severity of Illness Scale; PANSS = Positive and Negative Syndrome Scale; LOCF = last observation carried forward.

[a]Number of subjects with a reduction of ≥ 30% from baseline in PANSS Total Score or CGI-I Score of 1 or 2.

Results in subjects with response by LOCF and by OC indicate that the 95% CI does not overlap from week 3 to week 6 between adolescents and adults and that adults show greater efficacy compared to adolescents during this time frame.

As of Week 20, adolescents response rates are numerically higher than adults with overlapping 95% CIs. There is a drop-in response rate after week 6 due to the definition of response which includes CGI-I, evaluated as an improvement from baseline, considering the “new” baseline in the rollover trial (Table 5.4.2.3-1). To address this possibility, additional responder analyses based on the proportion of subjects with a reduction of ≥ 30% from baseline in PANSS Total Score (only) were performed. Results

indicate that the overlap in 95% CIs between the adolescent and adult populations was maintained for a majority of visits up to and including Week 32.

Efficacy analyses by Subgroups

Adolescents

Age group (< 15 years, ≥ 15 years old)

Results for the subgroup analysis of mean change from baseline in PANSS Total Score by visit by age group (< 15 years, ≥ 15 years old) for adolescents in Study 331-201-00185 are summarized below:

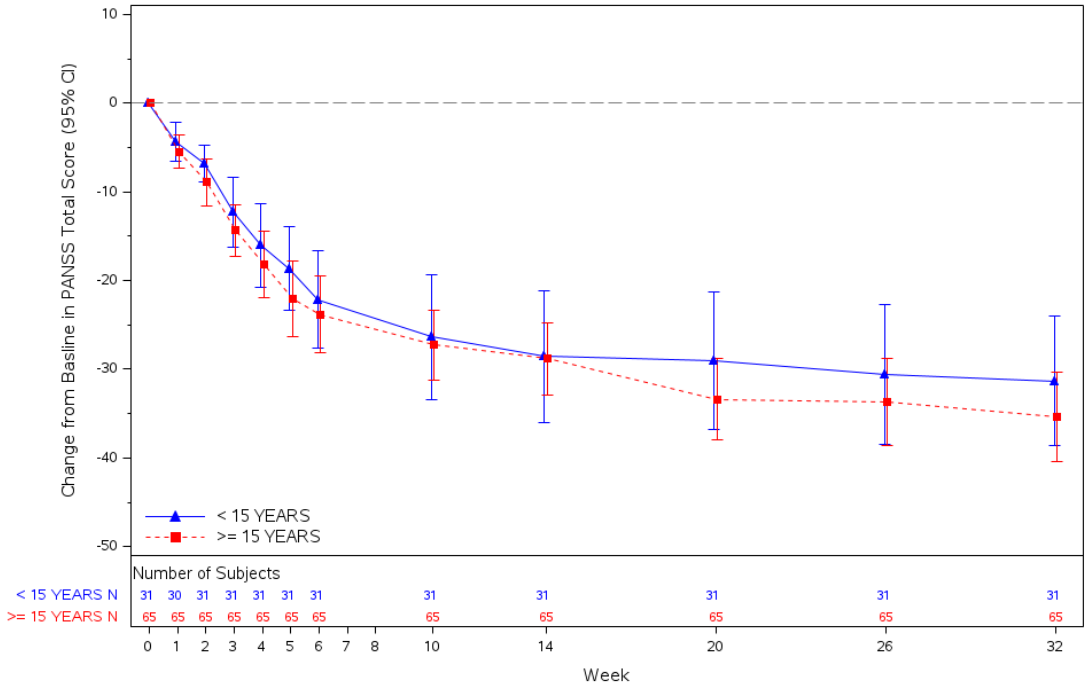


Figure 2.7.3.3.2.21 Mean Change from Baseline in PANSS Total Score in Adolescent Subjects by Age Group in Study 331-201-00185 -LOCF (Full Analysis Set)

CI = confidence interval; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale.
Bars represent 95% confidence intervals.

The results show that the 95% CIs overlapped with improvement from baseline in the subjects ≥ 15 years old at Week 32 (PANSS Total Score: -35.38 [-40.41; -30.36]) (Table 5.4.2.2.1-1). The 95% CI for subjects < 15 years old overlapped with the adults 95% CI at Week 32 (PANSS Total Score: -31.32 [-38.65; -24.00].

The efficacy in subjects ≥ 15 years old was higher than adults based on 95% CI at Week 32 with greater improvement for adolescents. These data must be interpreted in the context of small sample size in the by age subgroups of adolescents with wide confidence intervals. For reference: The change from baseline in PANSS Total Score for adults was - 28.11 [-30.13; -26.09].

Adult subgroups

Discontinuation Rates: Discontinuation rates in adult subjects were generally consistent across the 4 subgroups (duration of illness of ≤ 5 years in subjects age ≥ 40 or < 40 years, and duration of illness

of > 5 years in subjects age ≥ 40 or < 40 years), with discontinuation rates ranging from approximately 46% to 55%. The highest rate of discontinuation was in the subgroup with duration of illness ≤ 5yrs and age ≥ 40 (55.2%). Discontinuations due to lack of efficacy ranged from 1.9% to 3.9%, with the lowest incidence observed in subjects with duration of illness of > 5 years and age < 40 years, and similarly, by age only, in subjects < 25 years (0.0%).

Change From Baseline in PANSS Total Score and Proportion of Subjects With Response: change from baseline in PANSS Total Score in adult subjects by age group was mostly consistent across subgroups with the subjects < 25 years old showing numerically more improvement. The 95% CI for subjects < 25 years old overlaps with the adolescents at Week 32 suggesting similarity. For the subjects < 40, the overlap with adolescents is borderline (as for the adults overall) at week 32. Similar to the PANSS results, the response rates were consistent across subgroups with the subjects with duration of illness ≤ 5 years and age ≥ 40 showing a high response.

Comparison of Exposure and Exposure-Efficacy Relationships between Adolescents and Adults

Report 331-24-201 has been provided to compare the exposure and E/R relationship between adolescents and adults. Results showed that simulated brexpiprazole exposure were comparable between adolescents and adults, although the median Cmax,ss was slightly higher in adolescents. In line results were observed in the subgroup analysis in adolescents <15 years old and ≥15 years old.

The exposure/response relationship between adolescents and adults at Week 6 results comparable, with a slight difference in model predicted CFB in PANSS Total scores due to the difference in placebo effect parameter that is higher in adolescents. Subgroup analysis (< 15 years and ≥ 15 years) are in line with these results.

For further details on Report 331-24-201 see section 2.3.4.

Discussion on the study 331-201-00185

The MAH has conducted study 331-201-00185 to gain supportive evidence of maintenance of efficacy of brexpiprazole monotherapy based on extrapolation of data from adults and adolescents including 13-15 years.

Reference to the ICH E11A Guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022) and EMA's reflection paper on the use of extrapolation in the development of medicine for paediatrics (EMA/189724/2018) is made. However, it should be considered that the main assumption in applying an extrapolation strategy is similarity of disease and response so that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric and reference (adult or other paediatric) population.

In adolescents, schizophrenia may be preceded by prodromal cognitive impairment at a young age but these abnormalities have neither diagnostic specificity nor predictive value. With increasing age, symptoms increasingly resemble those of adults. However, negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning in adolescent patients. In addition, the disease tends to follow a more severe course, has lower response to treatment and a worse long-term prognosis than adult- onset schizophrenia.

In the study 331-201-00185, data from adolescent subjects who completed Trial 331-10-234 and rolled over to Trial 331-10-236 and adult subjects who completed Trial 331-10-230 or Trial 331-10-231 and rolled over to Trial 331-10-237 were compared based on the Full Analysis Set (FAS); 96 subjects were identified for the adolescent population and 346 subjects were identified for the adult population.

De novo subjects from Trials 331-10-236 (adolescents) and 33110237 (adults) were not included.

Hence, the extrapolation strategy is partial and based on observed data coming from the above mentioned studies.

Baseline disease characteristics are similar between adult and paediatric populations. When response to treatment is considered in the short term, the difference in the mean change of PANSS total score at week 6 is similar (mean change of around 20) in adult studies as compared to that obtained in the adolescents study 234.

The MAH concluded that results calculated using MMRM as a sensitivity analysis based on all available data (OC dataset) indicate overlap of CIs between the adolescents and adults from Week 10 to Week 32, indicating that the efficacy between the 2 populations is similar in the longer term (up to Week 32).

To assess the similarity of efficacy between adults and adolescents, the MAH considered that if the majority of the 95% CIs associated with the change from baseline in PANSS Total Score over 32 weeks of treatment in adolescents will overlap with the 95% CIs in adults the similarity will be established. This criterion was not clear since any equivalence margin was not defined; furthermore, each single visit for the comparison and not the temporal trend was considered for establish the similarity. Finally, the statistical analysis has not been considered fully appropriate and other sensitivity analyses have been requested to the MAH to better understand the possible differences between the two populations. Indeed, different temporal trends were observed based on the two analyses (last observation carried forward, LOCF) and observed case analysis.

The primary analysis was based on the LOCF approach, not showing a good overlapping of CIs between adolescents and adults in the early period and in particular in the maintenance period. A potential disadvantage of a single imputation method is that risks biasing the standard error downwards by ignoring the uncertainty of imputed values. Therefore, the confidence intervals for the treatment effect calculated using single imputation methods may be too narrow and give an artificial impression of precision that does not really exist (EMA/CPMP/EWP/1776/99 Rev. 1). In addition, the high rate of early termination in adults could affect the long-term efficacy. Therefore, if the use of retrieved dropout data is not feasible, a placebo-based multiple imputation method is considered more appropriate to handle missing data due to treatment discontinuation. In addition, the MAH used the mixed model for repeated measures (MMRM) as sensitivity analysis, however it was based only on available data that in case of many drop-outs may give biased estimates.
Therefore, the MAH has been requested to estimate the equivalence between adults and adolescents (with the 95% CI) considering the mean changes through the all follow-up period (32 weeks) using the MMRM with retrieved dropout or placebo-based multiple imputation method for handling missing data. In addition, the MAH has been requested to analyse two different periods separately, a short term follow-up (0-10 weeks) and a long term follow-up (10-32 weeks).
Given that a retrieved dropout multiple imputation method was not feasible, The MAH performed a sensitivity analysis based on multiple imputation with a delta (shift) method. The results are considered valuable.

Results in subjects with response (≥ 30% decrease in PANSS Total Score or CGI-I score of 1 or 2) by visit for the first 32 weeks of treatment with brexpiprazole by LOCF and by OC indicate that the that adults show greater efficacy compared to adolescents from early weeks and up to week 20. The better response at earlier timepoints in adults could be expected when compared to adolescents due to a potential more difficult disease to be treated. However, the same considerations raised for the primary endpoint apply to key the secondary endpoint, i.e. subjects with treatment response (percent of subjects ≥ 30% decrease in PANSS Total Score or CGI-I score of 1 or 2). Therefore, the MAH has been requested to perform a sensitivity analysis using retrieved dropout or placebo-based multiple imputation method for handling missing data through the entire follow-up period (32 weeks) and short/long term follow-up separately.

Results from subgroups of adults show some difference in similarity of PANSS total score response as compared with adolescents in particular for adults <40 years.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted an extension of indication for Rxulti for the “treatment of schizophrenia in adolescents aged 13 years and older”.

As known, the aim of conventional antipsychotic treatment could be acute treatment primarily to control positive symptoms, or maintenance treatment to consolidate stabilized control of symptoms and to prevent exacerbations.

Schizophrenia is very rare in pre-pubertal children and is more likely to be associated with chromosomal/cytogenetic variations. However, when it does occur, schizophrenia in pre-pubertal children is comparable at the symptom level to schizophrenia in adults. In adolescents, it may be preceded by prodromal cognitive impairment at a younger age, but these abnormalities have neither diagnostic specificity nor predictive value. With increasing age, symptoms increasingly resemble those of adults. However, there are a number of significant differences in the typical clinical presentation, severity and natural course of schizophrenia in adolescents compared to adults: negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning in adolescent patients; the disease tends to follow a more severe course, to have a lower response to treatment and a worse long-term prognosis than adult onset schizophrenia.

Because of the difficulties in diagnosis and low prevalence in younger children, it is not considered necessary to perform clinical studies in children under the age of 13 years; a waiver was granted by PDCO (opinion PIP EMEA-001185-PIP01-11).

To support the claimed indication the MAH has performed the following trials for efficacy:

- Trial 331-10-234 (completed): phase 3 short term (6 weeks) clinical trial in paediatric patients (13-17 years old);
- Trial 331-10-236 (currently ongoing): phase 3 long term (24 months) clinical trial including efficacy endpoints as secondary, in paediatric patients (13-17 years old);
- Study 331-201-00185 (completed): paediatric extrapolation study based on observed data in adults and adolescents.

The development could be considered compliant with the requirements of the EMA guideline as specified in the section dedicated to paediatrics, reporting that “efficacy in acute treatment should be demonstrated in at least one short term trial of 4-6 weeks' duration. Provided pharmacokinetic data for the different age groups are assessed and short-term efficacy is similar to adults, data on maintenance of effect for antipsychotic drugs may be extrapolated from adults to adolescents as of the age of 15 years. Alternatively, pre- or post-marketing long term safety studies in children and adolescents could be structured to include also efficacy endpoints to support extrapolation of long-term efficacy from 13 years onwards”. The cut-off lower age at 13 years reflects the waiver granted by PDCO as well as CHMP relevant guideline.

Based on this, in order to establish maintenance of Rxulti effect, the MAH is conducting a long-term OL study having efficacy endpoints as secondary and as further support a partial extrapolation study was conducted.

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.

Criteria for diagnosis of schizophrenia (DSM V) are adequate. 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. 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 was made, which is supported and it is consistent with EMA guideline (EMA/CHMP/40072/2010/Rev1) recommendation in view of the fact that clinical features and incidence of schizophrenia may differ between these two strata; the higher percentage of subjects in the ≥ 15-year-old age group (68.0%) as compared to the < 15-year-old age group is expected.

Trial 331-10-236 is an ongoing long-term (24-month), open-label trial designed to evaluate the long-term safety, tolerability, and measurements of efficacy of brexpiprazole in adolescent subjects, ages 13 to 17 years, with a DSM5 diagnosis of schizophrenia including subjects that received prior brexpiprazole, that had received aripiprazole, that received prior placebo, and also a subgroup of de novo subjects.

First the MAH submitted results from an interim analysis (data cutoff date: 10 Oct 2023) including 85.4% of the subjects in the safety analysis set exposed to open-label brexpiprazole for 6 months (mean daily dose of 2.475 mg for any exposure) and a total of 97.6% included in the efficacy analysis set as follow: 96 subjects (97.0%) that received prior brexpiprazole, 87 subjects (97.8%) that had received aripiprazole, 85 subjects (97.7%) that received prior placebo, and all 20 (100.0%) de novo subjects. However, since the data cutoff date was 10 Oct 2023, the MAH was requested to provide an update of efficacy and safety data within the LOQ. A more recent update of efficacy data has been provided with a cut-off date of 13 September 2024. A total of 168 subjects have completed the study, including 28 additional subjects since the previous 10 October 2023 data cut-off date, and 12 subjects are currently ongoing in Trial 331-10-236. A total of 288 (97.6%) subjects have been analysed for efficacy.

