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Brexpiprazole in patients with schizophrenia: overview of short- and long-term phase 3 controlled studies

Marder SR, Hakala MJ, Josiassen MK, Zhang P, Ouyang J, Weiller E, Weiss C, Hobart M. Brexpiprazole in patients with schizophrenia: overview of short- and long-term phase 3 controlled studies.

Objective: Review efficacy, safety, and tolerability of brexpiprazole in patients with schizophrenia in short- and long-term phase 3 studies.
Methods: Patients experiencing a current exacerbation of schizophrenia received brexpiprazole in two fixed-dose (2 and 4 mg), 6-week, placebo-controlled studies, one flexible-dose (2–4 mg), 6-week, placebo-control and active reference study, and one fixed-dose (1–4 mg), 52-week, placebo-controlled maintenance study.
Results: The efficacy of brexpiprazole was demonstrated in the two short-term fixed-dose studies with statistically significant improvements from baseline in Positive and Negative Syndrome Scale (PANSS) total score compared with placebo. In the flexible-dose short-term study, treatment with brexpiprazole resulted in numerically greater improvements in PANSS total score than with placebo that approached statistical significance ($p = 0.056$). A meta-analysis of these short-term studies showed a mean change in PANSS total score of −20.1, reflecting a clinically meaningful reduction in symptoms. In the maintenance study, brexpiprazole had a beneficial effect relative to placebo on time to exacerbation of psychotic symptoms/impending relapse ($p < 0.0001$). For all studies, brexpiprazole demonstrated clinically meaningful treatment effects on the Personal and Social Performance scale. Brexpiprazole had a favourable safety profile, with a relatively low prevalence of activating and sedating side effects. Weight gain in the short-term studies was ~1 kg greater than placebo. No safety concerns were observed with brexpiprazole in laboratory values, electrocardiogram, or vital signs.
Conclusions: Overall, the results indicate brexpiprazole, used either short-term or as part of a long-term maintenance treatment programme, is an efficacious therapy option in adults with schizophrenia and has a favourable safety/tolerability profile.

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Significant outcomes

- Overall, results from four completed phase 3 studies (three 6-week, short-term studies and one 52-week, long-term maintenance study) indicate that brexpiprazole is efficacious in the treatment of adults with schizophrenia as part of both a short- and long-term treatment programme.
- Brexpiprazole has a favourable tolerability profile with a notably low incidence of activating and sedating side effects.
- Brexpiprazole demonstrated substantial improvements on both social functioning and health-related quality of life.

Limitations

- Randomised controlled trials, like the ones presented in this overview, are primarily designed to provide reliable information on the efficacy and safety of therapeutic interventions (1–3). As such, they are highly regulated and often include a very specific and highly selective patient population (4). Such trials form the primary basis of the regulatory approval of a drug; however, they do not assess the real-world value of a drug (1–3). The use of real-world data would allow for a greater understanding of how a compound directly impacts the patient and their clinical management, in a real-life setting (3,4).
- Another limitation of these studies is the absence of comparison with other antipsychotics. The short-term flexible-dose study included quetiapine; however, this was introduced as an active reference for assay sensitivity only.

Introduction

Schizophrenia is a serious illness affecting ~1% of the world's population (5,6). Patients with schizophrenia experience an array of positive (e.g. hallucinations, delusions, thought disorders) and negative symptoms (e.g. social withdrawal and lack of emotion, energy, and motivation), in addition to cognitive symptoms and behavioural changes (7,8). Collectively, these symptoms can significantly affect the patient's ability to function socially and in the work environment, and have negative implications on their overall quality of life (9–11).

Individuals with schizophrenia often have heterogeneous and difficult-to-predict responses to their antipsychotic medication, and as such often require multiple treatment options (12). Once a patient's symptoms of schizophrenia are stabilised through adequate antipsychotic treatment, relapse prevention is extremely important. Relapse can have significant repercussions for patients with schizophrenia, including worsening of symptoms for each new relapse, progressive cognitive deterioration, impaired functioning, and reduced quality of life (13). The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia (14) emphasises the importance of a long-term treatment management plan in order to minimise the risk of relapse, monitor for and minimise the severity of side effects, improve functioning, and address residual symptoms, as this will help reduce the indirect costs of schizophrenia (15). The use of antipsychotic medications often forms part of a long-term maintenance treatment programme for patients with schizophrenia. However, many patients are not on maintenance therapy, due to non- or partial adherence to medication caused by adverse events (AEs), cognitive impairment, or lack of illness insight.

Current antipsychotics are associated with a multitude of adverse effects, including neurological symptoms, extrapyramidal symptoms (EPS), sedation, adverse metabolic effects (weight gain, hyperglycaemia and dyslipidaemia), hyperprolactinaemia, and cardiac events (QTc prolongation) (16), all of which may impair the patient's ability to perform everyday tasks and could diminish the patient's overall subjective well-being and quality of life, as well as adherence to treatment regime (17). Therefore, there is an urgent need for antipsychotic medications that can relieve the most common and debilitating symptoms of schizophrenia, but can also exhibit a favourable safety and tolerability profile.

Brexpiprazole is a serotonin-dopamine activity modulator that was approved in the United States in July 2015 for the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder. It acts as a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors, and as an antagonist at serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all at similar potency (18). The intrinsic activity of brexpiprazole at D_2 receptors is higher than that of pure antagonists, potentially resulting in fewer D_2 antagonist-like AEs (e.g. EPS, hyperprolactinaemia, tardive dyskinaesia), but lower than that of the first commercially available D_2 partial agonist, aripiprazole, which may translate into a reduced likelihood of inducing AEs potentially mediated by D_2 receptor agonism (e.g. akathisia, insomnia, restlessness, nausea) (19,20). In addition, relative to its potency for D_2/5-HT_{1A} receptors, brexpiprazole has a lower (more than 50-fold) affinity for histamine H_1 receptors (19), often associated with sedation and weight gain.

