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SCIENCE MEDICINES HEALTH

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Human Medicines Division

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

RXULTI

brexpiprazole

Procedure no: EMA/H/C/003841/P46/002 and EMA/H/C/003841/P46/003

Note

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



Status of this report and steps taken for the assessment

Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	20 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	n/a	☐
☒	CHMP adoption of conclusions:	14 Dec 2023	14 Dec 2023	☐

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1. Introduction

On 27th September 2023, the MAH submitted two completed paediatric studies for RXULTI (brexpiprazole), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

measure. Short critical expert overviews have also been provided.

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

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the two clinical Trials, 331-201-00148 and 331-201-00191 are part of a commitment with the US FDA, under a Paediatric Written Request, and were conducted beyond the studies included in the EU PIP. This combined Article 46 submission of two study reports within 6- month post-last patient last visit (LPLV) of Trial 331-201-00191 was agreed with the Agency on 21 December 2022.

The two studies were conducted in children and adolescents with irritability associated with autism spectrum disorder (iASD) to assess the efficacy and safety of brexpiprazole treatment. No regulatory consequences were identified by the MAH.

2.2. Information on the pharmaceutical formulation used in the studies

The following marketed dosage formulations of brexpiprazole were used in Trial 331-201-00148 and Trial 331-201-00191: 0.25-, 0.5-, 1-, 2-, and 3-mg tablets for oral use.

2.2.1. Introduction

The MAH submitted final reports for:

- **Study 331-201-00148**, a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder;
- **Study 331-201-00191**, A Phase 3, Multicenter, Open-label Trial to Evaluate the Long-term Safety and Tolerability of Brexpiprazole in the Treatment of Children and Adolescents with Irritability Associated with Autism Spectrum Disorder.

The results of these trials do not support seeking an indication of the treatment of iASD.

Clinical study number and title

Study number: 331-201-00148

Title: Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder.

Description

Trial 331-201-00148 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 8-week trial, designed to evaluate the effects of flexibly-dosed brexpiprazole 0.25 to 3 mg/day, compared with placebo on irritability in children and adolescent subjects, ages 5 to 17 years, with a diagnosis of ASD according to DSM-5.

Methods

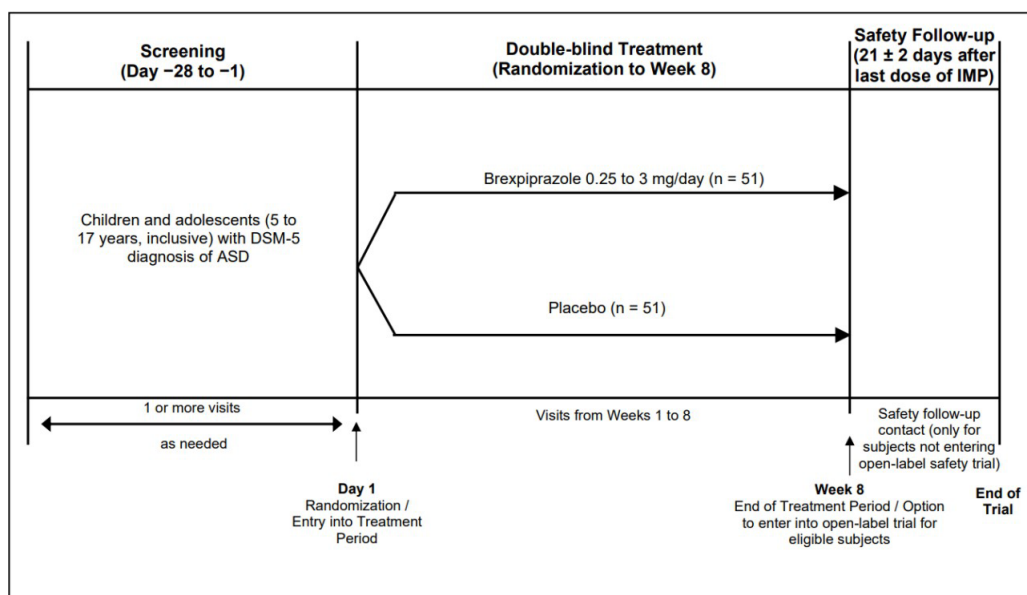
The trial consisted of a 1 to 28 day screening period, followed by an 8 week double-blind treatment period, and a 21-day post-treatment safety follow-up period. The trial was conducted on an outpatient basis.

Subjects who continued to meet entrance criteria at the baseline visit (Day 1) were randomized 1:1 to receive brexpiprazole or placebo daily. On Day 1 of the treatment period, subjects began titration to a target minimum dose of investigational medicinal product (IMP). The target dose range of IMP was determined for each individual subject based on body weight.

During the double-blind treatment phase, evaluations were planned on Day 1 (baseline) and at Weeks 1, 2, 3, 4, 6, and 8. Due to the COVID-19 pandemic, a protocol addendum was added stating that screening and baseline visits were required to be in office and all other visits could be virtual visits.

Where the investigator and caregiver made the decision to conduct a visit virtually, the visit was conducted by means of telecommunications technology. The caregiver and subject remained in their own home and completed trial assessments and questionnaires via an online technology. The caregiver and subject interacted with trial personnel using online communication tools which incorporated telemedicine. During virtual interactions (and at any other time), the trial personnel were able to assess the subject and determine if an additional in-office visit for a physical evaluation was required at the discretion of the investigator.

A schematic of this trial design is provided in figure below.



Study participants

A total of 260 subjects were screened for this trial and 119 subjects were randomized to double-

blind IMP. The Safety Sample comprised of 115 subjects who received at least 1 dose of IMP. One subject (in the placebo group) was included in the Safety Sample but not the Efficacy Sample (the subject's baseline ABC assessment occurred 3 days after the date of their first IMP dose and was not considered a valid baseline efficacy assessment).

Subjects had to meet the following key inclusion criteria at both baseline and screening:

- Male and female subjects 5 to 17 years of age, with a current primary DSM-5 diagnosis of ASD, as determined by the investigator and supported by the Autism Diagnostic Interview - Revised (ADI-R).
- Subjects with an ABC-I subscale score ≥ 18 and with a CGI-S scale score ≥ 4 pertaining to irritability at screening and at baseline (Day 1).
- Subjects must have had a mental age of ≥ 2 years, as determined by the investigator based on school participation, social history, or medical records.