Moreover, the DMC open session minutes and the DMC recommendation of the most recent DMC meeting (25 July 2024) have been provided by the MAH. Efficacy data were presented for the ongoing Trial 331-10-236 based on the data cut-off date of 15 May 2024. The DMC unanimously concluded that the trial could continue without modification based on the most recent data presentation.

The study design is open-label and only includes efficacy endpoints as secondary being the primary aim safety; however, it could be seen as appropriate in the context of paediatric schizophrenia development being in line with the relevant EMA GL referring to the possibility that “pre- or post-marketing long term safety studies in children and adolescents could be structured to include also efficacy endpoints to support extrapolation of long-term efficacy from 13 years onwards”.

Efficacy data and additional analyses

The primary efficacy endpoint of the 331-10-234 trial was the change from baseline to Week 6 in PANSS Total Score. This is a composite measure of schizophrenia symptoms (including positive and negative) and also an accepted measurement scale in schizophrenia trials.

The study results showed LS Mean (SE) Change at Week 6 in PANSS of –22.75, -23.95 and –17.42 for brexpiprazole, aripiprazole and PLB, respectively; PANSS improvement as compared with the placebo

group was statistically significant with LS mean difference between Brex and PLB of −5.33 [95% CI: −9.55, −1.10], p = 0.0136). A reduction of at least 15 points and up to 20 points on average at the PANSS scale is considered clinically relevant. However, the LS mean difference was lower than the assumption in treatment difference of -7.4 points made for sample size calculation. Thus, the results highlight that the impact of brexpiprazole short treatment on PANSS is of limited effect size over PLB response. It is however known that in recent trials in schizophrenia, the difference in efficacy between active treatments and placebo has tended to be smaller than the differences seen in the past due to a high PLB response. Of note a better trend is noted in the aripiprazole arm as compared to brexpiprazole although yet lower than the treatment difference used for sample size. Hence, the clinical relevance of these short term study results is uncertain however a high PLB response is noted and importantly due to the chronic course of schizophrenia and a continued need for treatment, the clinical relevance of the treatment effect should be seen in the context of long term treatment and of adolescents as target population characterized by a more difficult to treat disease and to achieve response.

Subjects enrolled in 331-10-236 trial, all subjects (efficacy set) had a decrease in the mean (SD) change of −19.18 (15.10), −25.87 (17.39), and −19.12 (17.61) from baseline in PANSS Total Score at Month 12, Month 24, and last visit, respectively; hence, data from long term treatment up to 24 months shows a consistent decrease in the PANSS score and a positive impact on symptoms.

Since the clinical features and incidence of schizophrenia may differ between strata, analysis of the primary endpoint (PANSS total score) was performed stratified by age (e.g. 13-15 years versus 16-18 years). Results are pointing out to inconsistent 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 (change of -22.98 in brexpiprazole and -14.92 in PLB with LS Mean Difference of -8.05, 95% CI -13.3, -2.80); but a dismal difference with large uncertainty was seen in the <15-year-old age subgroup (change of -20.62 in brexpiprazole with LS Mean Difference from PLB of -0.10, 95% CI-7.41,7.21). Although the results were obtained from subgroups limited in size particularly the subgroup of subjects under 15 years of age, this finding may reflect the difficulty of treating patients under 15 years of age, as early onset of schizophrenia is usually associated with a more severe/difficult to treat course, especially in the first weeks of treatment; also a different response of placebo is noted.

Results from subgroup analysis by age cut-offs obtained in the long-term trial, showed similar improvements in PANSS total score across the two different subgroups with a mean change of PANSS score of roughly 19-20 at last visit noting de novo subgroup showing a better change.

In the older subgroup (aged 15 to 17), a similar short-term response as in adults was observed (PANSS: -8.05 [-13.3, -2.80]). This is not unexpected since they are closer to the adult population. Therefore, to establish maintenance of effect, and considering that PK data for the different age groups are as would be expected, data may be extrapolated from adults to adolescents as of the age of 15 years, per EMA guidance (EMA/CHMP/40072/2010 Rev.1).

Regarding the subgroup 13-14 years, treatment effect is difficult to obtain since early onset schizophrenia is usually associated with a more severe course and a more prolonged treatment period would be required to achieve response. However, the observed placebo response in the subgroup of patients 13-14 years of age would be also compatible with a lack of efficacy of brexpiprazole. Considering that short-term effects in children below 15 years of age are not yet substantiated, and extrapolation of long-term effects from adults to children below 15 years of age is not straightforward, the MAH has been requested to further justify the clinical benefit in adolescents below 15 years. The MAH's response included some concise and valid considerations on recognition of the disease in adolescents <15 years of age with available diagnostic criteria, unmet medical need, efficacy results from both the short-term trial (331-10-234) and the ongoing 2-year open-label paediatric extension trial (331-10-236), including

updated data from Trial 331-10-236 (data cutoff date 13 September 2024) and similarity of safety profile based on observed TEAEs in adult vs younger adolescent population (< 15 years of age).

Change from baseline in PANSS total score observed in the younger age group (13-14 years old subjects) compared with the older age group (15-17 years old subjects) in the short-term trial (331-10-234) is consistent with the results observed for the aripiprazole arm of this trial.

The open-label paediatric extension trial (331-10-236) demonstrates to date (13 Sept 2024) continued symptom improvement and no change in brexpiprazole safety profile. These findings are similar to what was observed in the adult open-label extension study for brexpiprazole (CSR 331-10-237).

Keeping in mind that according to CHMP guidance (EMA/CHMP/40072/2010, brexpiprazole studies included an adequate representation of patients of each age range to reflect heterogeneity of the paediatric schizophrenia patient population, sample size of children aged 13-14 years was small and subgroup analyses were conducted post-hoc, it is considered that the results for the primary endpoint in the whole paediatric population, the consistency of short- and long-term treatment effects across age groups and biological plausibility all support the credibility of beneficial effect and extrapolation of efficacy results to the younger paediatric population.

Considering the two components of the primary outcome PANSS total score, results from the short term trial highlight only a limited impact of the treatment on negative symptoms as compared to the effect on positive symptoms (PANSS positive subscale scores at week 6, LS mean difference at Week 6 = −1.44 [95% CI: −2.65, −0.22], p = 0.0205 with nominal p-value < 0.05; PANSS Negative Subscale scores at Week 6, LS mean difference = −0.88 [95% CI: −2.04, 0.28], p = 0.1360, numerical change (not nominal p reached). These results could be expected from a clinical perspective since achieving an impact on PANSS Negative subscale scores (MMRM) is challenging in the short term, representing a known difficult clinical symptom to be impacted by treatment in adolescent schizophrenic patients.

Results from the long-term trial are somehow reassuring since improvement in both symptoms (PANSS Positive and Negative sub-scores) are impacted showing a similar trend in the mean change from baseline through Month 24.

Results from secondary endpoints at week 6 show some positive impact of the treatment on symptoms (excluding negative symptoms) and minimal impact on the Clinical Global Impression-Severity of Illness Scale (CGI-S, MMRN) scores. Results 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).

However, in the long-term trial, severity of illness, as measured by CGI-S improved from baseline to last visit for both rollover and de novo subjects thus providing support that an impact could be seen with a longer treatment. Moreover, subjects experienced continuous improvement in psychological, social, and school functioning as evaluated by the CGAS which is of value.

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 in the short-term trial and confirmed in the long term. In fact, a high percentage of subjects (68.8%, 83.6%, and 70.8%) scored ‘much’ or ‘very much’ improvement on the CGI-I during the open-label treatment period at Month 12, Month 24, and Last Visit. Of note, the improvement was sustained through the study, with lower scores in the last months of treatment.

Importantly, a high proportion of patients were considered responders at month 24 in 331-10-236 trial, with 112 (83.6%) of subjects showing a ≥ 30% improvement from baseline in PANSS Total Score or having a CGI-I Score of 1 or 2.

Overall, the positive effect across different efficacy outcomes could be supported. Moreover, in order to support brexpiprazole as maintenance treatment, the MAH has been requested to provide available data on exacerbations (positive and negative symptoms). The MAH highlighted that schizophrenia exacerbations (positive and negative symptoms) were not formally defined in the 331-10-236 trial protocol. Available data on exacerbations of schizophrenia are however captured in subjects that withdrew from the trial due to lack of efficacy and in subjects who experienced TEAEs of schizophrenia (including verbatim terms: schizophrenia exacerbation, exacerbation of schizophrenia, worsening/increase of symptoms of schizophrenia, schizophrenia/worsening of symptoms, exacerbation of paranoid schizophrenia, increase of schizophrenia symptoms) in Trial 331-10-236.

In support of the extension of indication, the MAH is providing data from a paediatric extrapolation study (Study 331-201-00185) to support the maintenance of efficacy in adolescents.

Reference to the ICH E11A Guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022) and EMA's reflection paper on the use of extrapolation in the development of medicine for paediatrics (EMA/189724/2018) is made. The main assumption in applying an extrapolation strategy is similarity of disease and response so that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric and reference (adult or other paediatric) population.

In adolescents, schizophrenia may be preceded by prodromal cognitive impairment at a young age but these abnormalities have neither diagnostic specificity nor predictive value. With increasing age, symptoms increasingly resemble those of adults. However, negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning in adolescent patients. In addition, as said, earlier onset schizophrenia tends to follow a more severe course, has lower response to treatment and a worse long-term prognosis than adult-onset schizophrenia.

In the study 331-201-00185, data from adolescent subjects who completed Trial 331-10-234 and rolled over to Trial 331-10-236 and adult subjects who completed Trial 331-10-230 or Trial 331-10-231 and rolled over to Trial 331-10-237 were compared based on the Full Analysis Set (FAS). Hence, the extrapolation strategy is partial and based on observed data coming from the above-mentioned studies.

Baseline disease characteristics between adult and paediatric populations were similar.

When response to treatment is considered in the short term, the difference in the mean change of PANSS total score at week 6 is similar (mean change of around 20) in adult studies as compared to that obtained in the adolescent study 234.

Comparison of exposure and E/R relationship between adolescents and adults was provided (Report 331-24-201). Results showed that simulated brexpiprazole exposure were comparable between adolescents and adults, although the median Cmax,ss was slightly higher in adolescents; the exposure/response relationship between adolescents and adults at Week 6 results comparable, with a slight difference in model predicted CFB in PANSS Total scores due to the difference in placebo effect parameter that is higher in adolescents. Subgroup analysis (< 15 years and ≥ 15 years) are in line with these results.

The MAH concludes that results calculated using MMRM, as a sensitivity analysis based on all available data (OC dataset), support the overlapping of CIs between the adolescents and adults from Week 10 to Week 32, indicating that the efficacy between the 2 populations is similar in the longer term (up to Week 32). To define the similarity of efficacy between adults and adolescents, the MAH considered that if the majority of the 95% CIs associated with the change from baseline in PANSS Total Score over 32 weeks of treatment in adolescents will overlap with the 95% CIs in adults the similarity will be established. However, this criterion was not clear since no equivalence margin was defined; furthermore, each single visit for the comparison and not the temporal trend was considered for establish the similarity.

Upon request, the MAH conducted further analysis to estimate the equivalence between adults and adolescents (with the 95% CI) considering the mean changes through the entire follow-up period (32 weeks) and using the MMRM with retrieved dropout or placebo-based multiple imputation method for handling missing data. In addition, the MAH analysed two different periods separately, a short-term follow-up (0-10 weeks) and a long-term follow-up (10-32 weeks).

The same considerations raised for the primary endpoint applied to the key secondary endpoint, i.e. subjects with treatment response (percent of subjects ≥ 30% decrease in PANSS Total Score or CGI-I score of 1 or 2).

As it was not possible to perform retrieved dropout or placebo-based multiple imputation methods for handling missing data, the MAH performed a sensitivity analysis based on multiple imputation with a delta (shift) method and on multiple imputation according to direct Bernoulli sampling approach.

The results up to Week 6 are similar to the main analysis due to the very low number of missing values, showing larger response rate for adults than for adolescents. At week 32, where missing values in adults is higher than for adolescents, the 95%CI of the response rate for adults and adolescents overlap suggesting no major differences between age groups.

2.4.4. Conclusions on the clinical efficacy

Results from the short-term study 331-10-234 suggest an overall positive effect of brexpiprazole in improving symptoms of schizophrenia in adolescents aged from 13 to 17 years. However, when looking at age subgroups (i.e. <15 years of age and >15 years of age), while clinical effect of brexpiprazole is confirmed in the older age group, a dismal effect with large uncertainty is found in the younger patient population.

Further, overall, data from long term treatment up to 24 months shows a consistent decrease in the PANSS score and a positive impact on symptoms, with no meaningful difference was seen in PANSS Total Score across age groups.

Keeping in mind that according to CHMP guidance (EMA/CHMP/40072/2010), brexpiprazole studies included an adequate representation of patients of each age range to reflect heterogeneity of the paediatric schizophrenia patient population, sample size of children aged 13- 14 years was small and subgroup analyses were conducted post-hoc, it is considered that the results for the primary endpoint in the whole paediatric population, the consistency of short- and long-term treatment effects across age groups and biological plausibility all support the credibility of beneficial effect and extrapolation of efficacy results to the younger paediatric population.

2.5. Clinical safety

Introduction

The safety and tolerability of brexpiprazole was evaluated in adolescent subjects aged 13 to 17 years in 4 phase 3 clinical trials.
The brexpiprazole paediatric schizophrenia clinical developmental program for safety consists of 2 phase 3 trials in this adolescent population: a 6-week double-blind placebo-controlled, active-referenced trial to assess efficacy and safety of brexpiprazole (completed Trial 331-10-234) and a 24-month trial to assess long-term safety and tolerability of brexpiprazole (ongoing; Trial 331-10-236). These are considered the pivotal trials.
To present the full paediatric safety database for brexpiprazole in paediatric subjects 13 to 17 years

old, safety data are also presented from 2 completed phase 3 trials to support short-term safety (Trial 331-201-00148) and long-term safety and tolerability (Trial 331-201-00191) of brexpiprazole in paediatric subjects 13 to 17 years old with irritability associated with autism spectrum disorder (ASD). These could be considered as supportive.

The treatment groups tabulated for the short-term controlled trials (331-10-234 and 331-201-00148) are as follows:

- Schizophrenia: Brexpiprazole 2 to 4 mg/day and Placebo
- ASD: Brexpiprazole 1 to 3 mg/day and Placebo
- Total (both indications pooled): All Brexpiprazole and Placebo

For subgroup analyses, data are presented as Total (all indications pooled): All Brexpiprazole and Placebo.

For the long-term trials (331-10-236 and 331-201-00191), data are presented overall (pooled) across doses, treatment duration, and prior treatment. In addition, schizophrenia and ASD groups are shown separately in the tabulated presentation as follows:

- Schizophrenia: Brexpiprazole 1 to 4 mg/day
- ASD: Brexpiprazole 1 to 3 mg/day
- Total (both indications pooled): All Brexpiprazole

An overview of these trials is presented in Table below.

Overview of Phase 3 Clinical Trials for Safety Assessment of Brexpiprazole in Paediatric Subjects

Trial Number	Type	Indication	Age	Number of Subjects in the Safety Analyses
331-10-234[a]	Short-term double-blind	Schizophrenia	13-17 years	110 (brexpiprazole) 104 (placebo)
331-201-00148	Short-term double-blind	Irritability associated with ASD	5-17 years[b]	9 (brexpiprazole) 13 (placebo)
331-10-236[c]	Long-term open label: rollover from 331-10-234 and de novo subjects	Schizophrenia	13-17 years[d]	294 (brexpiprazole)
331-201-00191	Long-term open label: rollover from 331-201-00148	Irritability associated with ASD	5-17 years[b,d]	20 (brexpiprazole)

ASD = autism spectrum disorder.