The efficacy, safety and tolerability of brexpiprazole in the treatment of an acute exacerbation of schizophrenia was demonstrated in two pivotal 6-week, fixed-dose, placebo-controlled studies [NCT01396421 (VECTOR trial); NCT01393613 (BEACON trial)] (21,22), and was evaluated in a 6-week, flexible-dose placebo controlled with active reference (quetiapine XR) study [NCT01810380 (LIGHTHOUSE trial)]. The efficacy and tolerability of brexpiprazole as a maintenance treatment for schizophrenia was also demonstrated in a 52-week maintenance study [NCT01668797 (EQUATOR trial)] (23). This paper provides a comprehensive

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overview of the short- and long-term efficacy, safety and tolerability of brexpiprazole in adult patients with schizophrenia using the results from all these four completed phase 3 studies.

Methods

Patients

Patients in the brexpiprazole phase 3 clinical studies were recruited at sites in North America, Europe, Asia, and Latin America. Male and female patients, aged 18–65 years with a current diagnosis of schizophrenia [Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)] were enrolled. In the short-term studies, patients included were those who would benefit from hospitalisation or continued hospitalisation for the treatment of an acute exacerbation of schizophrenia. In the maintenance study, patients included were those experiencing a current exacerbation of psychotic symptoms requiring stabilisation as demonstrated by a Positive and Negative Syndrome Scale (PANSS) total score >80 at screening. In the two short-term, fixed-dose studies, inclusion criteria included a total Brief Psychiatric Rating Scale score ≥40. In the short-term, flexible-dose study, acute exacerbation of psychotic symptoms and marked deterioration of usual function were evidenced by PANSS total score ≥80; and a score of ≥4 in at least two of the following PANSS items: hallucinatory behaviour, unusual thought content, conceptual disorganisation, or suspiciousness/persecution; and Clinical Global Impression-Severity of Illness Scale (CGI-S) score ≥4. In the maintenance study, patients had schizophrenia for ≥3 years, with a PANSS total score of ≥80 at entry into the study. In all studies, patients with first episode schizophrenia and patients with a current Axis I diagnosis (DSM-IV-TR criteria) other than schizophrenia, or substance abuse or dependence within the past 6 months, were excluded.

Study designs

The three short-term studies were randomised, double-blind, placebo-controlled studies consisting of a screening phase (up to 14 days), double-blind treatment phase (6 weeks), and a safety follow-up phase (30 days). Patients were hospitalised throughout the double-blind treatment period.

In the two fixed-dose studies, patients were randomised to brexpiprazole at fixed doses of 0.25, 2 or 4 mg (VECTOR trial) or 1, 2 or 4 mg (BEACON trial), or placebo. The 0.25-mg dose was predicted to be non-efficacious based on phase 2 studies; the 1-mg dose was included to evaluate the lower dose range. The 0.25-mg dose is not included in this overview. For a detailed description of the study design, see Kane et al. (21) and Correll et al. (22).

In the flexible-dose study, patients were randomised to flexible doses of 2–4 mg brexpiprazole, 400–800 mg quetiapine XR, or placebo. Quetiapine XR was included as an active reference to demonstrate assay sensitivity and validate the study methodology.

The maintenance study was a randomised, double-blind, placebo-controlled study consisting of a screening phase (up to 15 days), three treatment phases (washout/conversion phase, stabilisation phase, and maintenance phase), and a safety follow-up period (30 days). This study consisted of the standard maintenance study design requiring 12 weeks of stability before randomisation to brexpiprazole or placebo for 52 weeks. For a detailed description of the study design, see Fleischhacker et al. (23).

The studies were all conducted in compliance with the International Conference on Harmonization Good Clinical Practice Consolidated Guideline. The protocols were approved by independent ethics committees and all patients provided informed consent to participate.

Assessments

In all short-term studies, efficacy was assessed using the PANSS (24), CGI-S and Clinical Global Impressions-Improvement (CGI-I) scales (25), and the Personal and Social Performance (PSP) scale (26). In addition, in the flexible-dose study quality of life was assessed using the Schizophrenia Quality of Life scale (S-QoL) (27). In all of the short-term studies, the primary endpoint was the change from baseline to Week 6 in PANSS total score.

In the maintenance study, efficacy was assessed using the PANSS, CGI-S and CGI-I scales, PSP, and Global Assessment of Functioning (GAF) (28). The primary efficacy endpoint was the time from randomisation to exacerbation of psychotic symptoms/impending relapse. For a detailed description of the primary efficacy endpoint criteria please refer to Fleischhacker et al. (23).

Standard safety assessments [including AEs, laboratory parameters, and electrocardiograms (ECG)], as well as EPS rating scales [including the Simpson Angus Scale (SAS) (29), Abnormal Involuntary Movement Scale (AIMS) (25), and the Barnes Akathisia Rating Scale (BARS) (30)], and assessments of suicidality using the Columbia Suicide Severity Rating Scale (31) were performed in all studies.

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Data analyses

In the short-term studies, the efficacy populations comprised all patients who received at least one dose of study medication and had both a baseline assessment and at least one post-randomisation efficacy assessment during the double-blind treatment period. Data from the short-term flexible-dose study are presented separately and as part of a meta-analysis of all three short-term studies combined. The long-term maintenance study results are also presented separately.

For the short-term studies, the primary (change from baseline to Week 6 in PANSS total score) and key secondary (change from baseline in CGI-S score) endpoints were analyzed using a mixed model repeated measures (MMRM) analysis at the 0.05 significance level (two-sided). The MMRM model included fixed class-effect terms for treatment, site, visit week, and treatment-by-visit interaction. The model also included baseline score-by-visit interaction as a covariate. The primary comparison between the brexpiprazole groups and the placebo group was estimated as the difference between least squares means at Week 6.

For the meta-analysis, as the three short-term studies were identical in design, the original individual patient data from these studies were pooled and an intention-to-treat analysis used. Patients randomised to fixed-dose brexpiprazole 2 or 4 mg or to flexible-dose brexpiprazole 2–4 mg were grouped for the meta-analysis; the brexpiprazole low-dosing treatment groups (0.25 and 1 mg) were not included in the analysis. Patients randomised to placebo were also grouped together. Statistical comparison between the 2–4 mg brexpiprazole group and placebo group for the pooled meta-analysis was achieved using the MMRM model, which included fixed class-effect terms for treatment, site nested within trial, visit week, and treatment-by-visit week interaction. The model also included baseline-by-visit interaction as a covariate.