Treatments

Eligible subjects were allocated in a 1:1 ratio at randomization to one of the following two treatment groups:

- Flexibly-dosed brexpiprazole (0.25- 3 mg/day, weight based)
- Placebo

All doses of brexpiprazole and matching placebo were taken orally once daily, preferably in the morning, and were administered without regard to meals.

The target dose range of IMP was determined for each individual subject based on body weight. Subjects with body weight < 50 kg received a target dose range of 1 to 1.5 mg, and subjects with body weight ≥ 50 kg received a target dose range of 1.5 to 3 mg. Body weight at the time of randomization determined dose/titration requirements throughout the trial.

Objective(s)

The primary objective of this trial was to evaluate the efficacy, safety, and tolerability of brexpiprazole in reducing irritability in children and adolescents ages 5 to 17 years with a diagnosis of ASD.

Outcomes/endpoints

Primary Efficacy

Endpoint

The primary efficacy endpoint of this trial was the mean change from baseline to Week 8 in the Aberrant Behavior checklist Irritability (ABC-I) subscale score.

Secondary Efficacy Endpoint

The key secondary endpoint of this trial was the mean change from baseline to Week 8 in Clinical Global Impressions Severity (CGI-S) score for irritability.

Safety Endpoints

Safety was assessed by the following standard endpoints for clinical trials and trials of

antipsychotic drugs:

- Frequency and severity of adverse events (AEs), serious AEs (clinical and laboratory), and discontinuation from the trial due to AEs
- Weight, height, body mass index (BMI), and waist circumference
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs and electrocardiogram (ECG) parameters
- Extrapyramidal symptom (EPS) scale scores: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS)
- Potential suicide events recorded on suicidality scale scores (Columbia-Suicide Severity Rating Scale [C-SSRS])

Exploratory Endpoints

Exploratory efficacy endpoints included:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sample size

Determination of Sample Size: Approximately 102 subjects were estimated to be randomized (51 per treatment arm). A sample size of 51 subjects per arm provided at least 85% power at a nominal 2- sided alpha level of 0.05 to detect a 6.0-point reduction in change from baseline in ABC-I subscale score for brexpiprazole versus placebo, assuming a standard deviation (SD) = 10.

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

- *Randomized Sample:* All subjects who were randomized into the trial. Subjects were considered randomized when they were assigned a treatment number by interactive research technology (IRT) at the end of the screening period. Subjects receiving trial treatment outside of the IRT were not considered randomized, but such subjects were included into the Safety Sample as defined below.
- *Safety Sample:* All subjects who received at least 1 dose of IMP. Subjects were excluded from this population only if there was documented evidence (ie, drug dispensed = drug returned or no trial drug dispensed) that the subjects did not take IMP. If a subject was dispensed trial medication and was lost to follow up, he/she was considered exposed to IMP. Of note, a subject was deemed enrolled into the trial if the Informed Consent Form / Informed Assent Form had been obtained from the subject or his/her legally acceptable representative.
- *Efficacy Sample:* Comprised all randomized subjects who took at least 1 dose of the IMP, and had baseline and at least 1 post-baseline assessment of the primary efficacy variable ABC-I subscale score during the double-blind treatment phase

Randomisation and blinding (masking)

Treatment assignments were obtained by accessing eSource. Based on computer generated randomization, eligible subjects were allocated in a 1:1 ratio at randomization to 1 of the following 2 treatment groups:

- Flexibly-dosed brexpiprazole (0.25 - 3 mg/day, weight based)
- Placebo

Neither the investigator nor the subject was aware of the treatment assignment.

Statistical Methods

Efficacy: The primary efficacy endpoint was the change from baseline to Week 8 in the ABC-I subscale score. The primary statistical comparison of interest was the difference between brexpiprazole and placebo at Week 8, analyzed using a mixed-model repeated measures (MMRM) analysis with an unstructured variance covariance matrix for within subject variation. The model will include fixed-class effect terms of treatment, trial center, visit week, and an interaction term of treatment by visit week, and includes the interaction term of baseline values of ABC-I subscale score by visit week as a covariate.

The primary comparison between brexpiprazole and the placebo arm at Week 8 was estimated as the difference between least squares means.

To ensure that trial was adequately powered, the estimate of the trial variability was obtained in a blinded fashion upon approximately 75% of the subjects having completed or discontinued from the trial. The variability was estimated based on a blinded and pooled analysis of all treatment arms and sample size could be further increased.

Safety: The incidence of AEs and the incidence of abnormal findings in vital signs, ECGs, clinical laboratory tests, safety scales, and physical examinations were analyzed.

Results

Baseline data and Number analysed

A total of 260 subjects were screened for this trial and 119 subjects were randomized to double-blind IMP. The Safety Sample comprised of 115 subjects who received at least 1 dose of IMP. One subject (in the placebo group) was included in the Safety Sample but not the Efficacy Sample (the subject's baseline ABC assessment occurred 3 days after the date of their first IMP dose and was not considered a valid baseline efficacy assessment).

In the Randomized Sample (N = 119), 15 subjects (12.6%) discontinued during the trial. The subject disposition is reported in table 10.1-1.

Table 10.1-1 Subject Disposition			
	Brex	Placebo	Total
Number of Subjects	n (%)^a	n (%)^a	n (%)^a
Screened			260
Screen Failure			141
Randomized	60 (100.0)	59 (100.0)	119 (100.0)
Treated	58 (96.7)	57 (96.6)	115 (96.6)
Completed	52 (86.7)	52 (88.1)	104 (87.4)
Discontinued	8 (13.3)	7 (11.9)	15 (12.6)
Analyzed For Safety ^b	58 (96.7)	57 (96.6)	115 (96.6)
Analyzed For Efficacy ^c	58 (96.7)	56 (94.9)	114 (95.8)

^aPercentages were based on the number of randomized subjects.

^bRandomized subjects who received at least one dose of study medication were included in the safety analysis.

^cRandomized subjects who received at least one dose of study medication and had a baseline and one post-baseline ABC-I subscale score.