[a]An aripiprazole arm was included in this trial as an active reference for assay sensitivity.

[b]Only subjects 13 to 17 years were included in the safety analyses.

[c]Ongoing trial. Includes data collected prior to the cut-off date (10 Oct 2023).

[d]Subjects turning 18 years old during the parent trial were allowed to enter the rollover trial.

Subject sample

The Enrolled Sample comprises all subjects who signed informed consent and enrolled in the trial.

The Randomized Sample includes all subjects who were randomized in the short-term controlled trials (331-10-234 and 331-201-00148). Subjects were considered randomized when they were assigned a treatment number through the randomization scheme.

The Safety Sample includes all subjects who received at least 1 dose of IMP in the respective trial.

The Randomized Sample (for short-term controlled trials) and Enrolled Sample (for long-term open-label trials) are used for subject disposition and summaries of demographic and baseline characteristics unless otherwise specified.

All safety analyses are based on the Safety Sample.

Patient exposure

The safety analysis includes all subjects who received at least 1 dose of IMP. Due to differences in the nature of the trials, safety analyses are performed for each of the following pooled data sets (short-term controlled trials and long-term open label trials)

Short-term controlled trials

This data set includes 2 completed phase 3 double-blind placebo-controlled trials (331-10-234 and 331-201-00148) with treatment durations of 6 weeks and 8 weeks, respectively. In Trial 331-10-234, brexpiprazole was given in flexible doses of 2 to 4 mg/day for a duration of 6 weeks. In Trial 331-201-00148, brexpiprazole was given in flexible doses based on body weight for a duration of 8 weeks.

A total of 119 subjects were exposed to ≥ 1 dose of brexpiprazole in the pooled short-term controlled trials, 110 subjects in the schizophrenia trial and 9 subjects in the ASD trial. Overall, 107 (89.9) % of subjects were exposed to brexpiprazole for ≥ 42 days. The mean dose of brexpiprazole taken by 119 subjects in the pooled trials was 2.2 mg/day. At the end of the treatment periods in the combined trials, 42.0% of subjects were taking doses of 2 mg, 22.7% were taking 3 mg, and 33.6% were taking 4 mg.

Long-Term open-label trials

This data set includes long-term safety data from subjects in Trial 331-10-236 (24 months) and Trial 331-201-00191 (26 weeks). In the long-term Trial 331-10-236, subjects received flexible doses of 1 to 4 mg/day over a 24-month treatment period. In Trial 331-201-00191, subjects received brexpiprazole for a 26-week period in doses determined by body weight.

Overall, 314 subjects were exposed to ≥ 1 dose of brexpiprazole in the long-term trials. In the 24-month schizophrenia trial, 294 subjects were exposed to ≥ 1 dose of brexpiprazole, and mean treatment duration was 71.8 days. In the ASD trial, 20 subjects were exposed to ≥ 1 dose of brexpiprazole, and mean treatment duration was 19.3 days. The overall mean dose of brexpiprazole taken by 314 subjects in the pooled trials was 2.5 mg/day. The mean dose in each trial was 2.5 mg in the schizophrenia trial and 2.2 mg in the ASD trial.

Table 2.7.4.1.2.2-1 Brexpiprazole Duration of Exposure - Long-Term Open-Label Trials (Safety Sample)			
	Schizophrenia Brex 1-4 mg (N = 294)	**ASD Brex 1-3 mg (N = 20)**	**Total All Brex (N = 314)**
Treatment duration (days)			
n	294	20	314
Mean (SD)	71.8 (33.4)	19.3 (8.8)	68.4 (34.8)
Min,Max	1, 112	1.3, 28	1, 112
Treatment duration (days)			
1 - 27 days	294 (100.0)	20 (100.0)	314 (100.0)
≥ 28 days (4 weeks)	287 (97.6)	18 (90.0)	305 (97.1)
≥ 62 days (2 months)	273 (92.9)	15 (75.0)	288 (91.7)
≥ 93 days (3 months)	269 (91.5)	15 (75.0)	284 (90.4)
≥ 124 days (4 months)	264 (89.8)	14 (70.0)	278 (88.5)
≥ 155 days (5 months)	257 (87.4)	11 (55.0)	268 (85.4)
≥ 186 days (6 months)	251 (85.4)	2 (10.0)	253 (80.6)
≥ 279 days (9 months)	229 (77.9)	0 (0.0)	229 (72.9)
≥ 372 days (12 months)	205 (69.7)	0 (0.0)	205 (65.3)
≥ 465 days (15 months)	192 (65.3)	0 (0.0)	192 (61.1)
≥ 558 days (18 months)	172 (58.5)	0 (0.0)	172 (54.8)
≥ 651 days (21 months)	150 (51.0)	0 (0.0)	150 (47.8)
≥ 730 days (2 Years)	19 (6.5)	0 (0.0)	19 (6.1)
≥ 744 days (24 months)	5 (1.7)	0 (0.0)	5 (1.6)
Any exposure	294 (100.0)	20 (100.0)	314 (100.0)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (≥ 13 years old).
Note: Duration of exposure = (last IMP date – first IMP date) + 1.

Upon request the MAH provided updated safety data from the 331-10-236 study and submitted the most recent safety data with data cut-off 13 Sept 2024, DMC Open-session Minutes, DMC Recommendation.

Disposition

Short-term Controlled Trials

A total of 237 subjects (excluding 102 subjects randomized to aripiprazole in Trial 331 10-234) were randomized in the short-term controlled trials: consisting of 120 subjects randomized to brexpiprazole treatment and 117 subjects randomized to placebo. Safety data were analyzed for 236 randomized subjects who had received ≥ 1 dose of investigational medicinal product (IMP), including 119 in the all brexpiprazole group and 117 in the placebo group.

Overall, 19 (8.0%) subjects randomized to treatment in the short-term controlled trials were discontinued.

The majority of subjects who discontinued from the trials were withdrawn by a parent or guardian (7 subjects). A total of 4 subjects discontinued due to an AE, including 2 in the brexpiprazole group in the ASD trial and 2 in the placebo group in the schizophrenia trial. Lack of efficacy was the reason for discontinuation of 4 subjects who were receiving placebo, including 3 in the schizophrenia trial and 1 in the ASD trial. No subjects in the brexpiprazole group were discontinued due to lack of efficacy.

Disposition and reasons for discontinuation - Short-Term Controlled Trials - Randomized Sample						
	Schizophrenia		ASD		Total	
	Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=10)	Placebo (N=13)	All Brex (N=120)	Placebo (N=117)
Number of Subjects	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Randomized	110 (100.0)	104 (100.0)	10 (100.0)	13 (100.0)	120 (100.0)	117 (100.0)
Completed	107 (97.3)	92 (88.5)	7 (70.0)	12 (92.3)	114 (95.0)	104 (88.9)
Discontinued	3 (2.7)	12 (11.5)	3 (30.0)	1 (7.7)	6 (5.0)	13 (11.1)
Lost to follow-up	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Adverse events	0 (0.0)	2 (1.9)	2 (20.0)	0 (0.0)	2 (1.7)	2 (1.7)
Subject met withdrawal criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject was withdrawn from participation by the investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent to participate	1 (0.9)	2 (1.9)	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.7)
Withdrawal by parent/guardian	1 (0.9)	5 (4.8)	1 (10.0)	0 (0.0)	2 (1.7)	5 (4.3)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Site terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	0 (0.0)	3 (2.9)	0 (0.0)	1 (7.7)	0 (0.0)	4 (3.4)
Noncompliance with study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ASD = autism spectrum disorder; Brex = brexpiprazole; IMP = investigational medicinal product.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13-17 years old).
[a]Percentages are based on the number of subjects in randomized sample.

Long-term Open-label Trials

A total of 314 subjects were exposed ≥ 1 dose of IMP in the long-term open-label trials and were included in the safety analyses: 294 in the schizophrenia trial and 20 in the ASD trial (SCS Table 2.7.4.1.4.2-1). At the data cutoff date (10 October 2023), 152 (48.4%) subjects had completed the trial, 109 (34.7%) subjects had discontinued, and 53 (16.9%) subjects remained part of the ongoing trial.

The majority of subjects in the pooled trials discontinued due to withdrawal of consent by the subject (27 [8.6%] subjects) or withdrawal by a parent or guardian (26 [8.3%] subjects). A total of 12 (3.8%) subjects discontinued due to an AE, including 9 (3.1%) in the schizophrenia trial and 3 (15.0%) in the ASD trial. Lack of efficacy was the reason for the discontinuation of 7 subjects (2.2%) which included 6 (2.0%) in the schizophrenia trial and 1 (5.0%) in the ASD trial. Among the 17 (5.4%) subjects who were lost to follow-up, 16 (5.4%) were in the schizophrenia trial and 1 (5.0%) was in the ASD trial.

Disposition and reasons for discontinuation - Long-Term Open-Label Trials - Safety Sample			
	Schizophrenia Brex 1-4 mg (N = 294)	**ASD Brex 1-3 mg (N = 20)**	**Total All Brex (N = 314)**
Number of Subjects	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Treated	294 (100.0)	20 (100.0)	314 (100.0)
Completed	140 (47.6)	12 (60.0)	152 (48.4)
Ongoing	53 (18.0)	0 (0.0)	53 (16.9)
Discontinued	101 (34.4)	8 (40.0)	109 (34.7)
Lost to follow-up	16 (5.4)	1 (5.0)	17 (5.4)
Adverse events	9 (3.1)	3 (15.0)	12 (3.8)
Subject met withdrawal criteria	0 (0.0)	0 (0.0)	0 (0.0)
Subject was withdrawn from participation by the investigator	2 (0.7)	0 (0.0)	2 (0.6)
Subject withdrew consent to participate	26 (8.8)	1 (5.0)	27 (8.6)
Withdrawal by parent/guardian	24 (8.2)	2 (10.0)	26 (8.3)
Protocol deviation	2 (0.7)	0 (0.0)	2 (0.6)
Site terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	6 (2.0)	1 (5.0)	7 (2.2)
Non-compliance with study drug	3 (1.0)	0 (0.0)	3 (1.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	2 (0.7)	0 (0.0)	2 (0.6)
Other	11 (3.7)	0 (0.0)	11 (3.5)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (≥ 13 years old).
[a]Percentages are based on the number of subjects in the treated sample.

Key Demographics and Baseline Characteristics

Short-term Controlled Trials

Key demographic and baseline characteristics are presented for the randomized sample in the short-term controlled trials in table below. The characteristics were generally comparable between treatment groups overall and within the trials.

Long-term Open-label Trials

Key demographic and baseline characteristics are presented for the safety sample in the long-term trials in Table below. The majority of subjects enrolled in these trials were rollovers from the short-term trials which was reflected in the similarity of key characteristics between the long-term trials and the short-term lead-in trials.

Psychiatric and Medical History

The characteristics of psychiatric history were similar between subjects in the all brexpiprazole and placebo groups both in the short-term and long-term controlled trials.

No clinically important differences in medical histories were found among subjects enrolled in the trials

Adverse events

Short-term Controlled Trials

An overall summary of the incidence of treatment-emergent adverse events (TEAEs) in the short-term controlled trials is presented in Table below.

Adverse Events (All Causalities) - Short-Term Controlled Trials - Safety Sample

	Schizophrenia		ASD		Total	
	Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=9)	Placebo (N=13)	All Brex (N=119)	Placebo (N=117)
Event	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Subjects treated	110 (100.0)	104 (100.0)	9 (100.0)	13 (100.0)	119 (100.0)	117 (100.0)
Subject days of drug exposure	4632	4209	428	712	5060	4921
Subjects with AEs	46 (41.8)	44 (42.3)	5 (55.6)	3 (23.1)	51 (42.9)	47 (40.2)
AEs	86	100	8	5	94	105
Subjects with TEAEs	44 (40.0)	42 (40.4)	5 (55.6)	3 (23.1)	49 (41.2)	45 (38.5)
TEAEs	76	76	7	5	83	81
Subjects with serious TEAEs	1 (0.9)	3 (2.9)	0 (0.0)	0 (0.0)	1 (0.8)	3 (2.6)
Subjects with nonserious TEAEs	43 (39.1)	42 (40.4)	5 (55.6)	3 (23.1)	48 (40.3)	45 (38.5)
Subjects with severe TEAEs	2 (1.8)	1 (1.0)	0 (0.0)	0 (0.0)	2 (1.7)	1 (0.9)
Subjects discontinued IMP due to AEs	0 (0.0)	2 (1.9)	2 (22.2)	0 (0.0)	2 (1.7)	2 (1.7)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event; ASD = autism spectrum disorder; Brex = brexpiprazole; TEAE = treatment-emergent adverse event.

ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.

Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13-17 years old).

Note: In the ASD trial, dosing was based on body weight: < 50 kg = target dose range 1-1.5 mg/day and ≥ 50 kg = target dose range 1.5-3 mg.

Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Multiple occurrences of a treatment-emergent adverse event are counted once per Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

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

Long-term Open-label Trials

An overall summary of the incidence of TEAEs in the long-term trials is presented Table below.

Adverse Events (All Causalities) - Long-term Trials

	Schizophrenia Brex 1-4 mg N = 294	ASD Brex 1-3 mg N = 20	All Brex N = 314
Event	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Subjects treated	294 (100.0)	20 (100.0)	314 (100.0)
Subject days of drug exposure	147735	2703	150438
Subjects with AEs	184 (62.6)	11 (55.0)	195 (62.1)
AEs	517	25	542
Subjects with TEAEs	184 (62.6)	11 (55.0)	195 (62.1)

Adverse Events (All Causalities) - Long-term Trials			
	Schizophrenia Brex 1-4 mg N = 294	**ASD Brex 1-3 mg N = 20**	**All Brex N = 314**
Event	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
TEAEs	448	24	472
Subjects with serious TEAEs	9 (3.1)	1 (5.0)	10 (3.2)
Subjects with nonserious TEAEs	180 (61.2)	11 (55.0)	191 (60.8)
Subjects with severe TEAEs	9 (3.1)	0	9 (2.9)
Subjects discontinued IMP due to AEs	9 (3.1)	3 (15.0)	12 (3.8)
Deaths	0	0	0

AE = adverse event; ASD = autism spectrum disorder; Brex = brexpiprazole; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.

Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (13-17 years old).

Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Multiple occurrences of a treatment-emergent adverse event are counted once per MedDRA preferred term.

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

Treatment-emergent Adverse Events

Short-term Controlled Trials

Treatment-emergent AEs in the short-term trials were observed for nausea, headache, and somnolence each reported in 5.9% of subjects, followed by akathisia (4.2%), and hypersomnia (2.5%). There were no notable differences between the all brexpiprazole and placebo groups in the incidence of TEAEs.

Severe TEAEs were reported in 3 subjects in schizophrenia Trial 331-10-234, 2 of which occurred in the brexpiprazole group, TEAEs blood creatine phosphokinase (CPK) increased and schizophrenia.

In the short-term controlled trials TEAEs assessed by the investigator as potentially drug-related were reported in 28 (23.5%) subjects in the all brexpiprazole group and 19 (16.2%) subjects in the placebo group. In schizophrenia Trial 331-10-234, potentially drug-related TEAEs included somnolence, nausea, headache (each 5 subjects), and akathisia (4 subjects). None of the other potentially drug-related TEAEs in this treatment group were reported in more than 2 subjects.

