Efficacy and safety of brexpiprazole in adolescents with schizophrenia: a multicountry, randomised, double-blind, placebo-controlled, phase 3 trial with an active reference

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Summary

Background New treatment options are needed for adolescent schizophrenia, partly due to an unfavourable risk–benefit profile of current options. This trial aimed to evaluate the short-term efficacy and safety of brexpiprazole in adolescents with schizophrenia.

Methods This multicountry, randomised, double-blind, parallel-arm, placebo-controlled, phase 3 trial with an active reference was done at 62 outpatient sites in ten countries. Eligible patients were aged 13–17 years with a primary DSM-5 diagnosis of schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total score ≥80 at screening and baseline. Patients were randomly assigned (1:1:1) to oral brexpiprazole 2–4 mg/day, placebo, or aripiprazole 10–20 mg/day (active reference). Patients, investigators, and sponsor personnel were masked to treatment assignment. The primary efficacy endpoint was change from baseline to week 6 in PANSS total score (in randomly assigned patients who took at least one dose of study drug and had baseline and post-baseline PANSS evaluations). Safety was assessed in randomly assigned patients who took at least one dose of study drug. People with lived experience of schizophrenia were not involved in the research or writing process. The trial was registered with ClinicalTrials.gov, NCT03198078, and is complete.

Findings Between June 29, 2017, and Feb 23, 2023, 376 patients were screened, and 316 patients were randomly assigned to brexpiprazole (n=110), placebo (n=104), or aripiprazole (n=102). The mean age of patients was 15·3 years (SD 1·5). 166 (53%) of 316 patients were female and 150 (47%) were male. Of 316 patients, seven (2%) were American Indian or Alaskan Native, two (1%) were Asian, 21 (7%) were Black or African American, 204 (65%) were White, and 81 (26%) were other, as reported using US Census Bureau classifications. Mean doses of brexpiprazole and aripiprazole at last visit were 3·0 mg (SD 0·9) and 13·9 mg (4·7), respectively. Least squares mean change from baseline to week 6 in PANSS total score was –22·8 (SE 1·5) with brexpiprazole and –17·4 (1·6) with placebo (least squares mean difference –5·33 [95% CI –9·55 to –1·10]; p=0·014). The corresponding PANSS total score change at week 6 with aripiprazole was –24·0 (SE 1·6; least squares mean difference versus placebo –6·53 [95% CI –10·8 to –2·21]; $p_{nominal}$=0·0032, not adjusted for multiple testing). Treatment-emergent adverse events were reported in 44 (40%) of 110 patients in the brexpiprazole group, 42 (40%) of 104 in the placebo group, and 53 (52%) of 102 in the aripiprazole group. The most common (incidence ≥5%) treatment-emergent adverse events were headache (n=7) and nausea (n=7) with brexpiprazole and somnolence (n=11), fatigue (n=8), and akathisia (n=7) with aripiprazole. Serious treatment-emergent adverse events were reported by one (1%) of 110 patients in the brexpiprazole group, three (3%) of 104 in the placebo group, and one (1%) of 102 in the aripiprazole group. No deaths were reported.

Interpretation In adolescents with schizophrenia, brexpiprazole 2–4 mg/day was associated with greater reduction in symptom severity than placebo over 6 weeks. The safety profile of brexpiprazole in adolescents was consistent with trials in adult patients. These results add to the body of evidence for brexpiprazole in adolescents with schizophrenia and might help to inform treatment selection in clinical practice.

Funding Otsuka Pharmaceutical Development & Commercialization and H Lundbeck.

Lancet Psychiatry 2025; 12: 345–54

Published Online April 7, 2025 https://doi.org/10.1016/S2215-0366(25)00043-4

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Introduction

Schizophrenia onset in children or young adolescents (ie, very-early-onset [aged <13 years] or early-onset [aged <18 years] schizophrenia) is associated with more chronic and severe symptoms and poorer prognosis than adult-onset schizophrenia.[1–3] Specifically, patients who develop schizophrenia in adolescence often have a greater severity of cognitive deficits, increased disability, and lower socio-occupational functioning than patients with adult-onset schizophrenia.[4,5]

First-line treatment recommendations for schizophrenia in adolescents (per the UK National Institute for Health

Research in context

Evidence before this study

We searched PubMed from database inception to Sept 20, 2024, using the search terms "(adolescen* OR child OR early) AND (schizophrenia)", without language restrictions. The 17 923 results were evaluated qualitatively for studies of atypical antipsychotics in participants younger than 18 years with schizophrenia, with efficacy or safety results. Although several atypical antipsychotics are indicated for the treatment of schizophrenia in children or adolescents, high rates of adverse events and treatment discontinuation have been observed in this patient population. There is an unmet need for additional treatments that are efficacious against the symptoms of schizophrenia and are well tolerated. Brexpiprazole has demonstrated efficacy and safety in adult patients. Extrapolation of efficacy data from short-term studies of brexpiprazole in adults together with pharmacokinetic data and exposure-matching between adults and adolescents have indicated efficacy for brexpiprazole in adolescents. Safety was further supported by an interim analysis of data from an ongoing open-label extension study in adolescents, which is expected to complete in 2025. However, to our knowledge, no randomised controlled study has explored the efficacy and safety of brexpiprazole in adolescents with schizophrenia.

Added value of this study

To our knowledge, this is the first randomised controlled trial assessing the efficacy and safety of brexpiprazole in adolescents with schizophrenia, and the first placebo-controlled trial in adolescents with schizophrenia to include an active reference antipsychotic. Brexpiprazole demonstrated statistically significantly greater reductions in the severity of schizophrenia symptoms over 6 weeks than placebo. Although adolescents are generally more sensitive to antipsychotic-related adverse events than adults, safety outcomes with brexpiprazole were consistent with those observed in studies in adult schizophrenia and similar to longer-term safety outcomes in the open-label extension study in adolescents. The results support the short-term efficacy and safety of brexpiprazole in adolescent patients with schizophrenia.