The mean (SD) age at baseline was 9.9 (3.0) years and 96 subjects were in to 5- to 12-year-old age group versus 23 subjects in the 13- to 17-year-old age group. The mean (SD) weight at baseline was 43.6 (21.8) kg and 84 subjects were in the < 50 kg weight group versus 35 subjects in the ≥ 50 kg weight group. There was a lower proportion of female subjects (12.6%) than male subjects (87.4%) randomized in this trial. The proportion of black or African American subjects was 10.9% and of Hispanic or Latino subjects was 12.6% in this trial. Demographics and baseline characteristics were similar for most parameters between the brexpiprazole and placebo groups.

The baseline mean (SD) for ABC-I subscale score was 29.1 (7.8) and for CGI-S score was 4.8 (0.7). The baseline mean ABC-I subscale and CGI-S scores were similar between the brexpiprazole and placebo groups.

Efficacy results

Treatment with brexpiprazole did not demonstrate efficacy relative to placebo in reducing irritability in children and adolescents ages 5 to 17 years with a diagnosis of ASD.

The primary efficacy endpoint of mean change from baseline to Week 8 in ABC-I subscale score did not demonstrate a statistically significant improvement for the treatment with brexpiprazole compared to placebo with a treatment difference -1.22 (95% CI -4.49, 2.05), $p = 0.4597$, MMRM). A numerical reduction from baseline to Week 8 in mean ABC-I subscale score was seen in both the brexpiprazole (least squares [LS] mean standard error [SE] = -10.1 [1.28]) and placebo (LS mean [SE] = -8.87 [1.25]) groups.

A summary of efficacy results at week 8 is reported in table 11.4.1.1.1-1

Table 11.4.1.1.1-1 Summary of Mean Change from Baseline to Week 8 in ABC-Irritability Subscale Score - MMRM (Efficacy Sample)		
Variable	BREX	PLACEBO
ABC-IRRITABILITY SUBSCALE SCORE, MMRM	N=58	N=56
Baseline Mean (SD)	29.60 (8.05)	28.75 (7.69)
LS Mean (SE) Change at Week 8	-10.1 (1.28)	-8.87 (1.25)
Treatment Difference (95% CI) ^a	-1.22 (-4.49, 2.05)	
P-value ^a	0.4597	

^aMMRM method with model terms: treatment, trial site, baseline body weight stratum, visit, treatment-by-visit and baseline-by-visit interaction.

According to the prespecified hierarchical testing sequence, since the statistical test for the primary efficacy endpoint did not reach statistical significance, further formal statistical testing did not proceed for the key secondary endpoint, mean change from baseline to Week 8 in CGI-S score. A numerical reduction from baseline to Week 8 in mean CGI-S score was seen in both the brexpiprazole (LS mean [SE] = -1.16 [0.15]) and placebo (LS mean [SE] = -1.09 [0.15]) groups with a nominal $p = 0.7315$, MMRM (please refer to table below), showing that treatment with brexpiprazole did not demonstrate improvement compared to placebo.

Table 11.4.1.2.1-1 Summary of Mean Change from Baseline to Week 8 in Clinical Global Impression - Severity Score - MMRM (Efficacy Sample)		
Variable	BREX	PLACEBO
CGI SEVERITY SCORE, MMRM	N=57	N=56
Baseline Mean (SD)	4.86 (0.74)	4.68 (0.54)
LS Mean (SE) Change at Week 8	-1.16 (0.15)	-1.09 (0.15)
Treatment Difference (95% CI) ^a	-0.07 (-0.46, 0.32)	
P-value ^a	0.7315	

^aMMRM method with model terms: treatment, trial site, baseline body weight stratum, visit, treatment-by-visit and baseline-by-visit interaction.

Exploratory Efficacy Analyses

- Change From Baseline in Other Aberrant Behavior Checklist Subscale Scores

Numerical reductions from baseline to Week 8 in the ABC-I subscale scores for social withdrawal, stereotypic behavior, hyperactivity or noncompliance, and inappropriate speech were seen in both the brexpiprazole and placebo groups.

- Response Rate

Response was defined as having $\geq 25\%$ improvement (reduction) in ABC-I subscale score and ≥ 1 point improvement (reduction) in CGI-S score compared to baseline. There was no appreciable difference between the brexpiprazole and placebo groups in response rate at Week 8 or any of the study visits (LOCF [last observation carried forward] analysis). Responders were seen in both brexpiprazole and placebo groups.

- Change From Baseline in Pediatric Quality of Life Inventory

There was no appreciable difference between the brexpiprazole and placebo groups for mean change from baseline to Week 8 in PedsQL generic core scale score. There was a numerically greater LS mean (SE) change from baseline to Week 8 in PedsQL generic core scale score for the brexpiprazole group (14.13 [2.50]) compared to the placebo group (8.91 [2.37]; LS mean difference = 5.22 [95% CI:

-0.66, 11.11], $p = 0.0808$). Nominally greater LS mean (SE) change from baseline to Week 8 for brexpiprazole vs placebo was observed for PedsQL Emotional Function score (LS mean difference = 8.54 [95% CI: 1.73, 15.35], $p = 0.0147$; CT-5.6.4) and Social Function score (LS mean difference = 10.07 [95% CI: 0.85, 19.28], $p = 0.0327$; CT-5.6.5).

- Change From Baseline in Pediatric Quality of Life Inventory: Family Impact Total Score

There was no appreciable difference between the brexpiprazole and placebo groups for mean change from baseline to Week 8 in PedsQL Family Impact Module score. The baseline mean (SD) Family Impact Module score was 43.80 (15.67) in the brexpiprazole group, compared to 47.55 (21.19) in the placebo group. There was a numerically greater LS mean (SE) change from baseline to Week 8 in PedsQL Family Impact Module score for the brexpiprazole group (14.22 [2.58]) compared to the placebo group (9.16 [2.37]; LS mean difference = 5.06 [95% CI: -0.95, 11.08], $p = 0.0976$).

- Change From Baseline in Pediatric Anxiety Rating Scale

There was no appreciable difference between the brexpiprazole and placebo groups for mean change from baseline to Week 8 in PARS total score. The baseline mean (SD) PARS total score was 10.62 (5.88) in the brexpiprazole group, compared to 11.79 (5.40) in the placebo group. There were similar LS mean (SE) changes from baseline to Week 8 in PARS total score for the brexpiprazole (-2.63 [0.85]) and placebo (-2.56 [0.77]) groups (LS mean difference = -0.07 [95% CI: -2.04, 1.91], $p = 0.9443$).