Incidence of TEAEs in at Least 2% of Subjects in the All Brexpiprazole Group and Greater Than in the Placebo Group - Short-Term Controlled Trials - Safety Sample						
	Schizophrenia		**ASD**		**Total**	
	Brex 2-4 mg (N=110)	**Placebo (N=104)**	**Brex 1-3 mg (N=9)**	**Placebo (N=13)**	**All Brex (N=119)**	**Placebo (N=117)**
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders						
Nausea	7 (6.4)	4 (3.8)	0 (0.0)	1 (7.7)	7 (5.9)	5 (4.3)
Nervous System Disorders						
Akathisia	4 (3.6)	3 (2.9)	1 (11.1)	0 (0.0)	5 (4.2)	3 (2.6)

Incidence of TEAEs in at Least 2% of Subjects in the All Brexpiprazole Group and Greater Than in the Placebo Group - Short-Term Controlled Trials - Safety Sample

	Schizophrenia		ASD		Total	
	Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=9)	Placebo (N=13)	All Brex (N=119)	Placebo (N=117)
Headache	7 (6.4)	5 (4.8)	0 (0.0)	0 (0.0)	7 (5.9)	5 (4.3)
Hypersomnia	3 (2.7)	2 (1.9)	0 (0.0)	0 (0.0)	3 (2.5)	2 (1.7)
Somnolence	5 (4.5)	5 (4.8)	2 (22.2)	1 (7.7)	7 (5.9)	6 (5.1)

ASD = autism spectrum disorder; Brex = brexpiprazole; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13-17 years old).
Note: A TEAE is defined as an AE that started after start of drug treatment or that was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Subjects are counted once for the most severe of multiple occurrences of a specific MedDRA preferred term.
Note: Subjects with TEAEs in multiple SOCs were counted only once towards the total.

Long-term Open-label Trials

The incidence of TEAEs in the long-term open-label trials for events reported in at least 2% of subjects is presented in Table below. Weight increased and somnolence were the highest reported (each 11.5%), followed by headache (9.6%), and nasopharyngitis (6.1%).
The very commonly (≥ 10%) reported TEAEs in schizophrenia Trial 331-10-236 were weight increased and somnolence in 31 (10.5%) subjects each.

Incidence of TEAEs That Occurred in at Least 2% of Subjects in the All Brexpiprazole Group - Long-Term Open-Label Trials - Safety Sample

	Schizophrenia Brex 1-4 mg (N = 294)	ASD Brex 1-3 mg (N = 20)	Total All Brex (N = 314)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**
Gastrointestinal Disorders			
Nausea	8 (2.7)	0 (0.0)	8 (2.5)
Salivary Hypersecretion	9 (3.1)	0 (0.0)	9 (2.9)
Infections and Infestations			
Influenza	11 (3.7)	1 (5.0)	12 (3.8)
Nasopharyngitis	19 (6.5)	0 (0.0)	19 (6.1)
Urinary Tract Infection	10 (3.4)	0 (0.0)	10 (3.2)
Investigations			
Weight increased	31 (10.5)	5 (25.0)	36 (11.5)
Nervous System Disorders			
Akathisia	15 (5.1)	0 (0.0)	15 (4.8)
Dizziness	6 (2.0)	1 (5.0)	7 (2.2)
Headache	29 (9.9)	1 (5.0)	30 (9.6)
Somnolence	31 (10.5)	5 (25.0)	36 (11.5)

Incidence of TEAEs That Occurred in at Least 2% of Subjects in the All Brexpiprazole Group - Long-Term Open-Label Trials - Safety Sample			
	Schizophrenia Brex 1-4 mg (N = 294)	**ASD Brex 1-3 mg (N = 20)**	**Total All Brex (N = 314)**
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**
Psychiatric Disorders			
Anxiety	11 (3.7)	0 (0.0)	11 (3.5)
Insomnia	14 (4.8)	0 (0.0)	14 (4.5)
Irritability	6 (2.0)	1 (5.0)	7 (2.2)
Psychotic Disorder	7 (2.4)	0 (0.0)	7 (2.2)
Schizophrenia	8 (2.7)	0 (0.0)	8 (2.5)

ASD = autism spectrum disorder; Brex = brexpiprazole; MedDRA = Medical Dictionary for Regulatory Activities.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (13-17 years old).
Note: In the ASD trial, dosing was based on body weight: < 50 kg = target dose range 1-1.5 mg/day and ≥ 50 kg = target dose range 1.5-3 mg.
Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy.
Note: Subjects are counted once per term for the most severe of multiple occurrences of a specific MedDRA preferred term.

In the long-term open-label trials, 10 (3.2%) subjects reported at least 1 severe TEAE and all occurred in the schizophrenia Trial 331-10-236.
In the long-term trials TEAEs assessed by the investigator as potentially drug-related were reported in 98 subjects (31.2%). Potentially drug-related TEAEs with an incidence > 2% in schizophrenia Trial 331-10-236 were somnolence, weight increased, akathisia, and salivary hypersecretion.

Updated safety data from the 331-10-236 study with data cut-off on the 13 Sept 2024 showed consisted findings in terms of most commonly reported TEAEs (≥5%) and relative frequency.

Serious adverse event/deaths/other significant events

No deaths were reported in the short-term trials and in the completed long-term Trial 331-201-00191. No deaths were reported in the ongoing long-term Trial 331-10-236 as of the cutoff date (10 October 2023).

Serious Treatment-emergent Adverse Events

Short-term Controlled Trials

In the short-term controlled trials, 4 subjects experienced at least 1 serious TEAE, all of which occurred in the schizophrenia trial (Trial 331-10-234). Serious events included psychotic disorder (2 subjects) and schizophrenia (2 subjects). All serious events except 1 event were reported in the placebo group and all but 1 of these events were mild or moderate in severity. One subject in the brexpiprazole group experienced a serious TEAE of schizophrenia (worsening of symptoms) which was considered severe and not related to the IMP. The event occurred after the subject discontinued from the trial and the outcome of the event was recovered/resolved.

Long-term Open-label Trials

In the long-term trials, 10 (3.2%) subjects overall experienced a serious TEAE, 9 of which were in schizophrenia Trial 331-10-236. Serious TEAEs reported in more than 1 subject were schizophrenia in 3 subjects and psychotic disorder and suicide attempt each in 2 subjects. None of the other serious events were reported in more than 1 subject in the schizophrenia trial. One subject in the ASD trial reported a serious TEAE of dyskinesia.

AESI:

- Metabolic parameters (fasting serum glucose and lipids)
- Body weight and body mass index (BMI)
- Extrapyramidal Symptoms (EPS)
- Haematopoietic events and leukopenia (agranulocytosis, neutropenia, and leukopenia)
- Hepatic impairment
- Hypersensitivity (including skin reactions)
- Neuroleptic malignant syndrome
- Orthostatic hypotension, dizziness, and syncope
- Overdose
- Prolactin
- QT prolongation
- Rhabdomyolysis and CPK elevation
- Seizures
- Somnolence
- Suicidality
- Venous thromboembolism (VTE)

Consistent with the extensive brexpiprazole development program, brexpiprazole was evaluated in the context of these topics of special interest in the adolescent schizophrenia population.

Metabolic Parameters

Short-term Controlled Trials

Changes from baseline in metabolic parameters (fasting serum glucose, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, total cholesterol, and triglycerides) at the last visit for subjects in the short-term controlled trials are summarized in Table below.

Summary of Change from Baseline in Fasting Serum Glucose and Lipids - Short-Term Controlled Trials - Safety Sample

Parameter	Visit[a]	Statistic	Schizophrenia		ASD		Total	
			Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=9)	Placebo (N=13)	All Brex (N=119)	Placebo (N=117)
Glucose, fasting (mg/dL)	Baseline	n[b]	109	104	4	7	113	111
		Mean (SD)	90.8 (14.2)	88.9 (9.1)	95.3 (10.0)	89.3 (7.4)	91.0 (14.0)	88.9 (9.0)
		Median (Min, Max)	90.0 (56.0, 193.0)	88.5 61.0, 116.0)	93.0 (86.0, 109.0)	89.0 (77.0, 100.0)	90.0 (56.0, 193.0)	89.0 (61.0, 116.0)
	Change at Last	n[c]	102	96	3	6	105	102
		Mean	1.1 (12.1)	0.7 (14.7)	1.3 (11.6)	−0.2 (8.8)	1.1 (12.1)	0.6 (14.4)

Summary of Change from Baseline in Fasting Serum Glucose and Lipids - Short-Term Controlled Trials - Safety Sample								
	Visit	(SD)						
		Median (Min, Max)	1.0 (−43.0, 38.0)	0.0 (−27.0, 97.0)	7.0 (−12.0, 9.0)	−0.5 (−15.0, 10.0)	1.0 (−43.0, 38.0)	0.0 (−27.0, 97.0)
HDL-cholesterol, fasting (mg/dL)	Baseline	n[b]	107	101	4	7	111	108
		Mean (SD)	52.4 (12.9)	51.9 (15.0)	40.5 (3.1)	51.4 (17.7)	52.0 (12.9)	51.9 (15.1)
		Median (Min, Max)	50.0 (30.0, 87.0)	49.0 (30.0, 103.0)	39.5 (38.0, 45.0)	44.0 (38.0, 86.0)	49.0 (30.0, 87.0)	49.0 (30.0, 103.0)
	Change at Last Visit	n[c]	100	93	3	6	103	99
		Mean (SD)	−0.1 (9.5)	−2.1 (11.6)	7.3 (4.0)	−4.2 (13.3)	0.1 (9.5)	−2.2 (11.7)
		Median (Min, Max)	0.0 (−26.0, 32.0)	0.0 (−53.0, 37.0)	8.0 (3.0, 11.0)	−0.5 (−29.0, 7.0)	0.0 (−26.0, 32.0)	0.0 (−53.0, 37.0)
LDL-cholesterol, fasting (mg/dL)	Baseline	n[b]	107	101	4	7	111	108
		Mean (SD)	89.8 (30.1)	86.9 (29.3)	87.8 (49.8)	88.3 (20.2)	89.7 (30.7)	87.0 (28.7)
		Median (Min, Max)	88.0 (41.0, 210.0)	84.0 (31.0, 205.0)	72.5 (46.0, 160.0)	82.0 (68.0, 131.0)	85.0 (41.0, 210.0)	83.0 (31.0, 205.0)
	Change at Last Visit	n[c]	100	93	3	6	103	99
		Mean (SD)	0.2 (23.7)	−3.4 (25.7)	3.3 (10.7)	−1.8 (10.6)	0.3 (23.4)	−3.3 (25.0)
		Median (Min, Max)	3.0 (−97.0, 50.0)	−3.0 (−111.0, 87.0)	9.0 (−9.0, 10.0)	−1.0 (−19.0, 11.0)	3.0 (−97.0, 50.0)	−3.0 (−111.0, 87.0)
Total cholesterol, fasting (mg/dL)	Baseline	n[b]	109	104	4	7	113	111
		Mean (SD)	162.3 (35.1)	158.1 (34.6)	144.8 (54.7)	155.7 (25.0)	161.7 (35.7)	157.9 (34.0)
		Median (Min, Max)	159.0 (102.0, 290.0)	152.5 (100.0, 317.0)	126.0 (102.0, 225.0)	145.0 (129.0, 192.0)	157.0 (102.0, 290.0)	152.0 (100.0, 317.0)
	Change at Last Visit	n[c]	102	96	3	6	105	102
		Mean (SD)	−0.2 (28.9)	−5.2 (29.6)	12.0 (11.3)	−2.2 (14.0)	0.2 (28.6)	−5.0 (28.9)
		Median (Min, Max)	4.5 (−82.0, 62.0)	−4.5 (−105.0, 94.0)	18.0 (−1.0, 19.0)	0.5 (−28.0, 10.0)	5.0 (−82.0, 62.0)	−4.0 (−105.0, 94.0)
Triglycerides, fasting (mg/dL)	Baseline	n[b]	109	104	4	7	113	111
		Mean (SD)	102.3 (52.3)	94.1 (50.8)	82.3 (31.2)	79.9 (22.8)	101.6 (51.8)	93.2 (49.5)
		Median (Min, Max)	91.0 (27.0, 354.0)	82.5 (32.0, 393.0)	76.0 (53.0, 124.0)	76.0 (54.0, 116.0)	90.0 (27.0, 354.0)	82.0 (32.0, 393.0)
	Change at Last Visit	n[c]	102	96	3	6	105	102
		Mean (SD)	1.0 (55.3)	3.2 (49.6)	8.7 (18.6)	19.5 (52.6)	1.2 (54.6)	4.2 (49.7)
		Median	0.0	−1.0	11.0	1.5	1.0	−1.0

Summary of Change from Baseline in Fasting Serum Glucose and Lipids - Short-Term Controlled Trials - Safety Sample								
		(Min, Max)	(−253.0, 140.0)	(−215.0, 185.0)	(−11.0, 26.0)	(−39.0, 107.0)	(−253.0, 140.0)	(−215.0, 185.0)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13-17 years old).
[a]Baseline = last predose evaluation; Last visit = last available postbaseline evaluation including early termination.
[b]n = total number of treated subjects with evaluation of the given parameter at the specific visit.
[c]n = total number of treated subjects with both baseline and evaluation of the given parameter at the specific visit.

Mean changes from baseline at each visit for each of the metabolic parameters were small relative to baseline values and would not be expected to contribute to clinically important changes in baseline values. Differences between treatment groups were minor and not clinically important.

The incidence of potentially clinically relevant (PCR) abnormalities in the all brexpiprazole group was higher than in the placebo group for all metabolic parameters. The highest incidences of PCR abnormalities in both treatment groups in the pooled trials were observed in fasting serum triglycerides (30.2% in the all brexpiprazole group and 16.5% in the placebo group) and glucose (17.9% vs 12.6%, respectively). Potentially clinically relevant changes in LDL-cholesterol were reported in 10.6% of subjects in the all brexpiprazole group and 4.0% in the placebo group followed by total cholesterol (9.4% and 5.8%, respectively) and HDL-cholesterol (8.7% and 4.0%, respectively).

The incidence of treatment-emergent significant changes from baseline in fasting serum glucose and lipids was generally low across parameters. Shifts in total cholesterol were observed in subjects in every category of treatment-emergent changes with the highest incidence observed in shifts from baseline borderline total cholesterol levels to postbaseline high levels (42.3% and 12.5% in the all brexpiprazole and placebo groups, respectively) and from baseline normal to borderline/high levels (30.3% and 20.0%, respectively).

The incidence of TEAEs for effect in metabolic parameters was low, no events associated with serum lipids were reported in the all brexpiprazole group and 1 subject in the placebo group had an event of hypertriglyceridemia.

Long-term Open-label Trials

The summary of changes from baseline in metabolic parameters (fasting serum glucose, HDL-cholesterol, LDL-cholesterol, total cholesterol, and triglycerides) for the long-term clinical trials is provided in table below.