Implications of all the available evidence

The positive results of this trial, in combination with the prior extrapolation, pharmacokinetic, and long-term safety data, establish a body of evidence for brexpiprazole as a treatment option in adolescents with schizophrenia. This information might help in clinical decision making when selecting an efficacious treatment with little risk of compromising patient safety.

and Care Excellence and Canadian guidelines) include antipsychotics in combination with psychotherapy.[6,7] Although some antipsychotics (including several atypical antipsychotics) have demonstrated efficacy in adolescents with schizophrenia,[8,9] antipsychotics might have a less favourable risk–benefit profile in adolescents than in adults.[9–13]

The pathophysiology of schizophrenia involves several neurotransmitters.[14] Dopamine system dysfunction is considered a key factor in psychotic symptoms,[14] although there is growing evidence for the involvement of noradrenergic and serotonergic systems.[14,15] Brexpiprazole is an atypical antipsychotic acting across these three monoaminergic systems.[16] Brexpiprazole is approved for the treatment of schizophrenia in adults and adolescents (aged ≥13 years) in the USA and other countries (including Singapore, United Arab Emirates, and Brazil). The US Food and Drug Administration (FDA)'s approval of brexpiprazole in adolescents was based on the extrapolation of short-term efficacy data from studies in adults,[17–19] pharmacokinetics and exposure-matching between adults and adolescents,[20] and an interim safety analysis of a long-term, open-label study in adolescents.[21] However, to our knowledge, a placebo-controlled assessment of brexpiprazole in adolescents with schizophrenia has not been conducted. We aimed to evaluate the efficacy, safety, and tolerability of brexpiprazole in adolescent patients with schizophrenia in a placebo-controlled setting.

See Online for appendix

Methods

Study design

This multicountry, randomised, double-blind, parallel-arm, placebo-controlled, phase 3 trial with an active reference was done at 62 outpatient sites in ten countries (USA, Mexico, France, Italy, Poland, Romania, Serbia, Spain, Ukraine, and Russia). The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and local regulatory requirements. The trial protocol was approved by the governing institutional review board or independent ethics committee for each investigational site or country. The full trial protocol and statistical analysis plan are available in the appendix. The trial was registered with ClinicalTrials.gov, NCT03198078, and is complete.

Patients

Eligible patients were aged 13–17 years at the time of informed consent or assent and at baseline with a primary diagnosis of schizophrenia per DSM-5 criteria (confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version),[22] a 6-month or longer history of illness (ie, a diagnosis or symptoms) before screening, requiring treatment with antipsychotic medication per investigator decision, and a Positive and Negative Syndrome Scale (PANSS)[23] total score of 80 or more at screening and at baseline. Key exclusion criteria included a DSM-5 diagnosis other than schizophrenia that had been the

primary focus of treatment within 3 months of screening; clinical presentation or history consistent with delirium, dementia, amnesia, or other cognitive disorders; psychotic symptoms better accounted for by another general medical condition or a direct effect of a substance; hospitalised for more than 21 days for a current exacerbation of schizophrenia at baseline; treatment resistance to an antipsychotic medication (history of relapse due to poor compliance or substance misuse could be considered based on investigator decision); at high risk of serious self-harm or suicide or a high risk to others (eg, acting violently or homicidally); epilepsy or history of seizures, or severe head trauma or stroke; history or current evidence of other unstable medical conditions including hepatic, renal, respiratory, cardiovascular, endocrine, neurological, haematological, or immunological disease per investigator clinical decision that would expose the patient to undue risk of a clinically significant adverse event; comorbid serious systemic illness that required pharmacotherapy; history of electroconvulsive therapy; and a positive screening for drugs of abuse. A positive screening for prescription amphetamines, barbiturates, opiates, or benzodiazepines could be permitted. Limited use of benzodiazepines and non-benzodiazepine sleep aids was permitted. Prohibited medications included antipsychotics, antidepressants, mood stabilisers, stimulants, and other psychotropics. Those with a positive cannabis screening were evaluated by investigators for their ability to abstain from use during the trial. The full list of eligibility criteria is provided in the protocol (appendix).

Patients were enrolled by investigators and recruited from the site database or by other methods, including clinician referral, hospital admissions, community outreach, and social media. Sex, race, and ethnicity data were reported using US Census Bureau classifications; the protocol did not specify a method of data collection.

Patients or the guardian or legal representative, as applicable according to local laws, provided written informed consent. Patients who were too young to sign an informed consent form provided informed assent per local law and were required to understand that they could withdraw from the trial at any time, for any reason. No involuntary patients were included in the trial. People with lived experience of schizophrenia were not involved in the research or writing process.

Randomisation and masking

Patients were randomly assigned (1:1:1) using an interactive web response system (block sizes of 3) based on a computer-generated randomisation code provided by the sponsor and stratified by site. Brexpiprazole and aripiprazole tablets, and matching placebo tablets for each active treatment, were provided by the sponsor and packaged in numbered, weekly blister cards. Patients, investigators, and sponsor personnel were masked to treatment assignment, including those involved in data monitoring, data management, and data analysis. To maintain masking, all patients received two tablets: brexpiprazole or brexpiprazole–placebo, and aripiprazole or aripiprazole–placebo.

Procedures

After a minimum 3-day washout period for prohibited medications (≥7 days for oral antipsychotics), patients entered a 6-week, double-blind treatment period of brexpiprazole 2–4 mg/day, placebo, or aripiprazole 10–20 mg/day. The trial design is provided in the appendix (p 3). Brexpiprazole was titrated as follows: 0·5 mg/day on days 1–4, 1 mg/day on days 5–7, 2 mg/day on days 8–14, and 2 mg/day or 3 mg/day on days 15–21; dose adjustments by ±1 mg (within 2–4 mg) were permitted after the titration period (day 21). Aripiprazole was titrated as follows: 2 mg/day on days 1–4, 5 mg/day on days 5–7, 10 mg/day on days 8–14, and 10 mg/day or 15 mg/day on days 15–21; dose adjustments by ±5 mg (within 10–20 mg) were permitted after the titration period (day 21). Aripiprazole was included as an active reference to evaluate assay sensitivity because it is considered well tolerated and has shown efficacy in adolescents with schizophrenia.[8] Study drugs were taken orally once daily, without regard to meals.