Safety results

A summary of the safety results from the administration of brexpiprazole in children and adolescents (ages 5 to 17 years) with iASD in Trial 331 201-00148 were as follows:

- No deaths or serious treatment-emergent adverse events (TEAEs) were reported in this trial.

- A total of 30 subjects (51.7%) in the brexpiprazole group and 20 subjects (35.1%) in the placebo group experienced TEAEs.
- None of the TEAEs reported in this trial were severe. Twenty-two subjects (37.9%) in the brexpiprazole group and 17 subjects (29.8%) in the placebo group had TEAEs that were mild in severity. Fifteen subjects (25.9%) in the brexpiprazole group and 7 subjects (12.3%) in the placebo group had TEAEs that were moderate in severity.
- Treatment-emergent AEs that occurred at an incidence of at least 5% in the brexpiprazole group and greater than the placebo group were vomiting, headache, and somnolence.
- Three (2.6%) subjects had TEAEs leading to discontinuation, 2 subjects in (3.4%) in brexpiprazole group, and 1 subject (1.8%) in placebo group.
- The incidence of subjects with potentially drug-related TEAEs was 29.3% in the brexpiprazole group compared with 15.8% in the placebo group. In the brexpiprazole group, the only potentially drug-related TEAE that occurred in $\geq 5\%$ of subjects was somnolence (12.1% vs 5.3% for placebo).
- In the brexpiprazole group, 1 subject (1.7%) discontinued due to the TEAE of mental disorder. In the placebo group, 1 subject (1.8%) discontinued due to the TEAE of aggression.
- A total of 4 subjects (6.9%) in the brexpiprazole group and 2 subjects (3.5%) in the placebo group experienced EPS-related TEAEs. None of the TEAEs were serious or led to discontinuation. No clinically significant changes from baseline were observed in SAS, AIMS, or BARS scores.
- No TEAEs related to suicidality were reported. There were no clinically meaningful changes from baseline based on the review of the C-SSRS data. No suicidality was reported during the treatment or follow-up period based on the C-SSRS.
- Weight related TEAEs occurred in 1 subject (1.7%) in the brexpiprazole group (weight increased) and 1 subject (1.8%) in the placebo group (weight decreased). None of the TEAEs were serious or led to discontinuation.
- No meaningful differences between the brexpiprazole and placebo groups were observed for clinical laboratory results, vital signs, or ECGs.

Study number 331-201-00191

Title: Phase 3, Multicenter, Open-label Trial to Evaluate the Long-term Safety and Tolerability of Brexpiprazole in the Treatment of Children and Adolescents with Irritability Associated with Autism Spectrum Disorder.

Description

Trial 331-201-00191 was a multicenter, open-label trial conducted to evaluate the long-term safety and tolerability of brexpiprazole in children and adolescent subjects with irritability in ASD who have completed the corresponding double-blind, phase 3 efficacy trial, Trial 331-201-00148 (8 weeks of treatment) and, in the investigator's judgment, could potentially benefit from continued investigational treatment with oral brexpiprazole.

Methods

The trial was conducted as follows:

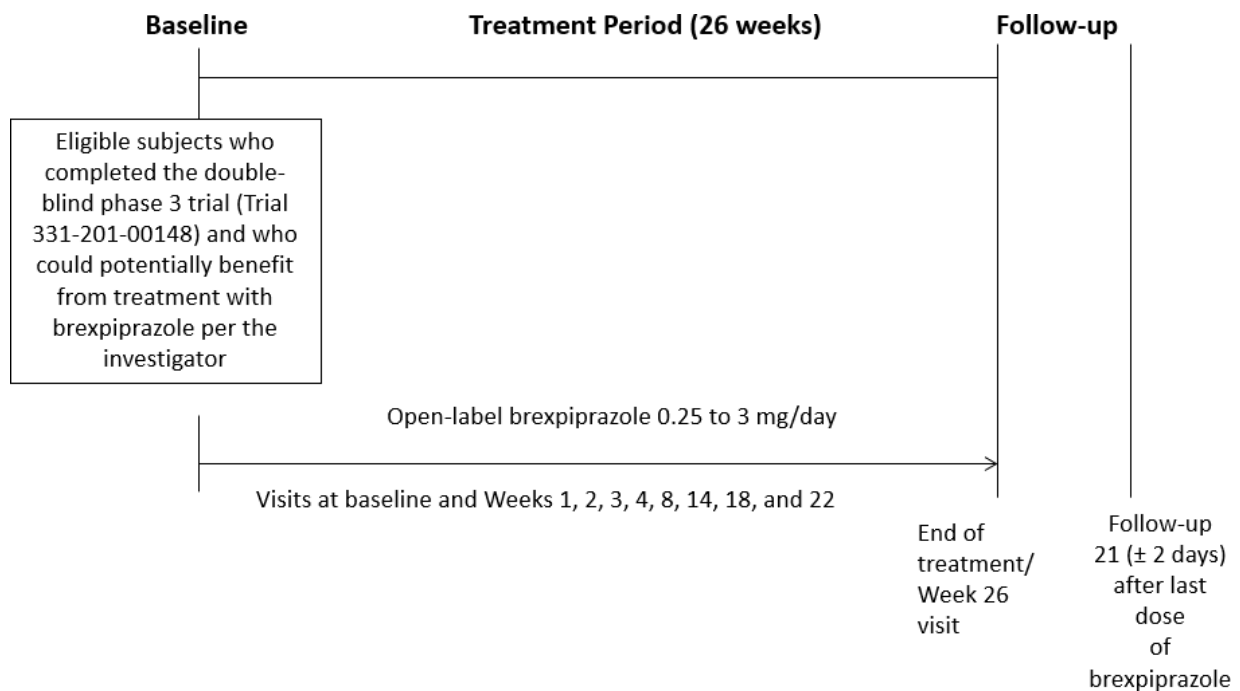
Screening/Baseline: Subjects who completed the treatment period of the double-blind trial and were deemed compliant with the protocol were screened for eligibility at the last visit of the double-blind trial (Week 8). A separate fully executed informed consent/assent was obtained for Trial 331-201- 00191 before any procedures specific to the open-label trial were performed. The assessments from the last visit of the double-blind trial served as the baseline measures for Trial 331-201-00191 for any assessment that was not unique to the open-label trial. Medical history was updated, if necessary.