In order to control for multiple comparisons, a hierarchical testing procedure approach was adopted (21,22). The average effect of 2 and 4 mg of brexpiprazole versus placebo for the primary efficacy variable was first tested and if the result was statistically significant ($p < 0.05$) then a comparison of each individual dosage versus placebo was analysed. Secondary efficacy endpoints were only assessed, using the same hierarchical testing procedure approach, if both the 2- and 4-mg dosages were statistically significant for brexpiprazole versus placebo.

In the maintenance study in order to minimise duration of therapy for patients receiving placebo, two interim efficacy analyses were planned at ~50% and 75% of events of impending relapse. At the first interim analysis efficacy was demonstrated (45 events reached) and the study was terminated early. The primary endpoint compared the time with exacerbation of psychotic symptoms/impending relapse in the brexpiprazole group versus the placebo group (maintenance phase) using a log-rank test, at the 0.05 significance level (two-sided). For a detailed description of the data analysis carried out in this study please refer to Fleischhacker et al. (23).

Results

Patients

Across all short-term studies, the completion rate was >60%, and was higher in the brexpiprazole groups than the placebo group. Patient disposition is presented in Table 1.

In the short-term studies, the most common reasons provided for study discontinuation were lack of efficacy/relapse, AEs, and withdrawal of consent (Table 1).

The early termination of the maintenance study, due to efficacy being demonstrated at the first pre-specified interim analysis, resulted in the discontinuation of 43.1% of patients. Other than this, the most frequent reason for study discontinuation was lack of efficacy/relapse (13.4% of brexpiprazole patients and 38.1% of placebo patients) (Table 1).

Demographic and baseline clinical characteristics

In both the flexible-dose study and the meta-analysis, the majority of patients were white (75.2% and 66.0%, respectively) and male (56.9% and 61.0%, respectively) (Table 2). Patients were markedly ill at entry to each of the short-term studies, with the mean PANSS total score ranging from 95.9 to 98.8 and CGI-S score from 4.9 to 5.0. The patient demographics in the maintenance study were similar to the short-term studies (Table 2). In addition, as per protocol, patients in the maintenance study who had already completed the stabilisation phase were more stable, with a PANSS total score <60 and CGI ~3 (Table 2).

Dosing

In the short-term, flexible-dose study, the mean average dose of brexpiprazole at last visit was 3.5 mg/day, and 674.4 mg/day for quetiapine. In the maintenance study, the mean average dose for brexpiprazole was 3.6 mg/day. In the short-term,

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Table 1. Patient disposition

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo (*N* = 163)	Brexpiprazole 2–4 mg (*N* = 151)	Placebo (*N* = 531)	Brexpiprazole 2–4 mg (*N* = 883)	Placebo (*N* = 105)	Brexpiprazole 1–4 mg (*N* = 97)
Randomised [*n* (%)]	163 (100.0)	151 (100.0)	531 (100.0)	883 (100.0)	105 (100.0)	97 (100.0)
Safety population [*n* (%)]	161 (98.8)	150 (99.3)	529 (99.6)	882 (99.9)	104 (99.0)	97 (100.0)
Completed [*n* (%)]	108 (67.1)	113 (75.3)	335 (63.1)	617 (69.9)	9 (8.6)	14 (14.4)
Discontinued [*n* (%)]	53 (32.9)	37 (24.7)	196 (36.9)	266 (30.1)	96 (91.4)	83 (85.6)
Reason for discontinuation						
Sponsor terminated the study [*n* (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (36.2)	49 (50.5)
Lack of efficacy/relapse [*n* (%)]	24 (14.9)	10 (6.7)	63 (11.9)	70 (7.9)	40 (38.1)	13 (13.4)
Adverse events [*n* (%)]	11 (6.8)	14 (9.3)	65 (12.2)	70 (7.9)	2 (1.9)	4 (4.1)
Withdrew consent [*n* (%)]	6 (3.7)	0 (0.0)	50 (9.4)	103 (11.7)	5 (4.8)	3 (3.1)
Lost to follow-up [*n* (%)]	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	6 (5.7)	4 (4.1)
Withdrawn by investigator [*n* (%)]	0 (0.0)	0 (0.0)	4 (0.8)	2 (0.2)	2 (1.9)	5 (5.2)
Met withdrawal criteria [*n* (%)]	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.3)	3 (2.9)	3 (3.1)
Protocol deviation [*n* (%)]	1 (0.6)	0 (0.0)	1 (0.2)	4 (0.5)	0 (0.0)	2 (2.1)
Other reasons [*n* (%)]	11 (6.8)	13 (8.7)	11 (2.1)	14 (1.6)	0 (0.0)	0 (0.0)
Efficacy population [*n* (%)]	159 (97.5)	150 (99.3)	517 (97.4)	868 (98.3)	104 (99.0)	96 (99.0)