Efficacy, adverse events, other safety outcomes, and concomitant medications were assessed in outpatient visits at 1-week intervals. Adverse events and concomitant medications were also assessed by telephone on day 4. At week 6, eligible patients who completed the double-blind treatment period could enrol in an open-label extension study.[21] Patients who did not enrol in the open-label study were followed up 21 days (±2) after the last dose of assigned treatment to record any new or ongoing adverse events and concomitant medications. The full schedule of assessments is presented in the protocol (appendix).

Treatment adherence (self-reported, then verified and recorded by investigators) was calculated as a percentage of the total planned number of tablets for each patient.

Notable protocol amendments included the introduction of an addendum to account for considerations and procedures related to the COVID-19 pandemic, and a sample size reduction (and associated decrease in power) to align with changes to the Paediatric Investigation Plan submitted to the European Medicines Agency.

Outcomes

The primary efficacy outcome measure was PANSS total score.[23] PANSS measures the severity of 30 schizophrenia symptoms (seven positive, seven negative, and 16 general psychopathology), each of which is rated from 1 (absent) to 7 (extreme).[23] These 30 symptom ratings are summed to give the PANSS total score (30–210).[23] PANSS total score was selected as the primary outcome measure as it is widely used throughout schizophrenia clinical trials (including in adolescents)[8,24–26] and it is considered the

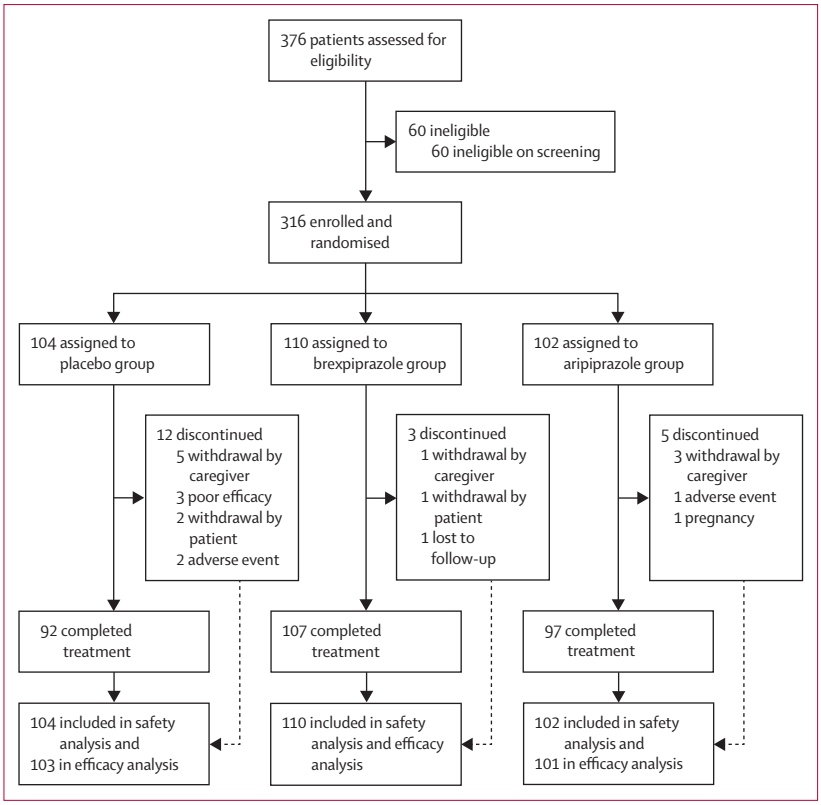

Figure 1: **Trial profile**

gold standard for assessing the efficacy of antipsychotic treatments. This widespread use facilitates comparisons between results of different trials. The validity and reliability of PANSS have been demonstrated in adults,[23] and analyses using the Clinical Global Impression (CGI) scale as an anchor have enabled estimation of clinically important PANSS outcomes (estimated minimum clinically important difference of 15 points or a 34% change from baseline).[27] PANSS takes approximately 45 min to complete[23] and was administered in English (ie, not translated) by a qualified and certified clinician at trial sites.

Secondary efficacy outcomes were PANSS Positive and Negative subscale scores, response rate (≥30% improvement from baseline in PANSS total score, or CGI–Improvement [CGI-I] score of 1 or 2), remission rate (score ≤3 on each of the following PANSS items: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms or posturing, blunted affect, passive or apathetic social withdrawal, and lack of spontaneity and conversation flow),[28] Children's Global Assessment Scale (CGAS) score, CGI–Severity of illness (CGI-S) score, and CGI-I score. The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-Q-LES-Q) total score was an exploratory outcome. PANSS General Psychopathology subscale score was calculated post hoc. Safety assessments included treatment-emergent adverse events, bodyweight, laboratory tests (including serum prolactin), vital signs, ECGs, extrapyramidal symptom rating scales (Simpson–Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale), the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment, the Columbia Suicide Severity Rating Scale (C-SSRS), and number of admissions to hospital for treatment (an exploratory outcome). More information on these efficacy and safety assessments is provided in the protocol (appendix).

Statistical analysis

A sample size of 105 patients per group was estimated to achieve at least 80% power at a two-sided α of 0·05 to detect a treatment effect of –7·4 points (SD 19·0) in PANSS total score change from baseline to week 6, based on the results of an aripiprazole trial in adolescent schizophrenia.[24] This resulted in a planned sample size of 315 patients.