Open-label Treatment Phase: Eligible subjects from Trial 331-201-00148 received 26 weeks of daily treatment with open-label brexpiprazole in Trial 331-201-00191. Visits occurred at the end of Weeks 1, 2, 3, 4, 8, 14, 18, 22, and 26. The baseline, Week 2, Week 14, and Week 26 visits occurred in the clinic. All other visits may have been conducted either virtually or in-clinic. Where the investigator and caregiver made the decision to conduct a visit virtually, the visit was conducted by means of telecommunications technology. The caregiver and the subject were to remain in their own home and complete trial assessments and questionnaires via an online technology. The caregiver and subject interacted with trial personnel using online communication tools which incorporated telemedicine.

During virtual interactions (and at any other time), the trial personnel were able to assess the subject and determine if an additional inoffice visit for a physical evaluation was required at the discretion of the investigator.

Follow-up: Subjects had a follow-up contact 21 ($\pm$ 2) days after the last dose of open-label brexpiprazole.

A schematic of this trial design is provided in figure below.



Study participants

A total of 95 subjects were enrolled and treated in this trial. The Safety Sample comprised 95 subjects who received at least 1 dose of IMP. One subject (in the prior brexpiprazole group) was included in the Safety Sample but not the Efficacy Sample (subject was missing an Aberrant Behavior checklist [ABC] score at baseline).

The trial population included:

- Subjects who, in the opinion of the investigator, could potentially benefit from administration of oral brexpiprazole for the treatment of irritability associated with ASD and who completed Trial 331-201- 00148.
- Male and female subjects 5 to 17 years of age, inclusive, at the time of informed consent/assent. Subjects who turned 18 years old during Trial 331-201-00148 were permitted in this trial.

Treatments

Brexpiprazole was supplied by the sponsor or designated agent in child-resistant blister cards, each containing sufficient tablets for 7 (+2) days. All doses of open-label brexpiprazole were taken orally once daily and could be administered without regard to meals. Every effort should have been made to administer the open-label brexpiprazole at the same time every day, preferably in the morning.

The first dose of open-label brexpiprazole was taken the following day after the last dose of double- blind investigational medicinal product (IMP) was taken in the parent trial so that treatment continued without interruption. Whenever possible, it was anticipated that the last dose of IMP in the double- blind, phase 3 efficacy trial was taken on the day of the baseline visit for the open-label trial. Subjects should not have been dosed using double-blind and open-label IMP on the same day.

The titration/dosing schedule was based on body weight. Body weight at the Week 8 double-blind visit/baseline visit for Trial 331-201-00191 was used to determine the starting dose. Those subjects with body weight < 50 kg received a target dose range of 1 to 1.5 mg, and those subjects with body weight ≥ 50 kg received a target dose range of 1.5 to 3 mg.

Brexpiprazole was supplied as 0.25-, 0.5-, 1-, 2-, and 3-mg tablets and matching placebo tablets. Each subject received 2 tablets every day independent of the dose levels. For low dose levels, one of the tablets was placebo.

Objective(s)

The primary objective was to assess the long-term safety and tolerability of brexpiprazole monotherapy in children and adolescents with irritability in ASD.

The secondary objective was to assess the long-term efficacy of brexpiprazole monotherapy in children and adolescents with irritability in ASD.

Outcomes/endpoints

Primary Endpoint

Safety: Safety was assessed by the following standard endpoints for clinical trials and trials of antipsychotic drugs:

- The frequency and severity of adverse events (AEs), serious AEs (SAEs), and

- discontinuation from the trial due to AEs.
- Change from baseline to post-baseline time points in 1) vital sign measurements, 2) electrocardiogram (ECG) parameters, 3) clinical laboratory tests (including prolactin) and urinalysis, and 4) physical examination findings.
- Analysis of potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Changes from baseline to post-baseline time points in results from EPS scales (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]).
- Percentage of subjects with clinically significant changes in weight (gain or loss) from baseline to specified time points.
- Time to discontinuation.

Secondary Endpoint

Efficacy:

- Change from baseline to Week 26 in the Aberrant Behavior Checklist – Irritability (ABC-I) subscale score.
- Change from baseline to Week 26 in Clinical Global Impression - Severity (CGI-S) scale score targeted on irritability.

Exploratory Endpoints

[REDACTED]

Sample size

The sample size was not based on statistical considerations, but rather on the number of subjects rolling over from the parent trial (Trial 331-201-00148). The trial population was derived from eligible subjects who completed the parent trial. The sample size of this open-label trial was limited by the number of subjects enrolled into the parent trial.

Subject Samples:

- Enrolled Sample:** Consists of subjects who completed the double-blind treatment period of the parent trial and who gave consent/assent for participation into this open-label trial and who also met all the eligibility criteria for this trial.
- Safety Sample:** Consisted of all Enrolled subjects who took at least one dose of the IMP as indicated on the dosing records of this open-label extension trial. A subject will be excluded from this population only if there is documented evidence that the subject has not taken the IMP (ie, number of tablets/capsules dispensed = number of tablets/capsules returned, or no IMP dispensed). If a subject is dispensed trial medications but subsequently lost to follow-up, the subject will be considered exposed to the IMP.
- Efficacy Sample:** All subjects in the Safety Sample who have a baseline assessment and at least one post-baseline assessment of the ABC-I subscale score.

The primary efficacy analysis will be based on the OC data only. The OC data refer to the actual observations or assessments of the outcomes that are recorded at all visits (including the ET visits) during the double-blind treatment phase, without imputation of any missing observations

or assessments.

The trial naturally seeks to clarify the efficacy of brexpiprazole in improving the ABC-I subscale in the idealistic scenario of full adherence to the assigned treatment in all subjects, through an hypothetical estimand.

Randomisation and blinding (masking)

This is an open-label trial and blinding procedures are not applicable.

Statistical Methods

Efficacy: The secondary endpoints for this trial were the ABC-I subscale score and the CGI-S score. Each of these variables and the change from baseline to Week 26 in each of them were summarized on the observed case data by visit and additionally on the last observation carried forward data by using descriptive statistics for continuous variables.

Safety: The incidence of AEs and the incidence of abnormal findings in vital signs, ECGs, clinical laboratory tests, and physical examinations were analyzed. In addition, data of extrapyramidal symptom (EPS) scales including SAS, AIMS, and BARS were analyzed. Potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS) were analyzed. Percentage of subjects with clinically significant changes in weight and time to discontinuation were assessed.