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

Table 2. Demographic and baseline clinical characteristics

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo (*N* = 161)	Brexpiprazole 2–4 mg (*N* = 150)	Placebo (*N* = 531)	Brexpiprazole 2–4 mg (*N* = 883)	Placebo (*N* = 105)	Brexpiprazole 1–4 mg (*N* = 97)
Demographic characteristics						
Age (years) [mean (SD)]	40.9 (10.6)	39.7 (10.9)	39.8 (10.8)	39.1 (10.9)	41.6 (10.6)	38.8 (10.7)
BMI (kg/m^2) [mean (SD)]	26.5 (5.3)	27.0 (5.9)	26.5 (5.5)	26.9 (6.1)	29.1 (6.9)	28.2 (6.7)
Female [*n* (%)]	70 (43.5)	66 (44.0)	209 (39.4)	342 (38.7)	40 (38.1)	39 (40.2)
White [*n* (%)]	123 (76.4)	113 (75.3)	354 (66.7)	575 (65.1)	65 (61.9)	62 (63.9)
Clinical characteristics						
Age at first diagnosis (years) [mean (SD)]	27.2 (8.9)	27.4 (9.6)	26.5 (9.1)	26.4 (8.5)	27.9 (8.3)	26.5 (8.2)
Duration of current episode (weeks) [mean (SD)]	N/A	N/A	2.7 (2.7)	2.5 (2.3)	N/A	N/A
PANSS total score [mean (SD)]	98.4 (10.3)	97.8 (10.3)	96.2 (11.7)	95.9 (12.4)	58.1 (8.1)	56.5 (8.7)
CGI-S score [mean (SD)]	4.9 (0.6)	5.0 (0.6)	4.9 (0.6)	4.9 (0.6)	3.1 (0.6)	3.0 (0.6)
PSP score [mean (SD)]	43.9 (10.7)	42.8 (10.4)	44.3 (10.3)	44.3 (10.9)	48.7 (11.7)	50.1 (12.4)
GAF score [mean (SD)]	N/A	N/A	N/A	N/A	63.1 (8.4)	64.3 (9.2)
S-QoL score [mean (SD)]	44.7 (17.8)	43.7 (18.9)	N/A	N/A	N/A	N/A

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impression-Severity of Illness Scale; GAF, Global Assessment of Functioning; N/A, not applicable; PANSS, Positive and Negative Symptom Scale; PSP, Personal and Social Performance; S-QoL, Schizophrenia Quality of Life scale.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

fixed-dose BEACON study, 186 patients received brexpiprazole 2 mg/day and 184 patients received brexpiprazole 4 mg/day (21). In the short-term, fixed-dose VECTOR study, 180 patients received brexpiprazole 2 mg/day and 178 patients received brexpiprazole 4 mg/day (22).

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Table 3. Efficacy endpoints

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 1–4 mg
PANSS total score (*n*)	111	114	517	868	9	15
LS mean change (SE)	−15.9 (1.5)	−20.0 (1.5)	−14.3 (0.90)	−20.1 (0.7)	6.9 (4.5)	0.6 (3.3)
Treatment difference (95% CI)	–	−4.1 (−8.2, 0.1)	–	**−5.8** (−8.0, −3.6)	–	−6.3 (−18.1, 5.5)
p-Value	–	0.0560	–	< 0.0001	–	0.2800
CGI-S total score (*n*)	111	114	521	872	9	15
LS mean change (SE)	−0.9 (0.1)	−1.2 (0.1)	−0.9 (0.1)	−1.2 (0.03)	0.3 (0.2)	−0.2 (0.2)
Treatment difference (95% CI)	–	**−0.3** (−0.5, −0.1)	–	**−0.3** (−0.4, −0.2)	–	−0.5 (−1.1, 0.1)
p-Value	–	0.0142	–	< 0.0001	–	0.0780
CGI-I score (*n*)	111	114	520	872	9	15
Mean at last week†	3.0 (0.1)	2.7 (0.1)	3.4 (1.4)‡	3.0 (1.3)‡	2. 9 (1.4)§	3.0 (1.3)§
Treatment difference (95% CI)	–	**−0.3** (−0.6, −0.0)	–	**−0.4** (−0.6, −0.3)	–	0.1 (−0.9, 1.2)
p-Value	–	0.0295	–	< 0.0001	–	0.8353
Response (*n*)	111	114	520	872	N/A	N/A
Rate (%)	44.1††	61.4‖	30.0¶	44.3¶		
Relative risk (95% CI)	–	**2.02** (1.18, 3.43)	–	**1.5** (1.3, 1.7)		
p-Value	–	0.0098	–	< 0.0001		
PSP scale score (*n*)	112	114	492	835	9	15
LS mean change (SE)	9.4 (1.0)	13.0 (1.0)	9.3 (0.6)	12.5 (0.5)	13.0 (3.5)	18.6 (2.8)
Treatment difference (95% CI)	–	**3.6** (0.9, 6.3)	–	**3.2** (1.8, 4.6)	–	6.1 (−2.7, 14.9)
p-Value	–	0.0101	–	< 0.0001	–	0.1677
S-QOL scale score (*n*)	108	111				
LS mean change (SE)§	3.9 (1.4)	11.2 (1.4)	N/A	N/A	N/A	N/A
Treatment difference (95% CI)	–	**7.2** (3.5, 11.0)				
p-Value	–	0.0002				
GAF scale score (*n*)					9	15
LS mean change (SE)	N/A	N/A	N/A	N/A	−0.2 (2.4)	5.7 (1.9)
Treatment difference (95% CI)					–	5.9 (−0.1, 11.8)
p-Value					–	0.0522

Results indicate mean (SD) at Week 6 in the short-term studies and mean (SD) at Week 52 in the long-term maintenance study.

All results represent mixed model repeated measures analysis unless stated otherwise.

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impression-Severity of Illness Scale; CI, confidence interval; GAF, Global Assessment of Functioning; LS, least squares; N/A, not applicable; OC, observed cases; PANSS, Positive and Negative Symptom Scale; PSP, Personal and Social Performance; S-QoL, Schizophrenia Quality of Life scale.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

† Mean (SD) at Week 6 for short-term fixed-dose studies; mean (SE) at Week 6 for short-term flexible-dose study; mean (SD) at Week 52 for maintenance study.

‡ Last observation carried forward (LOCF).

§ OC.

‖ OC. Response defined as a reduction of ≥30% from baseline in PANSS total score, or a CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6.

¶ LOCF. Response defined as a CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6.

Bold text indicates $p < 0.05$.