The primary estimand was defined by the following components: (1) the population, comprising adolescent patients (aged 13–17 years) with schizophrenia who would benefit from pharmacological treatment; (2) treatments, comprising brexpiprazole 2–4 mg/day, placebo, or aripiprazole 10–20 mg/day for 6 weeks; (3) the primary endpoint of change from baseline to week 6 in PANSS total score; (4) the measure of intervention effect—ie, mean difference between the brexpiprazole group and placebo group; (5) intercurrent events, comprising premature treatment discontinuation before week 6 attributable to adverse events, poor efficacy, withdrawal of consent or assent, or any other causes; and (6) the estimate of treatment effect, for which the hypothetical situation that no patients discontinued prematurely from treatment was applied (further details are provided in the appendix, p 2).

The primary statistical comparison of interest for the primary endpoint was analysed by a significance test of the least squares mean difference in PANSS total score between brexpiprazole and placebo at week 6, at a two-sided 0·05 level. This trial was not designed or powered for a direct head-to-head comparison of the efficacy of brexpiprazole and aripiprazole. There was no hypothesis testing hierarchy for this trial. Other than for the primary endpoint at week 6, all p values were nominal at a 0·05 level, without formal adjustments for multiplicity.

Efficacy was analysed in the efficacy population (a modified intention-to-treat population), comprising all randomly assigned patients who took at least one dose of study drug and had a baseline and at least one post-baseline PANSS total score measurement.

Changes in PANSS total score (primary efficacy analysis), PANSS Positive and Negative subscale scores, CGAS score, CGI-S score, and PANSS General

Psychopathology score were analysed using a mixed model for repeated measures (observed cases dataset; appendix p 2), with fixed-class effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week, and with fixed effect covariates of baseline score and the interaction term of baseline score by visit week. Response and remission rates were analysed using the Cochran–Mantel–Haenszel general association test, controlling for trial site by week in last observation carried forward analyses (appendix p 2) for the efficacy sample. CGI-I score was analysed using the Cochran–Mantel–Haenszel row mean scores differ test, controlling for trial site, in last observation carried forward analyses (appendix p 2). The change in P-Q-LES-Q total score (14 items) was evaluated using ANCOVA, including a main effect of treatment, and baseline value as covariate (observed cases dataset; appendix p 2).

Safety was analysed in the safety population, comprising all randomly assigned patients who took at least one dose of study drug. Age-adjusted and sex-adjusted Z scores for change in bodyweight were calculated using the US Centers for Disease Control and Prevention (CDC) approach (ie, the deviation of a patient's weight from the mean weight of the CDC reference population, divided by the SD for the CDC reference population). Bodyweight Z score is measured in SD; a change in Z score of ≥0·5 SD represents a clinically meaningful change. The percentage of patients with a bodyweight change ≥7% relative to baseline was also calculated.

Subgroup analyses of the primary efficacy endpoint, and of treatment-emergent adverse events, are described in the appendix (p 2).

All analyses were performed using SAS version 9.4 or later. A data monitoring committee provided oversight for safety monitoring.

Role of the funding source

The funders of the study had a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between June 29, 2017, and Feb 23, 2023, 376 patients were screened, and 316 patients were randomly assigned to brexpiprazole (n=110), placebo (n=104), or aripiprazole (n=102; figure 1) at sites in Ukraine (102 [32%] of 316 patients), Mexico (95 [30%]), the USA (43 [14%]), Serbia (31 [10%]), Romania (18 [6%]), Poland (11 [3%]), Russia (11 [3%]), Italy (three [1%]), France (one [<1%]), and Spain (one [<1%]). 107 (97%) of 110 patients in the brexpiprazole group, 92 (88%) of 104 in the placebo group, and 97 (95%) of 102 in the aripiprazole group completed treatment. 314 patients were included in the efficacy analysis (110 in the brexpiprazole group, 103 in the placebo group, and 101 in the aripiprazole group).

	Brexpiprazole group (n=110)	Placebo group (n=104)	Aripiprazole group (n=102)
Demographics			
Age, years	15·3 (1·5)	15·2 (1·4)	15·3 (1·4)
Age group			
<15 years	36 (33%)	35 (34%)	30 (29%)
≥15 years	74 (67%)	69 (66%)	72 (71%)
Weight, kg	64·6 (16·9)	68·0 (17·7)	61·4 (14·7)
BMI, kg/m²	23·2 (5·2)	24·1 (5·2)	22·4 (4·2)
Sex			
Female	58 (53%)	51 (49%)	57 (56%)
Male	52 (47%)	53 (51%)	45 (44%)
Race*†			
American Indian or Alaskan Native	2 (2%)	4 (4%)	1 (1%)
Asian	1 (1%)	0	1 (1%)
Black or African American	8 (7%)	6 (6%)	7 (7%)
White	70 (64%)	68 (65%)	66 (65%)
Other‡	29 (26%)	25 (24%)	27 (26%)
Ethnicity*			
Hispanic, Latino, Latina, or Latinx	34 (31%)	34 (33%)	32 (31%)
Not Hispanic, Latino, Latina, or Latinx	75 (68%)	68 (65%)	70 (69%)
Other	1 (1%)	1 (1%)	0
Clinical characteristics			
Age at first diagnosis for schizophrenia, years	13·9 (2·0)	14·1 (1·8)	13·9 (1·9)
Duration of illness, months	17·1 (15·6)	14·5 (12·7)	17·7 (17·1)
PANSS total score	101·1 (14·9)	102·1 (16·3)	101·0 (13·0)
PANSS Positive subscale score	24·2 (5·1)	23·9 (5·2)	24·9 (4·0)
PANSS Negative subscale score	25·8 (5·6)	25·7 (6·0)	25·1 (5·2)
PANSS General Psychopathology subscale score	51·1 (8·4)	52·4 (8·5)	51·0 (7·6)
CGAS score	48·1 (11·4)	47·7 (11·9)	48·1 (12·3)
CGI-S score	4·8 (0·7)	4·7 (0·7)	4·7 (0·7)
P-Q-LES-Q total score	40·8 (9·0); n=109	41·3 (9·6); n=104	41·4 (8·6); n=101

Data are mean (SD) or n (%). Data are shown in the randomly assigned population. CGAS=Children's Global Assessment Scale. CGI-S=Clinical Global Impression—Severity of illness. PANSS=Positive and Negative Syndrome Scale. P-Q-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire. *Data are missing for one patient in the placebo group. †US Census Bureau terms were used at the time of data collection. ‡Some patients who reported their race as other identified with more than one race.