Summary of Change from Baseline in Fasting Serum Glucose and Lipids- Long-Term Open-Label Trial in Schizophrenia - Safety Sample			
Parameter (Units)	**Visit**	**Statistic**	**Brex 1-4 mg N = 294**
Glucose, fasting serum (mg/dL)	Baseline[a]	n[b]	275
		Mean (SD)	90.7 (11.6)
		Median (Min,Max)	90.0 (59.0, 167.0)
	Change at Last Visit	n[c]	269
		Mean (SD)	0.5 (14.3)

Summary of Change from Baseline in Fasting Serum Glucose and Lipids- Long-Term Open-Label Trial in Schizophrenia - Safety Sample			
Parameter (Units)	**Visit**	**Statistic**	**Brex 1-4 mg N = 294**
		Median (Min,Max)	1.0 (-88.0, 96.0)
HDL-cholesterol, fasting serum (mg/dL)	Baseline[a]	n[b]	272
		Mean (SD)	52.3 (12.9)
		Median (Min,Max)	50.0 (22.0, 102.0)
	Change at Last Visit	n[c]	266
		Mean (SD)	0.6 (14.0)
		Median (Min,Max)	0.0 (-55.0, 60.0)
LDL-cholesterol, fasting serum (mg/dL)	Baseline[a]	n[b]	272
		Mean (SD)	85.4 (29.6)
		Median (Min,Max)	83.0 (36.0, 208.0)
	Change at Last Visit	n[c]	266
		Mean (SD)	5.2 (25.7)
		Median (Min,Max)	5.0 (-109.0, 90.0)
Total cholesterol, fasting serum (mg/dL)	Baseline[a]	n[b]	277
		Mean (SD)	156.6 (34.2)
		Median (Min,Max)	151.0 (92.0, 296.0)
	Change at Last Visit	n[c]	271
		Mean (SD)	7.0 (31.2)
		Median (Min,Max)	7.0 (-112.0, 112.0)
Triglycerides, fasting serum (mg/dL)	Baseline[a]	n[b]	277
		Mean (SD)	96.4 (49.0)
		Median (Min,Max)	86.0 (30.0, 342.0)
	Change at Last Visit	n[c]	271
		Mean (SD)	4.7 (52.1)
		Median (Min,Max)	2.0 (-195.0, 231.0)

Brex = brexpiprazole.
Includes schizophrenia Trial 331-10-236.

[a]Baseline = last predose evaluation; Last visit = last available postbaseline evaluation including early termination.

[b]n = Total number of treated subjects with evaluation of the given parameter at the specific visit.

[c]n = Total number of treated subjects with both baseline and evaluation of the given parameter at the specific visit.

Mean changes at the last visit in schizophrenia Trial 331-10-236 were small relative to baseline values for each parameter and would not be expected to contribute to clinically important changes.

The highest incidence of PCR abnormalities in metabolic parameters in Trial 331-10-236 were observed for glucose (28.3%) and triglycerides (27.6%). PCR changes reported in ≤ 10% of subjects were observed in total cholesterol (9.9%), LDL-cholesterol (8.5%), and HDL-cholesterol (7.8%).

Incidences of treatment-emergent significant changes from baseline in fasting serum glucose are summarised in table below.

Incidence of Treatment-Emergent Significant Change in Glucose and Lipids - Long-Term Open-Label Trial in Schizophrenia - Safety Sample					
			Schizophrenia Brex 1-4 mg (N=294)		
Parameter	Baseline[a]	Anytime Postbaseline	Ne[b]	n[c]	%
Glucose, fasting serum (mg/dL)	Normal <100	High ≥126	238	6	2.5
	Impaired 100 ─ <126	High ≥126	27	2	7.4
	Normal/Impaired <126	High ≥126	265	8	3.0
LDL-cholesterol, fasting serum (mg/dL)	Normal <110	High ≥130	218	19	8.7
	Borderline 110 ─ <130	High ≥130	30	10	33.3
	Normal/Borderline <130	High ≥130	248	29	11.7
	Normal <110	Borderline/High ≥110	218	48	22.0
HDL-cholesterol, fasting serum (mg/dL)	Normal >45	Low <40	180	30	16.7
	Borderline 45 ─ ≥40	Low <40	45	16	35.6
	Normal/Borderline ≥40	Low <40	225	46	20.4
	Normal >45	Borderline/Low ≤45	180	70	38.9
Total Cholesterol, fasting serum (mg/dL)	Normal <170	High ≥200	187	17	9.1
	Borderline 170 ─ <200	High ≥200	53	21	39.6
	Normal/Borderline <200	High ≥200	240	38	15.8
	Normal <170	Borderline/High ≥170	187	76	40.6
Triglycerides, fasting serum (mg/dL)	Normal <90	High ≥130	143	34	23.8
	Borderline 90 ─ <130	High ≥130	79	41	51.9
	Normal/Borderline <130	High ≥130	222	75	33.8
	Borderline 150 ─ <200	Borderline/High/Very High ≥90	143	70	49.0

Brex = brexpiprazole.
Includes schizophrenia Trial 331-10-236.

[a]For clinical laboratory data, baseline is the value obtained before the first brexpiprazole dose.

[b]Ne is the total number of subjects who had at least 1 post-baseline result for the given laboratory test.

[c]n is the number of subjects with 1 potential clinically relevant test abnormality observation.

[d]The denominator for the percentage calculation is Ne.

The pattern of shifts from baseline in metabolic parameters in the different categories of change varied for each parameter. The highest incidences for each parameter were generally observed in serum triglycerides ranging from 23.8% (normal to high) to 51.9% (borderline to high). The lowest incidences for each parameter were observed in serum glucose ranging from 2.5% (normal to high) to 7.4% (impaired to high). Shifts in fasting serum lipids generally followed a similar pattern with higher incidences of shifts to high levels postbaseline in subjects with borderline levels at baseline and shifts to borderline/high levels from normal baseline levels.

The incidence of TEAEs for effect in metabolic parameters for both glucose and lipids were low (< 1%) in the long-term trials; no glucose or lipid-related TEAE was reported by more than 1 subject in either the schizophrenia or ASD trial.

Body weight and body mass index (BMI)

Short-term Controlled Trials

Overall, in the all brexpiprazole group, the incidence of PCR weight gain ≥ 7% was reported in 12 (10.1%) subjects compared to a total of 3 (2.8%) subjects in the placebo group. When based on

weight Z-scores, 5 (4.2%) subjects in the all brexpiprazole group and 5 (4.3%) of subjects in the placebo group had PCR weight gain. Potentially clinically relevant weight gain based on BMI Z-score was reported in 11 (9.4%) subjects in the all brexpiprazole group.

TEAEs associated with abnormal weight gain in schizophrenia Trial 331-10-234 were reported in 6 (2.5%) subjects. Weight increased was reported in 2 (1.7%) subjects in the all brexpiprazole group and 4 (3.4%) subjects in the placebo group while increased appetite was reported in 1 (0.9%) subject in the placebo group. No TEAEs for effects on weight were reported in the short-term ASD trial.

Long-term Open-label Trials

Overall, PCR weight gain ≥ 7% was experienced by 139 (44.4%) subjects in the long-term trials. An increase of ≥ 0.5 in weight Z-score was observed in 64 (20.4%) subjects and an increase in BMI Z-score was observed in 55 (18.6%) subjects. When based on weight Z-scores, 64 (20.4%) subjects in the all brexpiprazole group had PCR weight gain and when based on BMI Z-scores, 55 (9.4%) subjects had PCR weight gain. In pooled trials, the highest incidence of PCR weight gain was observed in subjects who were underweight (BMI ≥ 18.5 and < 25 kg/m2) or at normal weight (BMI ≥ 25 and < 30 kg/m2). A total of 23 (56.1%) subjects with PCR weight gain were underweight, 78 (44.1%) were at normal weight, 24 (40.0%) were overweight, and 14 (40.0%) were obese.

Highest incidence of TEAEs associated with weight abnormalities in the long-term trials were weight increased reported in 39 (12.4%) subjects. Other weight-related TEAEs were BMI increased, increased appetite, and waist circumference increased; none were reported in more than 1.3% subject, as shown in table below.

Incidence of TEAEs for Effects on Weight - Long-Term Open-Label Trials - Safety Sample

	Schizophrenia Brex 1-4 mg (N = 294)	ASD Brex 1-3 mg (N = 20)	All Brex (N = 314)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**
Subject with any TEAE[a]	34 (11.6)	5 (25.0)	39 (12.4)
Effects on Weight	34 (11.6)	5 (25.0)	39 (12.4)
BMI increased	1 (0.3)	0 (0.0)	1 (0.3)
Increased appetite	2 (0.7)	2 (10.0)	4 (1.3)
Waist circumference increased	1 (0.3)	0 (0.0)	1 (0.3)
Weight increased	31 (10.5)	5 (25.0)	36 (11.5)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (≥ 13 years old).
Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.
[a]Subjects with TEAEs in multiple SOCs were counted only once towards the total.

Extrapyramidal Symptoms

The severity of extrapyramidal symptoms (EPS) during treatment was evaluated in the short-term and long-term trials based on scores from the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS).

Short-term Controlled Trials

Changes from baseline in Simpson-Angus Scale (SAS) total scores and Barnes Akathisia Rating Scale (BARS) global scores were generally unchanged at the last visit in both treatment groups in schizophrenia Trial 331-10-234. Mean AIMS total scores were low at baseline in both the brexpiprazole and placebo groups and decreased from baseline at most timepoints in both groups.

A total of 10 (8.4%) subjects in the brexpiprazole group and 5 (4.3%) subjects in the placebo group experienced an EPS-related TEAE. The incidence of individual EPS-related events by category was slightly higher in the all brexpiprazole group than in the placebo group for akathisia events (5.9% and 4.3%, respectively) and parkinsonian events (2.5% and 0.9%, respectively).

Akathisia events were the most frequently reported EPS-related TEAEs with 7 (5.9%) subjects in the all brexpiprazole group and 5 (4.3%) subjects in the placebo group experiencing at least 1 event of akathisia. Akathisia was the only event in any of the categories of EPS-related TEAEs reported in more than 2 subjects, including in 5 (4.2%) subjects in the schizophrenia trial and 3 (2.6%) subjects in the ASD trial.

A total of 7 (5.9%) subjects in the all brexpiprazole group and 3 (2.6%) subjects in the placebo group experienced EPS-related TEAEs after akathisia events were excluded. The incidence of akathisia TEAEs for subjects in the brexpiprazole group was 3.6% versus 2.9% subjects in the placebo group.

Incidence of EPS-Associated Treatment-Emergent Adverse Events by EPS Category - Short-Term Controlled Trials –Safety Sample

	Schizophrenia		ASD		Total	
	Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=9)	Placebo (N=12)	All Brex	Placebo
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subject with any TEAE[a]	9 (8.2)	5 (4.8)	1 (11.1)	0 (0.0)	10 (8.4)	5 (4.3)
EPS - Akathisia	6 (5.5)	5 (4.8)	1 (11.1)	0 (0.0)	7 (5.9)	5 (4.3)
Akathisia	4 (3.6)	3 (2.9)	1 (11.1)	0 (0.0)	5 (4.2)	3 (2.6)
Extrapyramidal Disorder	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)
Psychomotor Hyperactivity	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Restlessness	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
EPS - Dystonic Events	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Blepharospasm	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
EPS - Parkinsonian Events	3 (2.7)	1 (1.0)	0 (0.0)	0 (0.0)	3 (2.5)	1 (0.9)
Hypokinesia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Muscle Rigidity	1 (0.9)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.9)
Tremor	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13 - 17 years old).
Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption, or reduction of trial therapy. Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.
[a]Subjects with TEAEs in multiple SOCs were counted only once towards the total.

Although assessment of the comparative tolerability between treatment arms is limited by the relatively limited number of study participants, in Trial 331-10-234 extrapyramidal related symptom TEAEs were

reported for 8.2% in the brexpiprazole 2-4 mg/day group, 11.8% in the aripiprazole 10-20 mg/day group, and 4.8% in the placebo group. Also, the brexpiprazole arm showed lower incidence in anticholinergic effects TEAEs (2.7%) in respect to the aripiprazole (6.9%) group, with only non-serious, mild to moderate in severity.

Long-term Open-label Trials

In the long-term trials, changes from baseline in SAS total scores, BARS global scores, and AIM total scores were generally unchanged at the last visit.

A total of 32 (10.2%) subjects in the pooled long-term trials experienced an EPS-related TEAE. Akathisia events were the most frequent EPS-related TEAEs reported with 15 (4.8%) subjects experiencing at least 1 event. After excluding akathisia events, the incidence of EPS-related TEAEs was 7.6% (24 subjects).

The incidence of akathisia TEAEs for brexpiprazole-treated subjects was 5.1%.

Haematopoietic events and leukopenia (agranulocytosis, neutropenia, and leukopenia)

No TEAEs of haematopoietic or leukopenia events were reported in either the short-term trials or the long-term trials.

Hepatic Impairment

No liver injury-related changes in laboratory parameters were observed in any subjects except 2 in the all brexpiprazole group which included 1 subject with elevated alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN) and 1 subject with elevated ALT or aspartate aminotransferase (AST) ≥ 3 x ULN.

Short-term Controlled Trials

In the pooled short-term trials, TEAEs associated with hepatic impairment were reported in 2 subjects in the placebo group. One subject had a TEAE associated with hepatic impairment with a PCR value for laboratory test abnormalities related to liver injury and 1 subject had a TEAE associated with hepatic impairment without a PCR value. A total of 9 subjects had PCR values for laboratory test abnormalities related to liver injury but without any TEAEs associated with hepatic impairment. No subjects discontinued due to a TEAE associated with hepatic impairment.

Long-term Open-label Trials

No liver injury-related changes in laboratory parameters were observed in the long term trials except in 3 subjects with elevated ALT ≥ 3 x ULN and 3 subjects with elevated ALT or AST ≥ 3 x ULN.
In the pooled data from the long-term trials, TEAEs associated with hepatic impairment were reported in 3 subjects. Two subjects had a TEAE associated with hepatic impairment and a PCR value and 1 subject had a TEAE associated with hepatic impairment without a PCR value. A total of 27 subjects had PCR values for laboratory test abnormalities related to liver injury but no TEAEs associated with hepatic impairment. No subjects discontinued due to a TEAE associated with hepatic impairment.

Hypersensitivity Including Skin Reactions

Short-term Controlled Trials

No subjects in the all brexpiprazole group had a hypersensitivity-related TEAE. In the placebo group, pruritis and rash were each reported in 1 (0.9%) subject.

Long-term Open-label Trials

Hypersensitivity events were reported in 5 subjects (1.6%) in the pooled trials. Rhinitis allergic was reported in 2 (0.6%) subjects and rash, swelling face, and urticaria were each reported in 1 (0.3%) subject.

Neuroleptic Malignant Syndrome

No TEAEs for neuroleptic malignant syndrome were reported for subjects in the short-term controlled trials or in the long-term open-label trials.

Orthostatic Hypotension, Dizziness, and Syncope

Short-term Controlled Trials

In the all brexpiprazole group, dizziness postural and syncope were each reported in 1 (0.9%) subject. In the placebo group, dizziness was reported in 2 (1.7%) subjects and blood pressure systolic decreased and vertigo were each reported in 1 subject (0.9%).

Long-term Open-label Trials

In the pooled trials, 10 (3.2%) subjects had TEAEs related to orthostatic hypotension, dizziness, and syncope. Dizziness was reported in 7 (2.2%) subjects and hypotension, orthostatic hypotension and syncope were each reported in 1 (0.3%) subject.