Efficacy

Patients in the brexpiprazole treatment groups of the short-term studies had greater improvements from baseline in PANSS total score compared with placebo (Table 3). In the previously reported fixed-dose studies, brexpiprazole at a dosage of 4 mg resulted in a statistically significantly greater improvement in PANSS total score than placebo in both studies (21,22), whereas the 2-mg dose of brexpiprazole demonstrated a superior improvement compared with placebo in one study (22). In the flexible-dose study, the difference in change from baseline between brexpiprazole and placebo approached, but did not reach, statistical significance ($p = 0.056$) as assessed with PANSS total score. The mean (SD) reduction in PANSS total score from baseline to Week 6 was 20.0 (1.5) points in the brexpiprazole group, compared with 15.9 (1.5) points in the placebo group. The mean (SD) reduction from baseline to Week 6 in PANSS total score for the quetiapine group was 24.0 (1.5) points and was

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statistically significantly different ($p < 0.001$) from that in the placebo group (-15.9 ± 1.5), which validated the study methodology and the patient population included. In the meta-analysis, the brexpiprazole 2–4 mg group showed a mean (SD) change of 20.1 (0.7) points on PANSS score from baseline to Week 6, which was significantly greater than with placebo ($p < 0.0001$, -14.3 ± 0.90).

The secondary endpoints, including the change in CGI-S (pre-specified as key secondary endpoint), CGI-I score, and response rate, were all superior in the brexpiprazole group compared with that of placebo ($p < 0.05$), both in the flexible-dose study and according to the meta-analysis (Table 3). Similar results were observed for the brexpiprazole 4-mg group in both fixed-dose studies (21,22), and for the brexpiprazole 2-mg dose in one of these studies (22).

Brexpiprazole demonstrated improvements compared with placebo in PSP functioning ($p = 0.0101$) and quality of life ($p = 0.0002$) (Table 3), in the flexible-dose study. Similar results were seen in the meta-analysis, with brexpiprazole consistently showing greater improvement compared with placebo on functioning PSP ($p < 0.0001$) (Table 3).

In the maintenance study, the primary analysis showed a beneficial effect of brexpiprazole relative to placebo on the time to exacerbation of psychotic symptoms/impending relapse (log-rank test: hazard ratio = 0.292, $p < 0.0001$). In addition, significantly fewer patients relapsed in the brexpiprazole group compared with placebo during the 52-week maintenance period (13.5% vs. 38.5%, $p < 0.0001$) (23).

Improvement in clinical symptomatology, as assessed by PANSS, CGI-S, and CGI-I scores, was maintained with brexpiprazole treatment, whereas placebo showed a worsening in clinical symptomatology at Week 52 (Table 3). Furthermore, PSP and GAF scores showed a positive effect of brexpiprazole relative to placebo on functioning at Week 52 (Table 3).

Safety and tolerability

Treatment-emergent adverse events (TEAEs) are presented in Table 4. Overall, brexpiprazole was generally well tolerated in all studies. Across the studies, the incidence of AEs leading to withdrawal was lower in the brexpiprazole groups than with placebo.

Akathisia was the only TEAE reported by patients with an incidence of ≥5% and twice the rate of placebo in the flexible-dose study; the rates of akathisia for brexpiprazole versus placebo were 6.0% and 2.5%, respectively (Table 4).

In the flexible-dose study, the mean (SD) increase in body weight at Week 6 was 1.6 (2.9) kg in the brexpiprazole group, compared with 0.5 (2.4) kg in the placebo group. In the meta-analysis, the mean (SD) increase in body weight at last visit was 1.2 (3.3) kg in the brexpiprazole 2–4 mg group, compared with 0.2 (2.7) kg in the placebo group. In the maintenance study, there was only moderate mean changes in body weight to last visit following both the stabilisation phase (0.8 ± 4.0 kg in the brexpiprazole 1–4 mg group) and the maintenance phase (-0.3 ± 4.9 kg and -2.2 ± 3.6 kg, in the brexpiprazole 1–4 mg group and the placebo group, respectively).

Table 4. Treatment-emergent adverse events

	Short-term studies				Maintenance study		
	Flexible-dose study		Meta-analysis*		Stabilisation phase	Double-blind maintenance phase	
Number of patients [*n* (%)]	Placebo (*N* = 161)	Brexpiprazole 2–4 mg (*N* = 150)	Placebo (*N* = 529)	Brexpiprazole 2–4 mg (*N* = 882)	Brexpiprazole 1–4 mg (*N* = 464)	Placebo (*N* = 104)	Brexpiprazole 1–4 mg (*N* = 97)
At least one TEAE	88 (54.7)	81 (54.0)	304 (57.5)	511 (57.9)	277 (59.7)	58 (55.8)	42 (43.3)
Discontinuation due to AE	18 (11.2)	16 (10.7)	65 (12.2)	70 (7.9)	41 (8.8)	12 (11.5)	5 (5.2)
TEAEs occurring in ≥5% of patients in any group							
Insomnia	10 (6.2)	13 (8.7)	55 (10.4)	97 (11.0)	56 (12.1)	8 (7.7)	5 (5.2)
Headache	11 (6.8)	8 (5.3)	53 (10.0)	86 (9.8)	23 (5.0)	10 (9.6)	6 (6.2)
Agitation	7 (4.3)	7 (4.7)	39 (7.4)	60 (6.8)	30 (6.5)	3 (2.9)	1 (1.0)
Akathisia	4 (2.5)	9 (6.0)	21 (4.0)	51 (5.8)	42 (9.1)	1 (1.0)	1 (1.0)
Schizophrenia	15 (9.3)	9 (6.0)	53 (10.0)	47 (5.3)	28 (6.0)	7 (6.7)	3 (3.1)
Weight increase	6 (3.7)	8 (5.3)	12 (2.3)	37 (4.2)	24 (5.2)	0 (0.0)	1 (1.0)
Somnolence	8 (5.0)	7 (4.7)	18 (3.4)	25 (2.8)	13 (2.8)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (0.6)	2 (1.3)	6 (1.1)	11 (1.2)	16 (3.4)	7 (6.7)	3 (3.1)
Psychotic disorder	4 (2.5)	0 (0.0)	9 (1.7)	8 (0.9)	5 (1.1)	6 (5.8)	1 (1.0)

AE, adverse event; TEAE, treatment-emergent adverse event.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

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Table 5. Summary of extrapyramidal symptom-related adverse events