Table 1: **Baseline characteristics**

The safety analysis included all 316 randomly assigned patients. The trial completed on April 3, 2023.

Baseline demographic and clinical characteristics were generally similar between treatment groups, although there were small numerical differences in bodyweight (table 1). The mean age of randomly assigned patients was 15·3 years (SD 1·5). 166 (53%) of 316 patients were female and 150 (47%) were male. At last visit, the mean dose of brexpiprazole was 3·0 mg (SD 0·9) and of aripiprazole was 13·9 mg (4·7). Overall, the most commonly used antipsychotics before the trial were risperidone (184 [58%] of 316 patients), olanzapine

(67 [21%] of 316), haloperidol (46 [15%] of 316), quetiapine (45 [14%] of 316), and aripiprazole (44 [14%] of 316). 26 (24%) of 110 patients in the brexpiprazole group, 23 (22%) of 104 in the placebo group, and 23 (23%) of 102 in the aripiprazole group took at least one concomitant medication during the trial. Benzodiazepines were the most frequently reported class of concomitant medications (nine [8%] of 110 patients in the brexpiprazole group, six [6%] of 104 in the placebo group, and nine [9%] of 102 in the aripiprazole group); the most common individual concomitant medication was lorazepam (six [5%] of 110, five [5%] of 104, and six [6%] of 102). Treatment adherence ≥90% was reported for 107 (97%) of 110 patients in the brexpiprazole group, 103 (99%) of 104 in the placebo group, and 100 (98%) of 102 in the aripiprazole group.

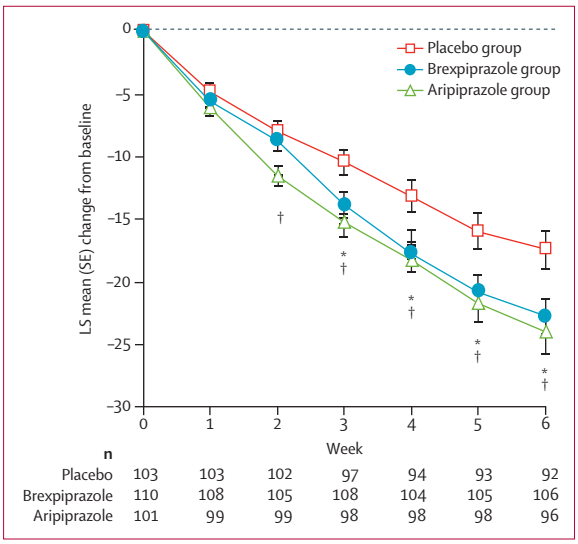

Figure 2: **Change in PANSS total score**
Scores are shown in the efficacy population. Active treatment was titrated for the first 3 weeks of the double-blind period. LS=least squares. PANSS=Positive and Negative Syndrome Scale. *p<0·05 with brexpiprazole *vs* placebo. †p<0·01 with aripiprazole *vs* placebo (except for the primary endpoint comparison of brexpiprazole *vs* placebo at week 6, all p values are nominal). Mixed model for repeated measures.

The brexpiprazole group demonstrated statistically significant greater improvement in PANSS total score (least squares mean change –22·8 [SE 1·5]) than the placebo group (–17·4 [1·6]) from baseline to week 6 (least squares mean difference –5·33 [95% CI –9·55 to –1·10]; p=0·014; figure 2; table 2). All p values, other than for the primary endpoint comparison of brexpiprazole versus placebo at week 6, are nominal and are presented for descriptive purposes only. PANSS total score change from baseline to week 6 was also greater in the aripiprazole group versus the placebo group (least squares mean difference –6·53 [–10·8 to –2·21]; $p_{nominal}$=0·0032; figure 2; table 2), validating the trial methodology and patient population.

PANSS Positive subscale score (appendix p 4), response rate (appendix p 5), and CGI-I score improved at week 6 in the brexpiprazole group versus the placebo group ($p_{nominal}$<0·05; table 2). PANSS Negative subscale score (appendix p 4), remission rate, and CGAS score numerically improved at week 6 in the brexpiprazole group versus the placebo group ($p_{nominal}$>0·05; table 2).

	Brexpiprazole group (n=110)			Aripiprazole group (n=101)			Placebo group (n=103)
	LS mean change (SE)	LS mean difference *vs* placebo (95% CI)	p value *vs* placebo	LS mean change (SE)	LS mean difference *vs* placebo (95% CI)	p value *vs* placebo	LS mean change (SE)
PANSS total score (primary)*	–22·8 (1·5)	–5·33 (–9·55 to –1·10)	0·014	–24·0 (1·6)	–6·53 (–10·8 to –2·21)	0·0032	–17·4 (1·6)
PANSS Positive subscale score*	–6·6 (0·4)	–1·44 (–2·65 to –0·22)	0·021	–7·3 (0·5)	–2·15 (–3·40 –0·91)	0·0008	–5·1 (0·5)
PANSS Negative subscale score*	–4·7 (0·4)	–0·88 (–2·04 to 0·28)	0·14	–4·8 (0·4)	–0·95 (–2·14 to 0·24)	0·12	–3·8 (0·4)
PANSS General Psychopathology subscale score*	–11·5 (0·8)	–2·89 (–5·08 to –0·70)	0·0098	–12·0 (0·8)	–3·31 (–5·55 to –1·07)	0·0039	–8·7 (0·8)
Response rate†‡	48 (43·6%)	RR 1·55 (1·09 to 2·20)	0·011	44 (43·6%)	RR 1·51 (1·06 to 2·16)	0·022	29 (28·2%)
Remission rate†§	32 (29·1%)	RR 1·18 (0·77 to 1·81)	0·44	36 (35·6%)	RR 1·48 (1·01 to 2·16)	0·047	24 (23·3%)
CGAS score*	10·6 (1·0)	2·48 (–0·35 to 5·31)	0·085	12·1 (1·1)	3·99 (1·09 to 6·88)	0·0072	8·1 (1·1)
CGI-S score*	–0·9 (0·1)	–0·11 (–0·36 to 0·13)	0·36	–1·0 (0·1)	–0·20 (–0·45 to 0·05)	0·11	–0·8 (0·1)
Mean CGI-I score¶	2·9 (SD 1·0)	–0·29 (–0·56 to –0·03)	0·029	2·8 (SD 1·0)	–0·34 (–0·62 to –0·06)	0·018	3·2 (SD 1·1)
P-Q-LES-Q total score‖	4·0 (0·7); n=104	0·44 (–1·62 to 2·50)	0·67	4·5 (0·8); n=93	1·04 (–1·08 to 3·16)	0·34	3·5 (0·8); n=92