Overdose

In the short-term and long-term trials in paediatric subjects aged 13 to 17 years old with diagnoses of schizophrenia or ASD, doses up to 4 mg/day were safe and well tolerated as shown by the low incidences overall in TEAEs, SAEs, severe TEAEs, and discontinuations resulting from TEAEs observed in subjects treated with brexpiprazole and the similarity of these observations between the all brexpiprazole group and the placebo group. At the last visits in these trials, 33.6% of subjects in the short-term trials and 28.7% in the long-term trials were taking 4 mg/day doses of brexpiprazole.

In the long-term Trial 331-10-236, intentional overdose was reported as a moderate TEAE in one adolescent subject.

Prolactin

Short-term Controlled Trials

Potentially clinically relevant high prolactin values in the short-term controlled trials were reported in 35 (30.7%) subjects in the brexpiprazole group and 11 (9.9%) subjects in the placebo group. The majority of subjects (26/35) who had PCR elevated prolactin levels had values > 1 × upper limit of normal (ULN) to ≤ 2 × ULN.

Higher incidence of treatment-emergent PCR elevated prolactin levels occurred among females compared to males. Among females, the incidence of treatment-emergent PCR elevated prolactin levels > 1 × ULN to ≤ 2 × ULN was 22.8% in all brexpiprazole group and 5.8% in the placebo group. Among males, the incidence of treatment-emergent PCR prolactin levels > 1 × ULN to ≤ 2 × ULN was 15.6% in the all brexpiprazole group and 1.7% in the placebo group.

No TEAEs associated with prolactin were reported for subjects in the short-term controlled trials.

Long-term Open-label Trials

Potentially clinically relevant changes in prolactin values were reported in 88 subjects in the long-term trials. The majority of subjects (71/88) with treatment-emergent PCR elevated prolactin levels had values > 1 × ULN to ≤ 2 × ULN. When reviewed by gender, the incidence of treatment-emergent PCR elevated prolactin levels > 1 × ULN to ≤ 2 × ULN among females was 17.2% compared to 30.2% among males.

A total of 7 (2.2%) subjects had TEAEs associated with prolactin, including 5 (1.6%) subjects with blood prolactin increased and 2 (0.6%) with hyperprolactinaemia.

QT prolongation

No TEAEs associated with QT prolongation were reported in subjects in the short-term controlled trials or in the long-term open-label trials.

Rhabdomyolysis and CPK Elevation

Short-term Controlled Trials

In the all brexpiprazole group, only 1 subject in the schizophrenia trial had a TEAE of blood CPK increased. No TEAEs related to rhabdomyolysis and CPK elevation were reported in either the brexpiprazole or placebo group in the ASD trial.

Long-term Open-label Trials

One subject in the schizophrenia trial had a TEAE of myalgia.

Seizures

No TEAEs for seizures were reported for subjects in either the short-term controlled trials or the long-term open-label trials.

Somnolence

Short-term Controlled Trials

TEAEs associated with somnolence were reported in 18 subjects overall, 10 (8.4%) subjects in the all brexpiprazole group and 8 (6.8%) subjects in the placebo group.

Table Error! No text of specified style in document.-1 Incidence of TEAEs for Somnolence - Short-Term Controlled Trials - Safety Sample

	Schizophrenia		ASD		Total	
	Brex 2-4 mg (N=110)	Placebo (N=104)	Brex 1-3 mg (N=9)	Placebo (N=13)	All Brex (N=119)	Placebo (N=117)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subject with any TEAEs[a]	8 (7.3)	7 (6.7)	2 (22.2)	1 (7.7)	10 (8.4)	8 (6.8)
Somnolence	8 (7.3)	7 (6.7)	2 (22.2)	1 (7.7)	10 (8.4)	8 (6.8)
Hypersomnia	3 (2.7)	2 (1.9)	0 (0.0)	0 (0.0)	3 (2.5)	2 (1.7)
Sedation	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)
Somnolence	5 (4.5)	5 (4.8)	2 (22.2)	1 (7.7)	7 (5.9)	6 (5.1)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.

Includes schizophrenia Trial 331-10-234 and ASD Trial 331-201-00148 (13 - 17 years old).
Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.
[a]Subjects with TEAEs in multiple SOCs were counted only once towards the total.

Long-term Open-label Trials

In schizophrenia patients TEAEs associated with somnolence were reported in 35 (11.9%) subjects overall. A total of 31 (10.5%) subjects experienced TEAEs of somnolence, 4 (1.4%) subjects experienced events of sedation, and 2 (0.7%) subjects experienced events of hypersomnia.

TEAEs associated with somnolence were reported in 41 (13.1%) subjects overall. A total of 36 (11.5%) subjects experienced TEAEs of somnolence, 5 (1.6%) subjects experienced events of sedation, and 2 (0.6%) subjects experienced events of hypersomnia.

Table 2.7.4.3.14.2-1 Incidence of TEAEs for Somnolence - Long-Term Open-Label Trials - Safety Sample

	Schizophrenia Brex 2-4 mg (N=294)	ASD Brex 1-3 mg (N=20)	All Brex (N=314)
System Organ Class MedDRA Preferred Term	**n (%)**	**n (%)**	**n (%)**
Subject with any TEAEs[a]	35 (11.9)	6 (30.0)	41 (13.1)
Somnolence	35 (11.9)	6 (30.0)	41 (13.1)
Hypersomnia	2 (0.7)	0 (0.0)	2 (0.6)
Sedation	4 (1.4)	1 (5.0)	5 (1.6)
Somnolence	31 (10.5)	5 (25.0)	36 (11.5)

ASD = autism spectrum disorder; Brex = brexpiprazole.
ASD dosing based on body weight: < 50 kg target dose range = 1-1.5 mg/day/day and ≥ 50 kg target dose range = 1.5-3 mg.
Includes schizophrenia Trial 331-10-236 and ASD Trial 331-201-00191 (≥ 13 years old).
Note: A TEAE is defined as an AE starting after start of drug treatment or was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, interruption or reduction of trial therapy. Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.

Suicidality

In the brexpiprazole schizophrenia clinical trials, suicidality was assessed based on 2 components: the incidence of TEAEs related to suicidality and the C-SSRS (assessment of treatment-emergent suicidal behaviour and/or ideation) at each study visit.

Short-term Controlled Trials

In the pooled trials, 7 (5.9%) subjects in the all brexpiprazole group and 6 (5.1%) subjects in the placebo group had a lifetime history of suicidal ideation. A total of 6 (5.0%) subjects in the all brexpiprazole group and 5 (4.3%) subjects in the placebo group had a lifetime history of suicidal behaviour.

In schizophrenia Trial 331-10-234, one subject (0.9%) had a TEAE associated with suicidality of intentional self-injury and judged not to be brexpiprazole-related. No suicidal behaviour was reported in either treatment group in the short-term controlled trials based on the Columbia-Suicide Severity Rating Scale (C-SSRS).

In addition, 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.

Long-term Open-label Trials

In ongoing long-term open label Trial 331-10-236, 8 of 294 subjects (2.7%) experienced suicide related TEAEs (suicidal ideation n = 5, suicide attempt n = 2, intentional self-injury n = 2 [both subjects that reported intentional self-injury also reported suicidal ideation], and intentional overdose n =1). None of the suicide related TEAEs were considered related to brexpiprazole by either the investigator or the sponsor.

In ongoing long-term Trial 331-10-236, the emergence of suicidal ideation was reported in 15 (5.1%) subjects (with the first appearance at Month 3) and the emergence of serious suicidal ideation (suicidal ideation rating 4 or 5) was reported in 2 (0.7%) subjects as assessed via the C SSRS. Two (0.7%) subjects had suicidal behaviour that resulted in a serious TEAE of suicide attempt. The suicide attempts were not successful, but one of them resulted in trial discontinuation.

Venous Thromboembolism

No TEAEs associated with VTEs were reported in either the short-term controlled trials or the long-term open-label trials

Laboratory findings

There were few TEAEs related to any laboratory, vital sign, or electrocardiogram (ECG) parameters in any of the brexpiprazole paediatric trials.

There were no clinically meaningful mean changes from baseline or PCR changes in haematology and urinalysis data, vital sign measurements (other than weight and orthostasis-related) or ECG data.

Safety in special populations

Intrinsic Factors

Changes from baseline to last visit, PCR abnormalities, and TEAEs were evaluated by age group (< 15 years and ≥ 15 years) in subjects in the short-term and long-term trials. None of these evaluations revealed any clinically meaningful differences between age groups in the parameters examined.

TEAEs were also evaluated by gender and across race groups with no clinically meaningful differences observed.

Safety related to drug-drug interactions and other interactions

A complete summary of drug-drug interaction trials conducted with brexpiprazole was previously provided in the original submission.

Effect of Alcohol

No trials have been conducted to evaluate the concomitant administration of alcohol and brexpiprazole. Patients will be advised not to drink alcohol when receiving brexpiprazole.

Use in Pregnancy and Lactation

Adequate and well controlled studies have not been conducted with brexpiprazole in pregnant women to inform drug-associated risks.

Two pregnancies were reported in the ongoing long-term Trial 331-10-236 as of the data cutoff date of 10 October 2023. Both were assessed by the investigator as not serious and not related to IMP.

Overdose

Combined data from the completed clinical pharmacology trials indicate that brexpiprazole is safe and well tolerated in healthy subjects at single oral doses of 0.2 mg to 6 mg and at multiple oral doses up to 12 mg/day in combination with sertraline. Data from the completed multiple-dose clinical trials indicate that brexpiprazole is well tolerated at multiple oral doses up to 4 mg/day as adjunctive therapy in subjects with major depressive disorder or ADHD and up to 2 mg/day of brexpiprazole alone in subjects with schizophrenia or schizoaffective disorder. A mild event of intentional overdose was reported in 1 subject in the long-term schizophrenia trial who took 84 mg of brexpiprazole triggered by a physical altercation with a family member.

Drug Abuse

Based on results from animal studies, brexpiprazole does not appear to have rewarding properties consistent with a drug of abuse. Likewise, animals that have received chronic administration of brexpiprazole did not demonstrate any withdrawal signs upon drug discontinuation. These findings suggest that brexpiprazole does not produce physical dependence.

Withdrawal and Rebound

No formal assessments of withdrawal have been conducted in human subjects.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No trials have been performed to evaluate any effects of brexpiprazole on the ability to drive, the ability to operate machinery, or the impairment of mental ability.

Treatment-emergent AEs related to somnolence have been reported with brexpiprazole which could affect the ability of some patients to drive or operate machinery.

Analyses were also conducted for TEAEs related to orthostatic hypotension, dizziness, and syncope which could also affect the ability to drive or operate machinery in some patients.

Discontinuation due to adverse events

Short-term Controlled Trials

In schizophrenia trial 15 (14.2%) subjects were discontinued due to adverse events in 0 (0%) subjects treated with brexpiprazole and 2 (1.5%) subjects in placebo group.

Long-term Open-label Trials

In long term study 101 (34.4%) subjects were discontinued due to adverse events in 9 (3.1%) subjects.

Post marketing experience

The cumulative number of patient-years treated with marketed brexpiprazole worldwide (based on data received until 30 Jun 2023, periodic safety update report [PSUR] 2023) was approximately 1,689,049.22 patient-years. The usual dose of brexpiprazole is 0.25 mg to 4 mg once daily.

Cumulatively, a total of 80 serious adverse events (SAEs) were received from spontaneous reports with a reporting rate of 0.05 serious events per 1000 patient-years of exposure. The most frequently reported SAEs were from the Psychiatric Disorders system organ class (SOC) with 32 (9 events of suicidal ideation, 4 events of psychotic disorder, 4 events of suicide attempt, 3 events of intentional self-injury, 2 events of mood swings, 2 events of paranoia, with the rest of the events each reported once); Nervous System Disorders SOC with 21 (4 events of dystonia, 3 events of seizure, 3 events of altered state of consciousness, 2 events of tardive dyskinesia, 2 events of neuroleptic malignant syndrome, with the rest of the events each reported once); Eye Disorders SOC (6 events); Investigations SOC (3 events); and SOCs of Gastrointestinal Disorders, General Disorders and Administration Site Conditions; Injury, Poisoning and Procedural Complications; Metabolism and Nutrition Disorders; and Musculoskeletal and Connective Tissue Disorders (2 events each).

In a total of 54 cases, the brexpiprazole dose was withdrawn in 29 events. In response to the action taken, 11 events were recovered/resolved, 3 events were recovering/resolving, 2 events were not recovered/not resolved, and outcomes for 13 events were unknown. No events with fatal outcome were reported. Of the 54 cases, 48 events (in 34 cases) were assessed as serious and related, 3 events were confounded by the patient's underlying medical conditions, 17 events were confounded by the concomitant medications and in 28 events, insufficient information was presented regarding one or more case parameters including event onset latency, concomitant medications, past medical history, concurrent medical conditions, action taken with brexpiprazole, event outcome and event details, precluding meaningful causality assessment.

Overall, post-marketing data have been reviewed as a part of annual aggregate safety reports and reported to regulatory agencies as a part of PSURs. A comprehensive and detailed review of all safety data from all available sources such as nonclinical, epidemiology, clinical, and post marketing experience did not reveal a change to the well-established and favourable benefit-risk profile of brexpiprazole for approved indications.

Further, cumulative data from global safety database were provided within the latest 3-year PSUR (Jul 2021 - Jul 2024). In the global safety database search including clinical and post marketing data up to 09 Jul 2024 paediatric adverse events reported for brexpiprazole accounted for 3.2% of all adverse events (1,699 out of 52,859 total AEs) with no new safety concern.

2.5.1. Discussion on clinical safety

The safety data in support of the claimed indication are derived from 2 phase 3 trials conducted in this adolescent population: a short term 6-week double-blind placebo-controlled, active-referenced (completed Trial 33110-234) and a 24-month trial to assess long-term safety and tolerability (ongoing; Trial 331-10-236). These are considered the pivotal trials.
To complement the main safety data set, the MAH is also including as supportive data those coming from 2 completed phase 3 trials (short-term safety, Trial 331-201-00148, and long-term safety and tolerability, Trial 331-201-00191, conducted in paediatric subjects 13 to 17 years old with irritability associated with ASD. The range of brexpiprazole dose tested is 1-4 mg/day.
Safety data from controlled trials are shown in tables showing side-by-side columns for brexpiprazole and placebo in adolescent subjects.

The Safety sample includes all subjects who received at least 1 dose of IMP in the respective trial. The dose range of brexpiprazole in these trials was 1-4 mg/day.
In the short-term dataset, safety data were analyzed for 236 randomized subjects who had received ≥ 1 dose of investigational medicinal product (IMP), including 119 in the all brexpiprazole group and 117 in the placebo group.
A total of 314 subjects were exposed ≥ 1 dose of IMP in the long-term open-label trials and were included in the safety analyses of these 294 in the schizophrenia trial.

Exposure: In the long-term schizophrenia trial 69.7% of subjects were exposed to brexpiprazole dose 1-4mg for 12 months and only 6.5% of subjects for 2 years. However, the EMA GL clearly states that "long term safety data (2 years) should be generated, with a requirement of 12 months safety data before licensing, and the other part finalized post-licensing, e.g. through observational studies and registries". Upon request the MAH provided updated safety data from the 331-10-236 study (data cut-off 13 Sept 2024), DMC Open-session Minutes, DMC Recommendation). Further, cumulative data from global safety database were provided.