Results

Baseline data and Number analysed

A total of 95 subjects were enrolled in this trial. All 95 (100.0%) subjects were analyzed for safety, and 94 (98.9%) subjects were analyzed for efficacy. One subject (in the prior brexpiprazole group) was included in the Safety Sample but not the Efficacy Sample (subject was missing an ABC score at baseline). A total of 25 subjects (26.3%) discontinued during the trial, including 10 (20.4%) prior brexpiprazole subjects and 15 (32.6%) prior placebo subjects. There were no deaths in the trial.

Primary reasons for discontinuations included withdrawal by caregiver (11 subjects) and AE (6 subjects).

Table 10.1-1 Subject Disposition (Enrolled Sample)			
	Prior Brex	Prior Placebo	Total
Number of Subjects:	n (%)^a	n (%)^a	n (%)^a
Enrolled	49 (100.0)	46 (100.0)	95 (100.0)
Treated	49 (100.0)	46 (100.0)	95 (100.0)
Completed	39 (79.6)	31 (67.4)	70 (73.7)
Discontinued	10 (20.4)	15 (32.6)	25 (26.3)
Analyzed For Safety ^b	49 (100.0)	46 (100.0)	95 (100.0)
Analyzed For Efficacy ^c	48 (98.0)	46 (100.0)	94 (98.9)

^aPercentages are based on the number of enrolled subjects.

^bSubjects having received at least one dose of the IMP in the open-label period are included in safety analysis.

^cSubjects enrolled and received at least one dose of trial medication and had a baseline and at least one post-baseline ABC-I subscale score.

The mean (standard deviation [SD]) age at baseline was 10.0 (3.1) years and 75 subjects were ages 5

- 12 years versus 20 subjects were ages ≥ 13 years. The mean (SD) weight at baseline was 42.9 (18.1) kg and 65 subjects had a body weight of < 50 kg versus 30 subjects had a body weight of ≥ 50 kg. There was a lower proportion of female subjects (12.6%) than male subjects

(87.4%) randomized in this trial. The majority of subjects were White (75 [78.9]) and not Hispanic or Latino (81 [85.3%]). Demographics and baseline characteristics were similar for most parameters between the prior brexpiprazole and prior placebo groups.

The baseline mean (SD) for ABC-I subscale score was 19.1 (9.9) and for CGI-S score was 3.6 (1.1). The baseline mean ABC-I subscale and CGI-S scores were similar between the prior brexpiprazole and prior placebo groups, as shown in figure below.

Table 11.2.1-1 Baseline Psychiatric Scale Evaluation (Enrolled Sample)			
Parameter	Prior Brex (N=49)	Prior Placebo (N=46)	Total (N=95)
ABC Hyperactivity/Noncompliance Score			
n	48	46	94
Mean (SD)	21.9 (10.6)	20.6 (11.4)	21.3 (11)
Median	23.5	18.5	21
Min, Max	0, 47	2, 46	0, 47
ABC Inappropriate Speech Score			
n	47	46	93
Mean (SD)	3.7 (3)	4.2 (3.3)	3.9 (3.2)
Median	3	3	3
Min, Max	0, 12	0, 12	0, 12
ABC Irritability Subscale Score			
n	48	46	94
Mean (SD)	18.5 (9.2)	19.6 (10.8)	19.1 (9.9)
Median	17	20.5	17.2
Min, Max	0, 39	0, 43	0, 43
ABC Social Withdrawal Score			
n	48	46	94
Mean (SD)	12 (8.8)	8.3 (8.4)	10.2 (8.8)
Median	12.5	5	8.5
Min, Max	0, 28	0, 32	0, 32
ABC Stereotypic Behavior Score			
n	48	46	94
Mean (SD)	5.7 (5.2)	4.1 (5)	4.9 (5.1)
Median	5	2	4
Min, Max	0, 21	0, 18	0, 21
CGI-S Severity Score			
n	49	46	95
Mean (SD)	3.6 (1.1)	3.7 (1.1)	3.6 (1.1)
Median	4	4	4
Min, Max	1, 7	1, 6	1, 7

Safety results (primary endpoint)

- The safety results from administration of brexpiprazole in children and adolescents with irritability associated with ASD are consistent with the known safety profile of brexpiprazole.
- No deaths were reported in this trial.
- A total of 47 subjects (49.5%) overall, with 23 subjects (46.9%) in the prior brexpiprazole group, and 24 subjects (52.2%) in the prior placebo group experienced TEAEs.
- Most TEAEs were mild or moderate in severity. Fifteen subjects (30.6%) in the prior brexpiprazole group and 19 subjects (41.3%) in the prior placebo group had TEAEs that were mild in severity. Eleven subjects (22.4%) in the prior brexpiprazole group and 12 subjects (26.1%) in the prior placebo group had TEAEs that were moderate in severity. Severe TEAEs occurred in 2 subjects (4.1%) in the prior brexpiprazole group and 2 subjects (4.3%) in the prior placebo group.
- Treatment-emergent AEs that occurred at an incidence of at least 5% were weight increased, increased appetite, and somnolence.
- Serious TEAEs occurred in 3 subjects (3.2%); 2 subjects (4.1%) in the prior brexpiprazole group (dyskinesia and suicidal ideation), and 1 subject (2.2%) in the prior placebo group (affective disorder).