Except for the primary endpoint comparison of brexpiprazole *vs* placebo, all p values are nominal. Data are shown in the efficacy population. CGAS=Children's Global Assessment Scale. CGI-I=Clinical Global Impression—Improvement. CGI-S=Clinical Global Impression—Severity of illness. LS=least squares. PANSS=Positive and Negative Syndrome Scale. P-Q-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire. RR=relative risk. *Mixed model for repeated measures. †Cochran–Mantel–Haenszel general association test, last observation carried forward. ‡Response was defined as a reduction of ≥30% from baseline in PANSS total score or a CGI-I score of 1 or 2. §Remission was defined cross-sectionally as a score ≤3 on each of the following PANSS items: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerisms or posturing, blunted affect, passive or apathetic social withdrawal, and lack of spontaneity and conversation flow. ¶Cochran–Mantel–Haenszel row mean scores differ test, last observation carried forward. ‖ANCOVA, observed cases.

Table 2: **Efficacy endpoints at week 6**

Post hoc, PANSS General Psychopathology subscale score improved at week 6 in the brexpiprazole group versus the placebo group ($p_{nominal}$<0·05; table 2).

At least one treatment-emergent adverse event was reported by 44 (40%) of 110 of patients in the brexpiprazole group, 42 (40%) of 104 patients in the placebo group, and 53 (52%) of 102 patients in the aripiprazole group (table 3). The most common (incidence ≥5%) treatment-emergent adverse events were headache (n=7) and nausea (n=7) with brexpiprazole and somnolence (n=11), fatigue (n=8), and akathisia (n=7) with aripiprazole (table 3). In all groups, most treatment-emergent adverse events were mild or moderate in severity.

Three patients discontinued due to treatment-emergent adverse events: two patients receiving placebo (exacerbation of schizophrenia symptoms and worsening of psychotic symptoms), and one patient receiving aripiprazole (akathisia; table 3). No patients discontinued due to treatment-emergent adverse events with brexpiprazole. No deaths were reported during the trial.

Extrapyramidal symptom-related treatment-emergent adverse events (eg, akathisia, muscle rigidity, tremor, extrapyramidal disorder, dystonia, psychomotor hyperactivity, and hypokinesia) occurred in seven (6%) of 110 patients in the brexpiprazole group, five (5%) of 104 in the placebo group, and 11 (11%) of 102 in the aripiprazole group.

Mean change in bodyweight from baseline to last visit was +0·8 kg (SD 2·6) in the brexpiprazole group (n=110), 0·0 kg (2·2) in the placebo group (n=103), and +0·5 kg (2·7) in the aripiprazole group (n=101). Weight gain ≥7% occurred in nine (8%) of 110 patients in the brexpiprazole group, five (5%) of 103 in the placebo group, and five (5%) of 101 in the aripiprazole group; weight loss ≥7% occurred in five (5%), four (4%), and two (2%) patients, respectively. Mean change in age-adjusted and sex-adjusted bodyweight Z score (ie, adjusting for natural growth of paediatric patients) from baseline to last visit was 0·0 (SD 0·3) in the brexpiprazole group, 0·0 (0·2) in the placebo group, and 0·0 (0·2) in the aripiprazole group.

Based on the C-SSRS, no patients had suicidal behaviour during treatment or follow-up. Emergence of suicidal ideation (measured with C-SSRS) was reported by one (1%) of 110 patients in the brexpiprazole group, two (2%) of 104 in the placebo group, and two (2%) of 102 in the aripiprazole group. There were no clinically meaningful differences between groups in mean laboratory test parameters, vital signs, ECG parameters, extrapyramidal symptom-rating scales, or cognitive adverse effects (appendix p 6). Mean change in fasting glucose from baseline to last visit was +1·1 mg/dL (SD 12·2) in the brexpiprazole group, +0·7 mg/dL (14·7) in the placebo group, and +0·8 mg/dL (11·4) in the aripiprazole group (appendix p 6).

Mean changes in prolactin concentrations for patients according to sex are presented in the appendix (p 6). Prolactin concentrations increased slightly from baseline to last visit in female patients treated with brexpiprazole, and were not clinically meaningful (normal range 3–30 ng/mL for female patients).[21] One mild treatment-emergent adverse event of galactorrhoea was reported by a male patient in the brexpiprazole group (considered unrelated to assigned treatment and resolved within the same day without changing brexpiprazole dose). Prolactin concentrations were within the normal range (ie, 2–18 ng/mL for male patients)[21] for this patient during the trial.

One patient each in the brexpiprazole and aripiprazole groups and three in the placebo group were admitted to and treated in hospital due to adverse events of worsening of schizophrenia. Hospital admission and treatment occurred once for each of the patients.

Data from subgroup analyses of the primary endpoint are presented in the appendix (p 7). Treatment-emergent adverse events by sex are presented in the appendix (p 8).