Discontinuation: in the short-term trials 8.0% subjects randomized to treatment in the short-term controlled trials were discontinued. The majority of subjects who discontinued from the trials were withdrawn by a parent or guardian (7 subjects). A total of 4 subjects discontinued due to an AE, including 2 in the brexpiprazole group in the ASD trial and 2 in the placebo group in the schizophrenia trial. Lack of efficacy was the reason for discontinuation of 4 subjects who were receiving placebo, including 3 in the schizophrenia trial and 1 in the ASD trial. No subjects in the brexpiprazole group were discontinued due to lack of efficacy.
In the long-term schizophrenia trial at the data cutoff date (10 October 2023), 47.6% subjects had completed the trial, 34.4% subjects had discontinued.
The majority of subjects in the pooled trials discontinued due to withdrawal of consent by the subject/parent or guardian; only a minority of subjects (3.1%) discontinued due to an AE.
Given that the discontinuation rate of antipsychotics in early-onset schizophrenia is a significant concern, usually due to side effects and challenges with adherence, the observed rates are considered acceptable.

The baseline characteristics were generally comparable between treatment groups and within the short-term trials. The majority of subjects enrolled in these trials were rollovers from the short-term trials which was reflected in the similarity of key characteristics between the long-term trials and the short-term lead-in trials.

Adverse events: The majority of adverse events occurred in brexpiprazole trials were mild or moderate in severity.
In short-term schizophrenia trials the incidence of TEAEs was similar between the brexpiprazole group and the placebo group (40% and 40.4%, respectively), same figure in the ASD study. A total of 4 subjects experienced serious TEAEs (1 Brex and 3 PLB). The majority of TEAEs were mild or moderate in intensity with severe events experienced by 2 (1.8%) subjects in the brexpiprazole group and 1 (0.9%) subject in the placebo group. Similar figure is in ADS group.
In the schizophrenia long-term open-label trials, the incidence of TEAEs was 62.6%. Serious TEAEs were experienced by 9 subjects (only 1 in ASD group). The majority of TEAEs were mild or moderate in intensity with severe events experienced by 9 (3.1%) subjects.
TEAEs: The incidence of individual TEAEs was generally low overall in the short-term and long-term trials.
TEAEs in short-term schizophrenia trial: nausea, headache, somnolence and akathisia were the most frequently reported TEAEs in the short-term trials with a slightly higher frequency (excluding somnolence) in the brexpiprazole group as compared with placebo. Type and frequency of TEAEs reported in adolescent schizophrenia Trial 331-10-234 were similar to those observed in adult schizophrenia trials. Overall, there has been no increase in frequency, severity, or relatedness of these AEs during adolescent schizophrenia Trial 331-10-234. No new safety issues or ADR identified in adolescent schizophrenia population.

Since “headache” and “somnolence” were missing in the PI, the MAH was asked to include them in section 4.8. For the AE “headache” the MAH argumentation for considering the event not specific for brexpiprazole were followed and “headache” was not included in section 4.8.
Regarding “somnolence”, even though it is acknowledged that somnolence-associated events in adolescents with schizophrenia may be due to several pharmacological and non-pharmacological causes, it should be considered that:
1) The overall incidence of TEAEs associated with somnolence tended to be higher in brexpiprazole arm compared to placebo arm (8.4% vs 6.8%) (see Table 2.7.4.3.14.1-1). Indeed, despite being the incidence of Somnolence AE in the short-term 331-10-234 trial similar in the brexpiprazole and placebo groups, in this small patient population it is noted that Hypersomnia was more frequent in the brexpiprazole group (2.7%) when compared to placebo (1.9%). Further, Sedation is a recognised ADR.
2) Updated data from long-term Trial 331-10-236 confirmed Somnolence as one of the most frequent TEAEs associated with brexpiprazole use. Somnolence associated TEAEs were reported in 11.9% of subjects with schizophrenia: 10.5% experienced events of Somnolence, 1.4% experienced events of Sedation, and 0.7% experienced events of Hypersomnia.
3) The inclusion of Sedation in table at section 4.8 as a recognised potential adverse event of brexpiprazole among ADRs supports biological plausibility of Somnolence also being associated with brexpiprazole use.
4) Inclusion of Somnolence in section 4.8 would not have effects on section 4.7 Effects on ability to drive and use machines as information on influence on the ability to drive and use machines due to potential nervous system effects is already included.
In conclusion, taking into account the aforementioned points and the relevant incidence rate observed in long-term treatment (Common), as well as the fact that a causal relationship between brexpiprazole and somnolence-related events is at least plausibly possible and cannot be ruled out, information regarding this undesirable effect has been included in the SmPC, along with a brief description under subsection Paediatric population.
Long term schizophrenia trial: weight increased, somnolence, headache, nasopharyngitis, and akathisia were the most frequently reported TEAEs in the long-term trials. No deaths occurred in either of the short or long-term controlled trials.

No new safety signals were observed in Trial 331-10-236, and the safety results were consistent with the current safety profile of brexpiprazole.

Akathisia, nausea, sedation, and weight increased have been reported in adult schizophrenia population and are considered as ADRs in the current 4.8 section of the SmPC. Evidence suggests a possible causal association between these events and use of brexpiprazole and they should be monitored.

There were no clinically important findings related to hepatic impairment, orthostatic hypotension, dizziness, and syncope in the brexpiprazole short- and long-term trials.

AESI of special interest
Extrapyramidal symptoms (EPS) are a known ADR. The incidence of these extrapyramidal symptoms in adolescent population was consistent with adult schizophrenia trials. Akathisia was the most frequently reported EPS related ADR in the brexpiprazole 1 mg/day to 4 mg/day group (3.6 %) compared to 2.9 % in placebo in the short-term study. In the ongoing long-term, open label study in paediatric patients with schizophrenia treated with 1 to 4 mg brexpiprazole, the incidence of akathisia events for brexpiprazole-treated paediatric subjects was 5.1 %. The aripiprazole arm from Trial 331-10-234 was not presented. It is noted, however, that rate of ADRs may differ between brexpiprazole and aripiprazole, suggesting a more favourable safety profile for brexpiprazole for akathisia and anticholinergic side effects (brexpiprazole has a negligible affinity for the muscarinic acetylcholine receptors) (*Huhn M et al, Lancet 2019*). The MAH has been requested to present comparative safety data for the three treatment arms (brexpiprazole, aripiprazole, placebo) from study 331-10-34. According to the data MAH presented, brexpiprazole appears to have a more favourable safety profile

regarding akathisia and anticholinergic side effects compared with aripiprazole for the treatment of schizophrenia.

Brexpiprazole may have the pharmacodynamic potential to induce Neuroleptic Malignant Syndrome, that is no more included in the RMP as it is considered a well-known ADR and does not require additional risk mitigation measures/activities.
Suicidality: Risk of suicidal behaviour is intrinsic to psychotic disorders and may be reported early after initiation or switch of antipsychotic treatment. The potential for the test product to precipitate suicidal thoughts and behaviour should be actively monitored, as recommended in Section 4.4 of the SmPC. In schizophrenia Trial 331-10-234, one subject had a TEAE associated with suicidality of intentional self-injury. In the long-term trials, treatment-emergent suicidal ideation was reported by 15 subjects (5.1%) during the treatment period with the first appearance at Month 3. No subjects reported emergence of serious suicidal ideation or worsening of suicidal ideation. Compared to lifetime history related to suicidality as reported by the adolescent study participants, reported long-term on-treatment rates seem to be higher. Further, in the Table in Section 4.8 of the SmPC Suicide attempt and Suicidal ideation are reported as uncommon ADRs (≥ 1/1 000 to < 1/100). The MAH was requested to discuss suicidality related ADRs in the adolescent population focusing on causal relationship based on Investigator- and Sponsor-judged relatedness to brexpiprazole, and on comparative incidence rates with the adult population and with aripiprazole treatment. Moreover, the MAH was asked to provide information for the suicidality-related ADRs (in short-term and long-term trials) in the appropriate sections of the SmPC (4.4 and 4.8). The MAH provided the requested details, and all reported events were considered not to be related to brexpiprazole. It was concluded that the observed frequency of suicidal events in the ongoing 2-year long-term open-label adolescent trial (2.7%) is similar to the incidence observed in the long-term open-label adult trials (1.6%) where subjects were treated up to a 1-year duration. As the frequency of suicidal events in the adult population with schizophrenia is considered ‘uncommon’ in the current brexpiprazole SmPC, it is concluded to be the same in the adolescent population with schizophrenia with no changes proposed for the SmPC.

Metabolic changes: antipsychotics have been associated with metabolic changes, including weight gain and dyslipidaemia. Metabolic adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients. Weight gain has been observed with brexpiprazole.
TEAEs associated with abnormal weight gain in schizophrenia Trial 331-10-234 were reported in 6 (2.5%) subjects. Weight increased was reported in 2 (1.7%) subjects in the all brexpiprazole group and 4 (3.4%) subjects in the placebo group.
Highest incidence of TEAEs associated with weight abnormalities in the long-term trials were weight increased reported in 39 (12.4%) subjects. Other weight-related TEAEs were BMI increased, increased appetite, and waist circumference increased; none were reported in more than 1.3% subjects. Weight increased, is consistent with the known safety profile of brexpiprazole for the adult population and should be monitored. The actual text in the 4.8 section of the SmPC was revised.
Related to metabolic changes is hyperglycaemia is considered a class effect for SGAs. Also, brexpiprazole use in patients with insulin-dependent diabetes mellitus (IDDM) is a missing information and regular monitoring of blood glucose is recommended in the proposed SmPC in Section 4.4.
With regard to sexual maturation, during the long-term trial, both genders showed an increase in Tanner stages in line with their age, transitioning from Stage 3 to Stage 5.
Laboratory tests: There were no clinically important differences between the all brexpiprazole and placebo groups in any laboratory test values or vital sign measurements in the short-term trials and no notable changes from baseline in any of these parameters were reported in the long-term trials.
Modest increases in serum prolactin were seen with brexpiprazole compared with placebo in the short-term trials but none of these changes were clinically significant.
Hyperprolactinaemia is a very common adverse event of brexpiprazole and a significant side effect of many antipsychotic medications, particularly those that strongly block dopamine receptors.
There were no clinically important findings related to QT prolongation Rhabdomyolysis and CPK Elevation in the brexpiprazole short- and long-term trials.

No clinically meaningful differences between age groups in all the parameters examined, although the sample size is limited particularly for the <15 years group.

2.5.2. Conclusions on clinical safety

Overall, the brexpiprazole safety profile is favourable and manageable in the adolescent population and seems not to differ from what is known for adult subjects.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation Use in elderly (age > 65)

Pharmacovigilance plan

Table 3.3-1	**III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities**			
Study and Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation - Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances - Not applicable				

Category 3- Required additional pharmacovigilance activities				
Data collection from participation in the Pregnancy Registry - NPRAA Ongoing	Primary: To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric medications Secondary: 1) To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics 2) To evaluate maternal health outcomes associated with use of psychiatric medication during pregnancy 3) To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to atypical antipsychotics	Missing Information: Use in pregnancy and lactation	Periodic updates	Data have been reviewed on an ongoing basis as it is provided to the MAH as per associated published literature, and utilised in signal detection and provided in the PBRER/ PSUR when available.

Risk minimisation measures

Table 5.3-1	V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC Sections 4.6, 5.3 • PL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Data collection from participation in the NPRAA
Use in elderly (age >65)	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, 5.2 • PL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance.

Changes were also made to the PI to bring it in line with the current Agency/QRD template and SmPC guideline, which were reviewed and accepted by the CHMP.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Rxulti. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Schizophrenia is a chronic debilitating illness with an approximate prevalence of 1% worldwide.

Childhood-onset psychotic disorders before the age of 13 years are rare, but there is a considerable increase in the prevalence during adolescence. Up to one-third of patients with schizophrenia develop the disease during adolescence.

The diagnosis of schizophrenia in children and adolescents is made using the same diagnostic criteria in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as for adult-onset

schizophrenia. Early-onset schizophrenia, defined as schizophrenia onset before 18 years of age, is phenomenologically continuous with schizophrenia in adulthood and has high diagnostic stability.

Data from phenomenological, cognitive, neuroimaging, and genetic studies suggest a similar profile of clinical and neurobiological abnormalities between early- and adult-onset patients. Though similar profiles, early onset patients tend to have more severe negative symptoms, cognitive impairment, impulsivity, frequent hospitalizations, and poor social functioning compared with adult-onset schizophrenia.

While a longer duration of untreated psychosis in adolescent schizophrenia patients was associated with a lower level of functioning, less functional improvement, and lower rates of clinical remission, there still remains limited availability of approved medications in the European Union (EU) for this patient population.

3.1.1. Disease or condition

Schizophrenia is a life-long psychiatric disorder. The cardinal symptoms fall into 3 domains: positive symptoms such as delusions and hallucination, negative symptoms such as lack of drive and social withdrawal, and cognitive symptoms such as problems with attention and memory.

3.1.2. Available therapies and unmet medical need

There are high unmet needs for a wider availability of antipsychotics with fewer side effects (eg, sedation, extrapyramidal symptoms [EPS], metabolic symptoms, prolactin changes, and suicidality), which may help lead to higher medication compliance in adolescents who may be more vulnerable and sensitive to antipsychotic side effects compared with adults.

Latuda (lurasidone) film-coated tablets, indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over, was approved in 2014 in adults and on 2020 variation II/29 was approved to extend indication in adolescents from 13 years of age.

3.1.3. Main clinical studies

The clinical development program consists of 3 trials: one phase 1 dose-escalation trial (Trial 331-10-233) and two phase 3 clinical trials (Trial 331 10 234 and ongoing Trial 331-10-236) to demonstrate a statistically significant improvement for brexpiprazole compared to placebo for the primary efficacy endpoint, mean change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score.

In addition, a paediatric extrapolation study was completed (Study 331-201-00185) to provide evidence of maintenance of efficacy of brexpiprazole monotherapy based on extrapolation of data from both adolescent and adult subjects with schizophrenia.

3.2. Favourable effects

In Trial 331 10 234, the primary efficacy endpoint (change from baseline to Week 6 in PANSS Total Score) results showed LS Mean Change from baseline to Week 6 in PANSS of –22.75, -23.95 and –17.42 for brexpiprazole, aripiprazole and PLB, respectively. LS mean difference between Brex and PLB of PANSS improvement was −5.33 [95% CI: −9.55, −1.10]), which is statistically significant (p = 0.0136). Results are considered of clinical relevance.

Subjects enrolled in the long-term 331-10-236 trial show a consistent decrease in the PANSS score and a positive impact on symptoms up to 24 months.

Results from subgroup analysis by age cut-offs obtained in the long-term trial, showed similar improvements in PANSS total score in respect to baseline across the two different subgroups with a mean change of PANSS score of roughly -19-20 at last visit, thus providing support that long term treatment would be needed to achieve a benefit in younger subjects.

Results from the long-term trial support improvement in both symptoms (PANSS Positive and Negative sub-scores) showing a similar trend in the mean change from baseline through Month 24.

Results from secondary endpoints at week 6 show some positive impact of the treatment on symptoms (excluding negative symptoms) and minimal impact on the Clinical Global Impression-Severity of Illness Scale (CGI-S, MMRN) scores. However, in the long-term trial, severity of illness, as measured by CGI-S improved from baseline to last visit for both rollover and de novo subjects thus providing reassurance that an impact could be seen with a longer treatment.

Continuous improvement in psychological, social, and school functioning as evaluated by the CGAS which is of value.