- Six subjects (6.3%) had TEAEs leading to discontinuation. In the prior brexpiprazole group, 2 subjects (4.1%) discontinued investigational medicinal product (IMP) due to the TEAEs of weight increased and irritability. In the prior placebo group, 4 subject (8.7%) discontinued IMP due to the TEAE of weight increased, affective disorder, anxiety, and blunted affect.
- The incidence of subjects with potentially drug-related TEAEs was 27.4% overall, with 24.5% in the prior brexpiprazole group compared to 30.4% in the prior placebo group. The potentially drug-related TEAEs that occurred in $\geq 5\%$ of subjects were weight increased (11.6% [10.2% in the prior brexpiprazole versus 13.0% in the prior placebo]), increased appetite (6.3%, [4.1% in the prior brexpiprazole versus 8.7% in the prior placebo]), and somnolence (5.3%, [8.2% in the prior brexpiprazole versus 2.2% in the prior placebo]).
- A total of 6 subjects (6.3%) reported EPS-related TEAEs; 2 subjects (4.1%) in the prior brexpiprazole group and 4 subjects (8.7%) in the prior placebo group. None of the TEAEs were serious or led to discontinuation. No clinically significant changes from baseline were observed in SAS, AIMS, or BARS scores.
- One serious TEAE of suicidal ideation was reported during the trial. Based on the C-SSRS, no suicidal behavior was reported during the treatment or follow-up period; however, suicidal ideation was reported for 6 subjects (6.3%) overall, with 4 subjects (8.2%) in the prior brexpiprazole group and 2 subjects (4.3%) in the prior placebo group. None of the suicidal ideations reported in the C-SSRS were considered a TEAE. There were no clinically meaningful changes from baseline based on the review of the C-SSRS data.
- Weight-related TEAEs occurred in 13 subjects (13.7%) overall; 5 subjects (10.2%) in the prior brexpiprazole group and 8 subjects (17.4%) in the prior placebo group. None of the TEAEs were serious, but 1 TEAE of increased weight resulted in the discontinuation of IMP.
- There were no clinically meaningful changes in clinical laboratory results, vital signs, or ECGs.
- While brexpiprazole is known to impact prolactin levels, very few subjects were assessed post baseline, precluding any conclusions from these data.
- **Efficacy results (secondary endpoint)**
- For the secondary endpoint change from baseline to Week 26 in the ABC-I subscale score, a change from baseline to Week 26 in mean (SD) ABC-I subscale score was seen overall -6.14 (8.16) and in both the prior brexpiprazole (-5.47 [8.06]) and prior placebo (-7.0 [8.36]) groups.
- For the secondary endpoint change from baseline to Week 26 in CGI-S scale score targeted on irritability, a change from baseline to Week 26 in mean (SD) CGI-S subscale score was seen overall (-0.73 [0.96]) and in both the prior brexpiprazole (-0.78 [0.99]) and prior placebo (-0.68 [0.94]) groups.
- Exploratory analyses showed results consistent with the other efficacy endpoint analyses.

2.2.2. Discussion on clinical aspects

Autism spectrum disorder is a neurodevelopmental disorder characterized by deficits in reciprocal

social communication and social interaction (verbal and nonverbal), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). The severity of ASD is defined by the degree of restricted, repetitive patterns of behaviour, interests, and activities. Symptoms are present from early childhood and contribute to difficulties in developing, maintaining, and understanding relationships.

In addition to the core symptoms that characterize the disorder, children and adolescents with ASD often suffer from problem behaviours such as symptoms of irritability and aggression, which may manifest as tantrums, self-injury, and aggressive behaviours toward others. Approximately 20% of people with ASD exhibit irritability and aggression with > 50% exhibiting significant emotion dysregulation. Irritability and aggression often negatively affect the lives of people with ASD and their families.

Globally, there are few to no therapeutic options for the treatment of patients with iASD. Risperidone and aripiprazole are the only two medications approved in the US and Japan for the treatment of iASD. There are no medications approved in the EU or UK for the treatment of this condition.

Two trials have been conducted to ascertain the effects of brexpiprazole on irritability in children and adolescent subjects, ages 5 to 17 years, with a diagnosis of ASD (Trial 331-201-00148) and to evaluate the long-term safety and tolerability of brexpiprazole in children and adolescent subjects with irritability in ASD who have completed the corresponding phase 3 efficacy trial.

Trial 331-201-00148

Trial 331-201-00148 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 8-week trial, designed to evaluate the effects of flexibly-dosed brexpiprazole 0.25 to 3 mg/day, compared with placebo on irritability in children and adolescent subjects, ages 5 to 17 years, with a diagnosis of ASD.

The trial consisted of a 1 to 28 day screening period, followed by an 8 week double-blind treatment period, and a 21-day post-treatment safety follow-up period.

Subjects were randomized 1:1 to receive brexpiprazole or placebo daily. On day 1 of the treatment period, subjects began titration to a target dose range of IMP based on body weight.

The study design is compliant with EMA Guidelines (EMA/CHMP/598082/2013).

Trial population: A total of 119 subjects were randomized.

Subjects (5 to 17 years of age, with a current primary DSM-5 diagnosis of ASD) with an ABC-I subscale score ≥ 18 and with a CGI-S scale score ≥ 4 pertaining to irritability at screening and at baseline were enrolled.

The eligibility criteria are considered adequate.

Demographics baseline characteristics were similar for most parameters between the brexpiprazole and placebo groups as well as the baseline mean ABC-I subscale and CGI-S.

Statistical methods: Approximately 102 subjects will be randomized (51 per treatment arm). A sample size of 51 subjects per arm will provide at least 85% power at a nominal 2-sided alpha level of 0.05 to detect a 6.0-point reduction in change from baseline in ABC-I subscale score for brexpiprazole versus placebo, assuming a standard deviation (SD) = 10. This assumption for calculation is considered acceptable.

The primary efficacy analysis will be based on the OC data only. The OC data refer to the actual observations or assessments of the outcomes that are recorded at all visits (including the ET visits) during the double-blind treatment phase, without imputation of any missing observations or assessments.

As the first confirmatory clinical trial of brexpiprazole in autistic children and adolescents, the proposed trial naturally seeks to clarify the efficacy of brexpiprazole in improving the ABC-I subscale in the idealistic scenario of full adherence to the assigned treatment in all subjects. In clinical trial practice, however, instances of non-adherence such as treatment discontinuation are likely to occur before the study endpoint (ie, the Week 8 visit for this trial). Therefore, the hypothetical estimand is considered appropriate to use for the primary efficacy analysis.

Primary endpoint: The primary efficacy endpoint of this trial was the mean change from baseline to Week 8 in the Aberrant Behavior checklist Irritability (ABC-I) subscale score.

The ABC-I is widely in use in clinical trials in the population of interest and its use as primary endpoint is considered adequate for the aim of the study.

The primary efficacy endpoint did not demonstrate a statistically significant improvement for the treatment with brexpiprazole compared to placebo showing a treatment difference of -1.22 (95% CI - 4.49, 2.05, $p = 0.4597$, MMRM).