	Brexpiprazole (n=110)	Placebo (n=104)	Aripiprazole (n=102)
At least one TEAE	44 (40%)	42 (40%)	53 (52%)
At least one serious TEAE	1 (1%)	3 (3%)	1 (1%)
Discontinuation due to TEAE	0	2 (2%)*	1 (1%)†
Potentially drug-related TEAEs	24 (22%)	17 (16%)	39 (38%)
At least one mild TEAE	33 (30%)	32 (31%)	47 (46%)
At least one moderate TEAE	17 (15%)	13 (13%)	16 (16%)
At least one severe TEAE	2 (2%)‡	1 (1%)§	0
At least one dose reduction due to TEAE	5 (5%)	2 (2%)	4 (4%)
Death	0	0	0
TEAEs with an incidence ≥5% in any group			
Headache	7 (6%)	5 (5%)	5 (5%)
Nausea	7 (6%)	4 (4%)	4 (4%)
Somnolence	5 (5%)	5 (5%)	11 (11%)
Akathisia	4 (4%)	3 (3%)	7 (7%)
Fatigue	2 (2%)	0	8 (8%)
Other TEAEs of interest			
Hypersomnia	3 (3%)	2 (2%)	5 (5%)
Sedation	2 (2%)	0	4 (4%)
Weight increased	2 (2%)	4 (4%)	2 (2%)
Insomnia	1 (1%)	4 (4%)	4 (4%)
Restlessness	1 (1%)	0	1 (1%)
Agitation	1 (1%)	0	0
Anxiety	0	1 (1%)	1 (1%)

Data are n (%). Data are shown in the safety population. TEAEs were graded on a 3-point scale as mild (1, discomfort noticed, but no disruption to daily activity), moderate (2, discomfort sufficient to reduce or affect normal daily activity), or severe (3, inability to work or perform normal daily activity). TEAE=treatment-emergent adverse event. *Due to a TEAE of schizophrenia (exacerbation of schizophrenia symptoms) and a serious TEAE of psychotic disorder (worsening of psychotic symptoms), both moderate in severity. †Due to a TEAE of akathisia, moderate in severity. ‡Severe TEAEs of increased blood creatine phosphokinase and schizophrenia (worsening of schizophrenia symptoms). §Severe TEAE of psychomotor hyperactivity.

Table 3: **Treatment-emergent adverse events**

Discussion

In this phase 3 trial of adolescent patients with schizophrenia, treatment with brexpiprazole resulted in

a statistically significant greater improvement versus placebo in PANSS total score. To our knowledge, this is the first placebo-controlled trial of brexpiprazole in adolescent schizophrenia, and the first trial in adolescent schizophrenia to include an antipsychotic active reference. The results of this trial add to the body of evidence for use of atypical antipsychotics in adolescent schizophrenia.[8,24–26]

The US FDA permits efficacy data for atypical antipsychotics in adults with schizophrenia to be extrapolated to adolescents if there is an established dosing regimen and long-term safety profile.[17] In previous 6-week, phase 3 trials in adults with schizophrenia, brexpiprazole demonstrated statistically significant greater improvement versus placebo on the PANSS total score.[18,19] Based on the data in adults, an exposure–response analysis predicted an efficacious response in adolescents receiving brexpiprazole.[17] Furthermore, pharmacokinetics and exposure-matching between adults and adolescents indicated that a target dose of brexpiprazole 2–4 mg would be suitable for adolescents with schizophrenia.[20] Although not required for US FDA approval of brexpiprazole in adolescents with schizophrenia, it was important to substantiate the extrapolated results of these previous analyses in a placebo-controlled setting (required by other regulatory authorities). This study supports the exposure–response and pharmacokinetic analyses by indicating that brexpiprazole 2–4 mg is efficacious in adolescent patients with schizophrenia, with a change in PANSS total score similar to score changes reported in adult trials.[18,19] Improvements appeared to be sustained over 6 months in an interim analysis of the long-term, open-label extension of the present adolescent trial.[21]

Evidence suggests that the placebo response might be higher in children or adolescents (especially in young adolescents) than in adults, although research is scarce.[29] Compared with previous trials of other atypical antipsychotics in adolescents with schizophrenia,[24–26] the placebo response in this trial (least squares mean change of –17·4 in PANSS total score from baseline to week 6) could be considered at the higher end of an expected range. The placebo response in this study might have been affected by the three-arm design with two active treatments (perceived 2:1 likelihood of receiving an active treatment, and perceptions resulting from administration of two tablets). The changes in PANSS total score with brexpiprazole and aripiprazole are similar to those observed in other trials of atypical antipsychotics in adolescents with schizophrenia.[8] However, the high placebo response prevents comparisons of between-group differences between trials.

Greater improvements were observed in the brexpiprazole group than in the placebo group in PANSS total score from week 3 onwards. Active treatment was titrated for the first 3 weeks of the double-blind period, which might limit conclusions relating to treatment effects during that time.

The brexpiprazole group had a high completion rate (107 [97%] of 110 patients). Most treatment-emergent adverse events were mild or moderate in severity, and headache and nausea were the only treatment-emergent adverse events with an incidence ≥5% in the brexpiprazole group (somnolence, fatigue, and akathisia had an incidence ≥5% in the aripiprazole group). Although adolescents are generally more sensitive to adverse events than adults, the overall safety profile of brexpiprazole in this study was similar to that seen in trials of adults with schizophrenia.[18,19,30–32] Changes in metabolic parameters (eg, fasting glucose) were small, aligning with the interim results from the adolescent long-term, open-label extension trial[21] and from adult trials of brexpiprazole in schizophrenia.[31] Importantly for adolescents who are undergoing active brain development and attending school, there was no meaningful difference between brexpiprazole and placebo in cognitive adverse effects, a safety outcome required by the European Medicines Agency.