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo ($N = 161$)	Brexpiprazole 2–4 mg ($N = 150$)	Placebo ($N = 529$)	Brexpiprazole 2–4 mg ($N = 882$)	Placebo ($N = 104$)	Brexpiprazole 1–4 mg ($N = 97$)
Withdrawals due to EPS TEAEs	1 (0.6)	3 (2.0)	2 (0.4)	3 (0.3)	0 (0.0)	0 (0.0)
EPS category						
Any EPS TEAE [*n* (%)]	10 (6.2)	16 (10.7)	41 (7.8)	103 (11.7)	5 (4.8)	6 (6.2)
Akathisia events [*n* (%)]	5 (3.1)	10 (6.7)	23 (4.3)	55 (6.2)	1 (1.0)	1 (1.0)
Parkinsonian events [*n* (%)]	1 (0.6)	6 (4.0)	9 (1.7)	42 (4.8)	2 (1.9)	3 (3.1)
Dystonic events [*n* (%)]	3 (1.9)	1 (0.7)	10 (1.9)	13 (1.5)	1 (1.0)	2 (2.1)
Residual events [*n* (%)]	1 (0.6)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)
Dyskinetic events [*n* (%)]	1 (0.6)	0 (0.0)	3 (0.6)	3 (0.3)	1 (1.0)	1 (1.0)

EPS, extrapyramidal symptoms; TEAE, treatment-emergent adverse events.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

In the flexible-dose study, the proportion of patients with EPS-related TEAEs was 6.2% ($n = 10$) for placebo group and 10.7% ($n = 16$) in the brexpiprazole group (Table 5). A similar proportion of patients with EPS-related TEAEs were seen in the meta-analysis, with a total of three patients (0.3%) from the brexpiprazole group and two patients (0.4%) from the placebo group withdrawing due to EPS-related TEAEs. In the maintenance study, five patients (4.8%) from the placebo group and six patients (6.2%) in the brexpiprazole 1–4-mg group reported EPS-related TEAEs (Table 5). No patients withdrew from the maintenance study due to EPS-related TEAEs.

In the short-term studies, the reported incidence of sedation and somnolence TEAEs were similar between placebo and brexpiprazole groups (3.1% vs. 2.7% in the flexible-dose study and 1.5% vs. 2.3% in the meta-analysis, respectively, for sedation TEAEs; and 5.0% vs. 4.7% in the flexible-dose study and 3.4% vs. 2.8% in the meta-analysis, respectively, for somnolence TEAEs). Reports of both sedation and somnolence TEAEs were low (<3.0%) for both the brexpiprazole and placebo groups in the maintenance study. No patients withdrew due to somnolence-related TEAEs in any of the studies.

Across the studies, there were no clinically relevant findings with regard to formal EPS rating scales (Supplementary Table 1), suicidality, prolactin (Table 6), metabolic parameters (Table 6), or ECG assessments (Table 7).

Discussion

Overall, results from these completed, phase 3 studies in adult patients with schizophrenia have demonstrated the efficacy, safety and tolerability of brexpiprazole as part of both a short- and long-term treatment programme.

Results from the meta-analysis of the short-term studies demonstrated that brexpiprazole 2–4 mg is efficacious in the treatment of adults with an acute exacerbation of schizophrenia as shown by the significant improvements from baseline to Week 6 in PANSS total score ($p < 0.0001$) compared with placebo, supporting the results from the individual studies (21,22). In the fixed-dose studies, brexpiprazole 4 mg resulted in a statistically significantly greater improvement in PANSS total score than placebo (21,22), with brexpiprazole 2 mg demonstrating a statistically superior improvement compared with placebo in one study (22), and a numerical improvement seen in the second study (21). In the flexible-dose study, the difference in change from baseline in PANSS total score between brexpiprazole and placebo approached statistical significance ($p = 0.056$). A reduction in PANSS total score of ~15–18 points can be considered clinically meaningful (32). In the flexible-dose study, we observed a mean decrease in PANSS total score from baseline to Week 6 of 20 points in the brexpiprazole group, which suggests a clinically meaningful improvement. Despite the magnitude of change, the difference between the brexpiprazole and placebo groups just failed to reach statistical significance ($p = 0.056$) as a consequence of the larger than expected improvements in PANSS total score (16.2% reduction) seen in the placebo group. A significant difference in PANSS reduction was, however, observed with the assay sensitivity control (quetiapine) versus placebo.

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Table 6. Mean changes (SD) in fasting metabolic parameters and prolactin from baseline to last visit

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 1–4 mg
Fasting metabolic parameters						
Cholesterol (mg/dl)	4.1 (34.6) ($n = 128$)	2.6 (26.9) ($n = 125$)	−1.2 (30.8) ($n = 466$)	2.4 (28.9) ($n = 803$)	−3.6 (45.9) ($n = 80$)	−4.01 (27.3) ($n = 79$)
HDL cholesterol (mg/dl)	0.4 (12.9) ($n = 128$)	0.5 (8.3) ($n = 125$)	−1.2 (10.1) ($n = 466$)	0.9 (9.8) ($n = 803$)	1.8 (9.9) ($n = 80$)	0.5 (8.2) ($n = 79$)
LDL cholesterol (mg/dl)	4.1 (28.7) ($n = 128$)	2.6 (24.6) ($n = 125$)	−0.3 (26.6) ($n = 466$)	1.4 (24.8) ($n = 797$)	−4.2 (39.5) ($n = 77$)	−2.5 (23.5) ($n = 77$)
Triglycerides (mg/dl)	−3.6 (84.8) ($n = 128$)	−1.0 (60.4) ($n = 125$)	−0.2 (68.2) ($n = 466$)	−0.8 (74.7) ($n = 803$)	−13.0 (61.8) ($n = 80$)	−11.0 (65.1) ($n = 79$)
Glucose (mg/dl)	3.2 (28.4) ($n = 128$)	0.9 (23.9) ($n = 125$)	1.3 (19.5) ($n = 466$)	0.8 (17.1) ($n = 800$)	−1.6 (28.9) ($n = 79$)	2.1 (15.0) ($n = 79$)
HbA1c (%)	0.03 (0.5) ($n = 107$)	0.1 (0.5) ($n = 113$)	0.0 (0.3) ($n = 466$)	0.0 (0.4) ($n = 805$)	−0.1 (0.7) ($n = 94$)	0.1 (0.3) ($n = 91$)
Prolactin (ng/ml)						
Females (ng/ml)	−3.5 (17.9) ($n = 61$)	2.5 (20.3) ($n = 55$)	−5.4 (27.1) ($n = 194$)	−0.7 (26.0) ($n = 320$)	−4.3 (19.2) ($n = 36$)	−2.2 (22.4) ($n = 38$)
Males (ng/ml)	−2.6 (11.9) ($n = 68$)	−1.8 (8.3) ($n = 64$)	−1.2 (10.6) ($n = 288$)	−1.0 (10.3) ($n = 505$)	1.4 (12.2) ($n = 58$)	−1.7 (6.1) ($n = 53$)