Secondary endpoints: The key secondary endpoint of this trial was the mean change from baseline to Week 8 in Clinical Global Impressions Severity (CGI-S) score for irritability. The choice of CGI-S, largely used in CNS trials, is supported.

Due to the hierarchical testing sequence established, further formal statistical testing did not proceed for the key secondary endpoint. Only a numerical reduction from baseline to Week 8 in mean CGI-S score was seen in both the brexpiprazole (LS mean [SE] = -1.16 [0.15]) and placebo (LS mean [SE] = -1.09 [0.15]) groups, nominal $p = 0.7315$, MMRM thus not supporting the effect of brexpiprazole on CGI-S as compared to placebo.

Safety: in 331-201-00148 study, safety was assessed by standard endpoints for clinical trials and trials of antipsychotic drugs.

Brexpiprazole was found to be well tolerated as evidenced by the high and comparable completion rates in subjects treated with brexpiprazole and placebo (86.7% and 88.1%, respectively). No deaths, serious TEAEs, or severe TEAEs were reported in this trial. Mild TEAEs occurred in 37.9% of the subjects in the brexpiprazole group and 29.8% of the subjects in the placebo group. Moderate TEAEs occurred in 25.9% of the subjects in the brexpiprazole group and 12.3% of the subjects in the placebo group. The TEAE with the highest incidence was somnolence, which occurred in 12.1% of subjects in the brexpiprazole group and 5.3% of subjects in the placebo group.

The overall incidence of TEAEs related to EPS after brexpiprazole treatment was low. The most frequently reported TEAEs related to EPS in the brexpiprazole group were akathisia and tremor, which occurred in 2 subjects (3.4%) each. All TEAEs related to EPS were considered mild and none of them led to discontinuation.

Evaluation of ECGs, vital signs, laboratory measurements (including liver function tests and bilirubin, hematology; and serum lipids) and urinalysis did not show any clinically meaningful differences between the brexpiprazole and the placebo groups. No incidence of suicidal behavior or ideation was reported after brexpiprazole treatment.

Safety results of Trial 331-201-00148 were consistent with the current known safety profile of brexpiprazole.

Trial 331-201-00191

Trial 331-201-00191 was a multicenter, open-label trial conducted to evaluate the long-term safety and tolerability of brexpiprazole in children and adolescent subjects with irritability in ASD who have completed the corresponding double-blind, phase 3 efficacy trial, Trial 331-201-00148 and, in the investigator's judgment, could potentially benefit from continued investigational treatment with oral brexpiprazole.

Eligible subjects received 26 weeks of daily treatment with open-label brexpiprazole, with a follow-up contact 21 days after the last dose of open-label brexpiprazole.

Trial population: A total of 95 subjects were enrolled and treated in this trial. The Safety Sample comprised 95 subjects who received at least 1 dose of IMP.

Statistical methods: The sample size planned for this open-label extension trial is not based on considerations of statistical power.

Safety was assessed by standard primary and secondary endpoints for clinical trials and for trials with antipsychotic drugs.

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the latest version (Version 25.0 or newer) of Medical Dictionary for Regulatory Activities (MedDRA).

Safety results (primary endpoint)

Brexpiprazole was found to be well tolerated as evidenced by the high and comparable completion rates in subjects previously treated with brexpiprazole and placebo (73.7% overall).

No deaths were reported in this trial. Serious TEAEs were reported for a total of 3 subjects (3.2%) and were dyskinesia, suicidal ideation, and affective disorder. The serious TEAE of suicidal ideation was considered not related to IMP and was recovered/resolved. The incidence of TEAEs was slightly higher in the prior placebo group (52.2%) compared to the prior brexpiprazole group (46.9%). Most TEAEs were mild or moderate in severity. The overall incidence of subjects with severe TEAEs was 4.2%, similar in the prior brexpiprazole group and the prior placebo group.

With regard to weight increase, the TEAE occurred in 13.7% of subjects overall, and was more common in the prior placebo group (17.4%) than in the prior brexpiprazole group (10.2%).

None of the TEAEs related to weight gain were serious, but 1 TEAE related to weight gain resulted in the discontinuation of IMP.

Of the enrolled subjects, 73.9% had gained $\geq 7\%$ of their body weight by Week 26.

A total of 6 subjects (6.3%) reported EPS-related TEAEs. All of which were considered mild to moderate in severity.

Evaluation of ECGs, vital signs, laboratory measurements (including liver function tests and bilirubin, hematology; and serum lipids) and urinalysis did not show any clinically meaningful differences between the prior brexpiprazole and the prior placebo groups.

Of note, while brexpiprazole is known to impact prolactin levels, very few subjects were assessed post baseline, precluding any conclusions from these data.

Overall, trial 331-201-00191 showed that brexpiprazole at a dose of 0.25 mg to 3 mg was safe and well tolerated in children and adolescents when taken for up to 26 weeks.

Efficacy results (secondary endpoint)

Overall, subjects had a mean (SD) change from baseline of –6.14 (8.16) to Week 26 in ABC-I subscale score, with 62/94 subjects completing the Week 26 visit. Thus, there was minimal difference between prior brexpiprazole subjects and prior placebo subjects (–5.47 [8.06] vs –7.0 [8.36]) at Week 26.

In addition, subjects had a mean (SD) change from baseline of –0.73 (0.96) to Week 26 in CGI-S scale score, with 64/94 subjects completing the Week 26 visit. Prior brexpiprazole subjects had a mean (SD) change from baseline of –0.78 (0.99) and prior placebo subjects had a change of –0.68 (0.94) at Week 26. The mean change in this endpoint appears to be consistent between prior brexpiprazole subjects and prior placebo subjects.

3. Rapporteur's CHMP overall conclusion and recommendation

Trial 331-201-00148 did not meet its primary endpoint thus failing to demonstrate Brexpiprazole efficacy in the treatment of children and adolescents with iASD.

Therefore, there is no data to support an indication for brexpiprazole in the treatment of iASD.

In the open label trial 331-201-00191, brexpiprazole at a dose of 0.25 mg to 3 mg was safe and well tolerated in children and adolescents (ages 5 to 17 years) when taken for up to 26 weeks. The safety results from Trial 331-201-00148 and Trial 331-201-00191 are consistent with the known safety profile of brexpiprazole. No new safety signals for brexpiprazole have been observed.

☒ **Fulfilled:**

No regulatory action required.