A positive impact (nominal p) of brexpiprazole on CGI-I (Clinical global impression-improvement) scores, was seen in the short-term trial and confirmed in the long term. A high percentage of subjects (68.8%, 83.6%, and 70.8%) scored ‘much’ or ‘very much’ improvement on the CGI-I during the open-label treatment period at Month 12, Month 24, and Last Visit. Of note, the improvement was sustained through the study, with lower scores in the last months of treatment.

83.6% of subjects responders at month 24 in 331-10-236 trial (showing a ≥ 30% improvement from baseline in PANSS Total Score or having a CGI-I Score of 1 or 2) which is clinically relevant.

Comparison of exposure and E/R relationship between adolescents and adults was provided (Report 331-24-201) showed that simulated brexpiprazole exposure were comparable between adolescents and adults, although the median Cmax,ss was slightly higher in adolescents.

Results of study 331-201-00185 meant to define the similarity of efficacy between adults and adolescents. Upon request of further sensitivity analysis on primary and secondary endpoints, and given that it was not possible to perform retrieved dropout or placebo-based multiple imputation methods for handling missing data, the MAH performed a sensitivity analysis based on multiple imputation with a delta (shift) method and on multiple imputation according to direct Bernoulli sampling approach.

The results up to Week 6 are similar to the main analysis due to the very low number of missing values, showing larger response rate for adults than for adolescents. At week 32, where missing values in adults is higher than for adolescents, the 95%CI of the response rate for adults and adolescents overlap suggesting no major difference between age groups.

3.3. Uncertainties and limitations about favourable effects

Although the evaluation of treatment difference based on the primary efficacy endpoint in the 331-10-234 trial reached statistical significance the LS mean difference was smaller than in the assumption (-7.4 points) made for sample size calculation. Thus, the results highlight that the impact of brexpiprazole short-term treatment on PANSS is of limited effect size over PLB response, which instead is high. Hence, the clinical relevance of these short-term study results is uncertain however a high PLB response is noted and importantly, due to the chronic course of schizophrenia and a continued need for treatment, the clinical relevance of the treatment effect should be seen in the context of long-term treatment and of

adolescents as target population characterized by a more difficult to treat disease and to achieve response.

Analysis of the primary endpoint (PANSS total score) was performed stratified by age (e.g. <15 years versus ≥15 years old) showing inconsistent results between groups with dismal difference seen in the <15-year-old age subgroup (change of -20.62 in brexpiprazole with LS Mean Difference from PLB of -0.10, 95% CI-7.41,7.21). This finding may reflect the difficulty of treating patients under 15 years of age, as early onset of schizophrenia is usually associated with a more severe/difficult to treat course, especially in the first weeks of treatment; also, a different response of PLB is noted.

In addition, considering the two components of the primary outcome PANSS total score, results from the short-term trial highlight only a limited impact of the treatment on negative symptoms as compared to the effect on positive symptoms. Achieving an impact on PANSS Negative subscale scores (MMRM) is challenging in the short term, representing a known difficult clinical symptom to be impacted by treatment in adolescent schizophrenic patients.

Even if results from secondary endpoints at week 6 show some positive impact of the treatment on symptoms, a minimal impact on the Clinical Global Impression-Severity of Illness Scale (CGI-S, MMRN) scores in the short-term trial.

However, in the long-term trial, severity of illness, as measured by CGI-S improved from baseline to last visit for both rollover and de novo subjects thus providing support that an impact could be seen with a longer treatment. Moreover, subjects experienced continuous improvement in psychological, social, and school functioning as evaluated by the CGAS which is of value.

In order to support brexpiprazole as maintenance treatment, available data on exacerbations (positive and negative symptoms) have been requested. The MAH highlighted that schizophrenia exacerbations (positive and negative symptoms) were not formally defined in the 331-10-236 trial protocol. Available data on exacerbations of schizophrenia are however captured in subjects that withdrew from the trial due to lack of efficacy and in subjects who experienced TEAEs of schizophrenia (including verbatim terms: schizophrenia exacerbation, exacerbation of schizophrenia, worsening/increase of symptoms of schizophrenia, schizophrenia/worsening of symptoms, exacerbation of paranoid schizophrenia, increase of schizophrenia symptoms) in Trial 331-10-236.

Similarity of disease between adults and adolescents, as assumption for an extrapolation strategy, has some uncertainty since negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning in adolescent patients and the disease tends to follow a more severe course, has lower response to treatment and a worse long-term prognosis than adult-onset schizophrenia.

3.4. Unfavourable effects

The majority of TEAEs were mild or moderate in intensity in both short- and long-term studies. Severe events experienced by 2 (1.8%) subjects in the brexpiprazole group and 1 (0.9%) subject in the placebo group in the Trial 331-10-234 and 9 (3.1%) subjects in the Trial 331-10-236. No deaths occurred in either of the short or long-term controlled trials.

There has been no increase in frequency, severity, or relatedness of these TEAEs during adolescent schizophrenia short term Trial 331-10-234. No new safety issues or ADR identified in adolescent schizophrenia population.

Nausea, headache, somnolence and akathisia were the most frequently reported TEAEs in the short-term trials with a slightly higher frequency (excluding somnolence) in the brexpiprazole group as compared with placebo.

Weight increased, somnolence, headache, nasopharyngitis, and akathisia were the most frequently reported TEAEs in the long-term trials.

With regard to AESI of special interest Extrapyramidal symptoms (EPS) are a known ADR. The incidence of these extrapyramidal symptoms in adolescent population was consistent with adult schizophrenia trials. Akathisia was the most frequently reported EPS related ADR in the brexpiprazole 1 mg/day to 4 mg/day group (3.6 %) compared to 2.9 % in placebo in the short-term study. In the ongoing long-term, open label study in paediatric patients with schizophrenia treated with 1 to 4 mg brexpiprazole, the incidence of akathisia events for brexpiprazole-treated paediatric subjects was 5.1 %.

No Neuroleptic Malignant Syndrome cases are registered.

In schizophrenia Trial 331-10-234, one subject had a TEAE associated with suicidality of intentional self-injury. In the long-term trials, treatment-emergent suicidal ideation was reported by 15 subjects (5.1%) during the treatment period with the first appearance at Month 3. No subjects reported emergence of serious suicidal ideation or worsening of suicidal ideation. Episodes of suicidal behaviour were reported in 4 adolescents (1.4%). All events were considered not related to IMP and the suicide-related safety profile observed in the adolescent population appears to be similar to that observed in the adult population. The data provided are considered sufficient and, at the moment, an update of the SmPC with regard to suicidality in adolescents is not needed.

Metabolic changes antipsychotics have been associated with metabolic changes, TEAEs associated with abnormal weight gain in schizophrenia Trial 331-10-234 were reported in 6 (2.5%) subjects. Weight increased was reported in 2 (1.7%) subjects in the all brexpiprazole group and 4 (3.4%) subjects in the placebo group.

Highest incidence of TEAEs associated with weight abnormalities in the long-term trials were weight increased reported in 39 (12.4%) subjects. Other weight-related TEAEs were BMI increased, increased appetite, and waist circumference increased; none were reported in more than 1.3% subjects.

With regard to sexual maturation, during the long-term trial, both genders showed an increase in Tanner stages in line with their age, transitioning from Stage 3 to Stage 5.

Laboratory tests: There were no clinically important differences between the all brexpiprazole and placebo groups in any laboratory test values or vital sign measurements in the short-term trials and no notable changes from baseline in any of these parameters were reported in the long-term trials.

Modest increases in serum prolactin were seen with brexpiprazole compared with placebo in the short-term trials but none of these changes were clinically significant. Hyperprolactinaemia/Related Disorders is an important Potential Risk.

There were no clinically important findings related to QT prolongation Rhabdomyolysis and CPK Elevation in the brexpiprazole short- and long-term trials.

3.5. Uncertainties and limitations about unfavourable effects

In the long-term schizophrenia trial 331-10-236, 69.7% of subjects were exposed to brexpiprazole dose 1-4 mg for 12 months and only 6.5% of subjects for 2 years. Long-term safety data from the last PSUR (DLP: 10 Jul 2021 – 09 Jul 2024) and the last DMC meeting minutes (May 2024) have been provided.

Antipsychotics have been associated with metabolic changes, including weight gain and dyslipidaemia. Metabolic adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients. Weight gain is an important identified risk in the RMP and a higher frequency of weight increased has been observed with longer exposure and hence, its related impact on risk of obesity and metabolic disturbances cannot be ruled out in clinical trials and post marketing data are needed.
No clinically meaningful differences between age groups in the parameters examined, however, the sample size is limited particularly for the <15 years group.

3.6. Effects Table

Effects Table for Rxulti indicated for the treatment of schizophrenia in adults and adolescents aged 13 years and older (data cut-off: 10 October 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
LS Mean (SE) Change at Week 6 in PANSS	−22.75, -23.95 and −17.42 for Brex, Ari and PLB.	Brex and PLB of −5.33 [95% CI: −9.55, −1.10], p= 0.0136).			A reduction of at least 15 points and up to 20 points on average at the PANSS scale is considered clinically relevant. However, the LS mean difference was lower than the assumption in treatment difference of -7.4 points made for sample size calculation. Thus, the results highlight a high PLB response (seen in schizophrenia trials).	Trial 331-10-234
LS Mean (SE) Change until Week 24 in PANSS	mean (SD) change of −19.18 (15.10), −25.87 (17.39), and −19.12 (17.61) from baseline in PANSS Total Score at Month 12, Month 24, and last visit					Trial 331-10-236
Unfavourable Effects						
TEAEs in short term schizophrenia trial					Nausea, headache, somnolence and akathisia were the most frequently reported TEAEs in the short-term trials with a slightly higher frequency (excluding somnolence) in the brexpiprazole group as compared with placebo.	Trial 331-10-234
Long term schizophrenia trial					Weight increased, somnolence, headache, nasopharyngitis, and akathisia were the most frequently reported TEAEs in the long-term trials. In Schizophrenia Trial 331-10-234, TEAE suicidal ideation and TEAE suicidal behaviour were 5.1% and 1.4%, respectively	Trial 331-10-234

Abbreviations: PANSS= Positive and Negative Syndrome Scale; TEAE= treatment-emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Brexpiprazole demonstrated efficacy as measured by reduction at the PANSS scores from baseline to week 6 and to long term.

In the short-term trial, an aripiprazole arm was included in addition to a placebo arm, to provide assay sensitivity. The magnitude of treatment effect of brexpiprazole similar to that of aripiprazole, and this puts the efficacy of brexpiprazole in context even though it is acknowledged that the trial is not powered for superiority or head-to-head comparison.

For the PANSS total scores at weeks 6, brexpiprazole showed a statistically significant improvement with a LS mean (SE) change of -22.75 (1.49) (p=0.0136), similar to that found for the aripiprazole group (LS mean (SE) change: -23.95 (1.57), nominal p = 0.0032). This is considered of clinical relevance.

Notably, a high placebo response was observed in this study (LS mean (SE) change: -17.42 (1.58). The placebo response in clinical trials with adolescent schizophrenia is an area of increasing concern, as it tends to be even higher than in adult trials. Other trials evaluating antipsychotics in adolescent schizophrenia have shown high placebo response rates, reflecting the challenges seen ins this population.

Of note, adolescents are often more susceptible than adults to the psychological and environmental factors that contribute to placebo effects.

Given that a reduction of at least 15 points and up an average of 20 points on average at the PANSS scale is considered clinically relevant, the overall response in the brexpiprazole arm is considered clinically relevant.

The result for the primary efficacy endpoint is supported by the findings for some secondary endpoints (PANSS Positive Subscale scores, CGI-I scores, and response rates) which showed an improvement with nominal p-values < 0.05.

Considering the above and given the history of large placebo effects in the adolescent disease setting, the efficacy of brexpiprazole in the short term is considered sufficiently demonstrated for the adolescent population, whilst the large improvement observed in the placebo arm.

Regards to maintenance of effect, data from long term treatment up to 24 months shows, in respect to baseline, a consistent decrease in the PANSS score and a positive impact on symptoms, providing support that long term treatment would be needed to achieve a benefit in younger subjects.

In addition, considering the two components of the primary outcome PANSS total score, results from the short term trial highlight only a limited impact of the treatment on negative symptoms as compared to the effect on positive symptoms (PANSS positive subscale scores at week 6, LS mean difference at Week 6 = −1.44 [95% CI: −2.65, −0.22], p = 0.0205 with nominal p-value < 0.05; PANSS Negative Subscale scores at Week 6, LS mean difference = −0.88 [95% CI: −2.04, 0.28], p = 0.1360, numerical change (not nominal p reached). These results could be expected from a clinical perspective since achieving an impact on PANSS Negative subscale scores (MMRM) is challenging in the short term, representing a known difficult clinical symptom to be impacted by treatment in adolescent schizophrenic patients.

Results from the long-term trial are somehow reassuring since improvement in both symptoms (PANSS Positive and Negative sub-scores) are impacted showing a similar trend in the mean change from baseline through Month 24.

Subgroups of patients above and below 15 years of age

In the pivotal study, no short-term clinical benefit was observed in the subgroup of children below 15 years. Data are limited, but in line with previous aripiprazole data in the youngest adolescents. Placebo response was rather high in this age subgroup. However, a similar placebo response was observed in the aripiprazole adolescent study (~-20 points reduction).

In the older subgroup (aged 15 to 17), on the contrary, a similar short-term response as in adults was observed (PANSS: -8.05 [-13.3, -2.80]). This is not unexpected since they are closer to the adult population. Therefore, to establish maintenance of effect, and considering that PK data for the different age groups are as would be expected, data may be extrapolated from adults to adolescents as of the age of 15 years, per EMA guidance (EMA/CHMP/40072/2010 Rev.1).

Results from subgroup analysis by age cut-offs obtained in the long-term trial, showed similar improvements in PANSS total score across the two different subgroups with a mean change of PANSS score of roughly 19-20 at last visit noting de novo subgroup showing a better change.

In consideration of the results obtained at primary endpoint analysis for the whole paediatric population, the consistency of short- and long-term treatment effects across age groups as well as biological plausibility the credibility of beneficial effect and extrapolation of efficacy results to the younger paediatric population is supported.

The extrapolated efficacy taken together with the similar safety profile based on observed TEAEs in adult vs younger adolescent population, supports a favourable B/R of brexpiprazole in children aged 13-14 years.

3.7.2. Balance of benefits and risks

Results from the short-term trial suggest an overall positive effect of brexpiprazole in improving symptoms of schizophrenia in adolescents. Long-term open label efficacy data show an overall decrease of PANSS total score and maintenance of effect over time.

In the younger paediatric population (i.e. 13-14 years of age) beneficial effect is considered credible, although with some degree of uncertainty. Overall, the brexpiprazole safety profile is favourable and manageable in the adolescent population, and it does not seem to differ from what is known for adult subjects.

3.7.3. Additional considerations on the benefit-risk balance

There are no additional considerations on the benefit-risk balance.

3.8. Conclusions

The overall B/R of Rxulti in the sought indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of schizophrenia in adolescent patients aged from 13 years to 17 years for RXULTI, based on results from the following clinical studies: one phase 1 dose-escalation trial (Trial 331-10-233) and two phase 3 clinical trials (Trial 331-10-234 and ongoing Trial 331-10-236). In addition, a paediatric extrapolation study was completed (Study 331-201-00185). These studies investigated the efficacy and safety of brexpiprazole in paediatric patients (13-17 years old) with schizophrenia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, and to bring the PI in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

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.

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Rxulti-H-C-003841-II-0015’