HbA1c, haemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

Table 7. Mean (SD) change from baseline at last visit in ECG results at last visit

	Short-term studies					
	Flexible-dose study		Meta-analysis*		Maintenance study (double-blind maintenance phase)	
	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 1–4 mg
ECG parameters						
Heart rate (bpm)	2.2 (12.7) ($n = 136$)	1.0 (12.5) ($n = 132$)	2.3 (13.2) ($n = 492$)	1.6 (12.8) ($n = 842$)	2.1 (13.8) ($n = 100$)	2.6 (12.2) ($n = 95$)
PR interval (ms)	0.0 (11.1) ($n = 136$)	1.7 (17.5) ($n = 132$)	−0.3 (12.8) ($n = 492$)	−0.4 (14.6) ($n = 841$)	−1.4 (13.9) ($n = 100$)	−1.1 (11.0) ($n = 95$)
QRS interval (ms)	0.0 (6.8) ($n = 136$)	0.7 (6.9) ($n = 132$)	0.8 (7.3) ($n = 492$)	0.8 (7.2) ($n = 842$)	0.0 (7.7) ($n = 100$)	0.1 (6.2) ($n = 95$)
QT interval (ms)	−0.7 (26.5) ($n = 136$)	0.4 (24.5) ($n = 132$)	−1.5 (28.9) ($n = 492$)	−1.8 (25.7) ($n = 841$)	−4.0 (26.6) ($n = 100$)	−1.3 (26.2) ($n = 95$)
QTcB interval (ms)	5.5 (21.8) ($n = 136$)	3.1 (21.1) ($n = 132$)	4.7 (21.7) ($n = 492$)	2.5 (21.3) ($n = 841$)	2.5 (21.7) ($n = 100$)	4.9 (21.7) ($n = 95$)
QTcF interval (ms)	3.3 (17.3) ($n = 136$)	2.1 (16.1) ($n = 132$)	2.5 (18.2) ($n = 492$)	1.0 (16.7) ($n = 841$)	0.2 (15.8) ($n = 100$)	2.7 (17.1) ($n = 95$)
RR interval (ms)	−23.9 (139.9) ($n = 136$)	−12.4 (132.4) ($n = 132$)	−26.4 (147.7) ($n = 492$)	−19.2 (142.9) ($n = 842$)	−33.5 (154.5) ($n = 100$)	−23.0 (144.3) ($n = 95$)

bpm, beats per minute; ECG, electrocardiogram; QTcB, QT interval corrected for heart rate by Bazett's formula; QTcF, QT interval corrected for heart rate by Fridericia's formula.

* Placebo and brexpiprazole 2–4 mg groups from the two fixed-dose phase 3 studies and the one flexible-dose phase 3 study were combined and analysed using individual patient data meta-analysis.

In the meta-analysis, the mean change in PANSS total score was −20.1, suggesting a clinically detectable improvement equivalent to a reduction in CGI severity of ≥1 severity step, thus demonstrating the efficacy of brexpiprazole across these studies. This finding further demonstrates the clinical improvements observed following brexpiprazole 2–4 mg and is consistent with results from the pivotal BEACON and VECTOR trials (21,22), where decreases in PANSS total score from baseline to Week 6 were seen for both 2 mg brexpiprazole (−16.6 and −20.7, respectively) and 4 mg brexpiprazole (−20.0 and −19.7, respectively) groups.

Furthermore, improvements from baseline to Week 6 in CGI-S scores, as well as CGI-I scores and responder rate at Week 6 observed in the fixed-dose studies (21,22), the flexible-dose study and the meta-analysis, confirmed the efficacy of brexpiprazole as a treatment for acute schizophrenia in adult patients.

In the maintenance study, the efficacy of brexpiprazole as a maintenance treatment in adults with schizophrenia was demonstrated by the beneficial effect of brexpiprazole relative to placebo on the time to exacerbation of psychotic symptoms/impending relapse ($p < 0.0001$). Furthermore, significantly fewer patients relapsed in the brexpiprazole group compared with placebo ($p = 0.0008$). The efficacy of brexpiprazole as a maintenance therapy for patients with schizophrenia was also shown in PANSS and

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CGI scores, with symptom stability being maintained for patients in the 1–4 mg brexpiprazole treatment group. Conversely, patients in the placebo group showed a worsening in clinical symptomatology at Week 52 (Table 3).

Collectively, findings from these short-term studies and the long-term maintenance study indicate that brexpiprazole is a suitable treatment option for patients with schizophrenia presenting with both acute and stable illness.

Schizophrenia is a complex and multidimensional illness, with a number of elements contributing to the burden of disease. It is known that expression of prominent and numerous symptoms is associated with increased functional impairment (33). Therefore, improved functioning is crucial for patients with schizophrenia. Previous research in schizophrenia has noted that the PSP is reliable for detecting functional improvements in schizophrenia and that an increase of at least 7 points in PSP total score can be considered clinically meaningful to patients in terms of their overall functional capacity (34). In the flexible-dose study, there was a mean increase in PSP total score of 13 points in the brexpiprazole group, a similar 12.6 point increase across short-term studies, and in the maintenance study there was an increase of almost 19 points in the 1–4 mg brexpiprazole group. These data suggest that brexpiprazole, when taken as both a short- and long-term treatment, has a clinically relevant effect on the overall psychosocial functioning of patients with schizophrenia. The GAF assessment used in the maintenance study is a clinician-rated scale that measures the subject's psychological, social, and occupational functioning, and was used in the maintenance study to help assess long-term overall functioning. There was a 5.7 point increase from baseline in GAF total scores for the brexpiprazole group at Week 52. This increase would suggest that brexpiprazole has a positive effect on functioning in adult patients with schizophrenia. However, despite the GAF assessment being widely used to determine functioning in patients with schizophrenia, there is no currently agreed acceptable value with regard to the minimum clinically important difference (MCID) (35). As such, there is insufficient evidence in the literature to allow any conclusions to be drawn as to if the improvements in GAF scores observed in the phase 3 maintenance study represents a clinically relevant improvement.