The therapeutic effects of brexpiprazole in schizophrenia might result from modulation of the noradrenaline, serotonin, and dopamine monoamine systems.[16] α_{2C} and 5-HT_{2A} receptor antagonism and 5-HT_{1A} receptor partial agonism of brexpiprazole might contribute to antipsychotic and pro-cognitive effects.[16] D_2 receptor partial agonists (eg, aripiprazole, brexpiprazole, and cariprazine) have antipsychotic effects and are generally associated with better tolerability than D_2 receptor agonists and antagonists.[16,33] Brexpiprazole has low D_2 receptor intrinsic activity, which might further improve tolerability.[16]

As seen in adults with schizophrenia,[34] common side effects of antipsychotics in adolescents include activating and sedating effects, such as akathisia and somnolence,[8,9,26] which are associated with impaired functioning.[34] In adults with schizophrenia, brexpiprazole is considered to be neither activating nor sedating.[35] The incidence of akathisia with brexpiprazole was low (four [4%] of 110 patients) in the present trial (three [3%] of 104 with placebo and seven [7%] of 102 with aripiprazole) and in the interim analysis of the long-term, open-label extension study (four [2%] of 167).[21] Five (5%) patients in the brexpiprazole group had somnolence (five [5%] with placebo and 11 [11%] with aripiprazole) and 17 (10%) of 167 in the interim analysis of the extension study.[21]

Several limitations require consideration when interpreting the results of this trial. First, exclusion of patients with certain comorbidities, and restrictions on concomitant pharmacotherapy, limit the generalisability of the findings, which might not be fully applicable to patients in clinical practice. Although generalisability is increased by the inclusion of patients from multiple sites across ten countries, the proportion of patients identifying as American Indian or Alaskan Native, Asian,

or Black or African American was small. Second, the trial was not powered for statistical comparisons on the secondary endpoints, or for comparisons with aripiprazole. Third, this trial cannot provide guidance on necessary treatment duration as it was limited to 6 weeks; the ongoing open-label extension study will provide data over a longer duration.[21] Fourth, despite the short-term duration of this trial, the time between trial initiation and completion was approximately 6 years. Recruiting adolescents with schizophrenia for a 6-week placebo-controlled trial is challenging for many reasons, including local regulatory requirements and the competitive landscape with approved antipsychotics. Ethical considerations include concerns about the long-term impact of being without efficacious treatment, and specific risks such as suicidal behaviours. Ultimately, given these long-standing challenges, endorsement was obtained from the Paediatric Committee of the European Medicines Agency to reduce the initial sample size and associated statistical power in a protocol amendment. Fifth, the emergence of the COVID-19 pandemic coincided with the original estimated trial completion date. The impact of COVID-19 was explored via sensitivity analyses introduced in a protocol addendum during the trial (data not shown). However, as the distribution of sites and countries differed before and after the COVID-19 pandemic, no conclusions can be drawn. Finally, people with lived experience of schizophrenia were not involved in the research or writing process.

In conclusion, in this phase 3 trial of adolescent patients with schizophrenia, treatment with brexpiprazole 2–4 mg/day was associated with greater reductions in global symptom severity compared with placebo. The safety profile of brexpiprazole was favourable and consistent with that observed in adults with schizophrenia. The overall incidence of treatment-emergent adverse events was similar between brexpiprazole and placebo, and higher with aripiprazole. The incidence of activating and sedating treatment-emergent adverse events was low with brexpiprazole. The most frequent treatment-emergent adverse events with brexpiprazole were headache and nausea. The positive results of this trial, combined with previous extrapolation, pharmacokinetic, and long-term safety data, establish a body of evidence for brexpiprazole as a treatment option in adolescents with schizophrenia. This information might help in clinical decision making when selecting an efficacious treatment with little risk of compromising patient safety.

Contributors

EK, CUC, NH, and MH: study conceptualisation or design. CW, CA, EK, MH, and MPM: data acquisition. CW and DC: data analysis. CW, EK, CUC, and NH: data interpretation. CW, NH, DC, CA, KGL, MH, and CUC: raw data verification. All authors were involved in drafting the manuscript and providing critical revision of the manuscript for intellectual content. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CW, DC, and MH are full-time employees of Otsuka Pharmaceutical Development & Commercialization. MPM reports honoraria for presenting at sponsored events or CME symposia from Janssen, Richter, and Servier. EK and CA were full-time employees of Otsuka Pharmaceutical Development & Commercialization at the time of this study. NH and KGL are full-time employees of H Lundbeck. CUC reports consulting fees from AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals; honoraria for presenting at sponsored events or CME symposia from AbbVie, Angelini, Aristo, Boehringer-Ingelheim, Bristol-Myers Squibb, Cerevel, Darnitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, Lundbeck, Mitsubishi Tanabe Pharma, Mylan, Otsuka, Recordati, Seqirus, Sunovion, Tabuk, Takeda, and Viatris; providing expert testimony for Janssen, Lundbeck, and Otsuka; fees for participating on a data safety monitoring board or advisory board from AbbVie, Allergan, Angelini, Boehringer Ingelheim, Bristol-Myers Squibb, Cerevel, Compass Pathways, Denovo, Gedeon Richter, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Neurelis, Neurocrine, Newron, Novo Nordisk, Otsuka, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, Life Science, Sunovion, Supernus, Teva, Vertex, and Viatris; grant support from Boehringer-Ingelheim, Janssen, and Takeda; royalties from UpToDate; and holding stock options with Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, and Terran.

Data sharing

Requests for trial data can be submitted at the Otsuka Pharmaceutical Clinical Trial Data Transparency website (https://clinical-trials.otsuka.com/). Requests for the clinical study report, analytical code, and anonymised individual participant data will be considered for researchers who provide a methodologically sound proposal for use of this information. Otsuka will share anonymised individual participant data on a remotely accessible data sharing platform for all approved access requests for individual participant data. Data will be available immediately following publication of this manuscript, with no anticipated end date.

Acknowledgments

This study was funded by Otsuka Pharmaceutical Development & Commercialization and H Lundbeck. The results of this trial were previously presented at the Schizophrenia International Research Society Annual Congress (April 3–7, 2024, Florence, Italy). Medical writing support was provided by Zoe Aliwell and colleagues of Cambridge (a division of Prime, Knutsford, UK) and was funded by Otsuka Pharmaceutical Development & Commercialization and H Lundbeck. We would like to thank Marianne Dragheim for her contributions to the study.

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