The patient-reported S-QoL was developed through interviews with patients to identify dimensions of quality of life that are relevant to patients with schizophrenia (27), and was carried out in the short-term, flexible-dose study. Patients included in the brexpiprazole group had an 11-point increase in their S-QoL scores, resulting in a statistically significant treatment difference ($p = 0.0002$) when compared with patients in the placebo group. One study has reported that an improvement of ≥1.13 on the S-QoL assessment represents a clinically important improvement (36), which suggests administration of brexpiprazole 2–4 mg does result in an overall clinically relevant improvement in the quality of life of patients. However, it must be noted that there is a paucity of additional literature supporting the suggested MCID value, and therefore the conclusions with respect to brexpiprazole treatment on quality of life must be cautiously interpreted. Nevertheless, the S-QoL results do indicate that brexpiprazole can exhibit substantial improvements on health-related quality of life, which is a key factor in the treatment of schizophrenia. Taken together, these results have shown that brexpiprazole may produce beneficial treatment effects on social functioning and quality of life in patients with schizophrenia.

Overall, brexpiprazole was found to be well tolerated in the short-term and maintenance studies, with the incidence of withdrawals due to AEs lower in the brexpiprazole groups than in the placebo groups, for all of the studies. Notably, the incidence of activating and sedating side effects was relatively low for all studies. In addition, changes in the EPS-scale scores (SAS, AIMS, and BARS) were minimal in the short-term studies and in the maintenance study.

In the flexible-dose study, the only TEAE in patients treated with brexpiprazole with an incidence of ≥5%, and twice the rate of placebo, was akathisia. This was not the case in the meta-analysis, where the incidence of akathisia was similar between the placebo and brexpiprazole 2–4 mg groups (4.0% vs. 5.8%, respectively). Furthermore, the incidence of akathisia in the maintenance study was similar between brexpiprazole and placebo groups (1% for both groups), suggesting that, over time, the incidence of akathisia events may be reduced with continued brexpiprazole use. In addition, no patients withdrew due to akathisia in the flexible-dose study, the fixed-dose studies (21,22), or the maintenance phase of the maintenance study [one patient (0.2%) discontinued due to akathisia in the single-blind stabilisation phase]. Akathisia is a common side effect of some antipsychotic treatments (37–39). Similar to brexpiprazole, both aripiprazole and cariprazine act as partial agonists at the dopamine D_2 receptor and antagonists at the 5-HT_{2A} receptor; however, both of these antipsychotics have been associated with inducing high rates of akathisia, possibly due to their activity at these receptors (40–43). Although brexpiprazole is also a serotonin-dopamine activity modulator, it has lower intrinsic activity at D_2 receptors and higher intrinsic

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antagonistic activity at 5-HT_{2A} receptors compared with both aripiprazole and cariprazene (18,19,44,45), which may at least partly explain the reduced akathisia and other activating side effects seen in these studies.

Antipsychotic drugs have long been associated with sedative adverse effects in patients with schizophrenia (12,46). Across the phase 3 studies, patients treated with brexpiprazole experienced low rates of somnolence (<5%) and sedation (<3%). Sedation induced by antipsychotic agents such as chlorpromazine, clozapine, quetiapine, and olanzapine has been associated with blockade of histamine receptors (12,19). Brexpiprazole, on the other hand, has a much higher affinity for dopamine receptors than for histamine receptors, potentially explaining its low level of sedation-related adverse effects (19).

Weight gain has also been associated with a number of antipsychotic treatments (47,48). The results revealed a mean weight gain of ~1 kg greater than placebo in the short-term studies. These results compare favourably to previous short-term studies in patients with schizophrenia who were taking olanzapine and gained between 3.3 and 4.0 kg, following 6–8 weeks of treatment (49–51), or risperidone who gained 1.5 kg after 8 weeks of treatment (51). Although patients gained some weight (mean increase of 0.8 kg) during the stabilisation phase of the maintenance study (23), the mean change in body weight decreased for both brexpiprazole and placebo following the maintenance phase in the long-term placebo-controlled study. However, due to the high rate of patient discontinuations in the study following the positive interim analysis, the trial population within the maintenance study may not be representative of the population intended to be analysed.

Brexpiprazole treatment induced small changes on prolactin in patients from the short-term studies and in patients from the long-term maintenance study. In addition, very few patients reported hyperprolactinaemia as an AE (0.7%, 0.3% and 0%, from the flexible-dose study, the meta-analysis and the long-term maintenance study, respectively).

There were only small changes in lipid or glucose concentrations in patients from the short-term studies or the long-term maintenance study, suggesting brexpiprazole did not have a clinically significant effect on these metabolic parameters in patients with schizophrenia. These results are important as a number of second generation antipsychotics have been associated with serious adverse metabolic side effects (47,48,52).

In addition to these findings, no further clinically significant safety concerns in terms of AEs, safety laboratory test values, ECG, or vital signs were observed with brexpiprazole in the short-term studies or the maintenance study, confirming the overall favourable safety and tolerability profile of brexpiprazole.

In summary, results from two fixed-dose, 6-week, placebo-controlled studies (21,22), one flexible-dose, 6-week, control- and active-reference study, and one fixed-dose, 52-week, placebo-controlled maintenance study (23) together suggest that brexpiprazole is an efficacious therapy option as part of a short-term or long-term maintenance treatment programme in adults with schizophrenia, and that it is characterised by a favourable safety and tolerability profile.

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Conflicts of Interest

The authors have no specific statements of interest associated with these studies.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2016.57

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