Original Paper

Efficacy and safety of brexpiprazole in patients with schizophrenia presenting with severe symptoms: *Post-hoc* analysis of short- and long-term studies

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Abstract

Background: The treatment of patients with severe schizophrenia symptoms can be complicated and expensive.

Aims: The purpose of this study was to evaluate the short- and long-term effects of brexpiprazole in patients with schizophrenia presenting with severe symptoms.

Methods: Data were pooled from three six-week, randomized, double-blind, placebo-controlled studies and two 52-week, open-label extension studies. In the short-term studies, 1405 patients received placebo or brexpiprazole 2–4 mg/day; 412 brexpiprazole-treated patients rolled over into the long-term studies and received brexpiprazole 1–4 mg/day. More severe symptoms were defined as a Positive and Negative Syndrome Scale Total score >95 (median score at baseline). Outcomes included change in Positive and Negative Syndrome Scale Total and Personal and Social Performance scale scores.

Results: Brexpiprazole improved Positive and Negative Syndrome Scale Total score over 6 weeks among more severely ill patients, with a least squares mean difference versus placebo of –6.76 (95% confidence limits: –9.80, –3.72; $p<0.0001$; Cohen's *d*: 0.43). Brexpiprazole also improved Personal and Social Performance scale score over 6 weeks in more severely ill patients (least squares mean difference: 4.38; limits: 2.14, 6.62; $p=0.0001$; Cohen's *d*: 0.38). Improvement of functioning was greatest in the 'Self-care' domain, followed by 'Personal and social relationships'. Among less severely ill patients, brexpiprazole was superior to placebo on Positive and Negative Syndrome Scale Total and Personal and Social Performance scale at Week 6. Improvements were maintained over 58 weeks. No new safety or tolerability concerns were observed.

Conclusions: Brexpiprazole is an efficacious and well-tolerated treatment for schizophrenia in patients with more severe, and less severe, symptoms.

Keywords

Brexpiprazole, schizophrenia, patient function, severe symptoms, treatment outcome

Introduction

Schizophrenia is a chronic, disabling and progressive disease, with heterogeneous symptoms and disease course between individuals (Modestin et al., 2003; Owen et al., 2016). As the severity of schizophrenia symptoms increases, patients have an increased risk of non-adherence to medication (Dassa et al., 2010; Yang et al., 2012) and of psychiatric hospitalization (Glick et al., 2015). The cost of treatment increases with increasing symptom severity (Mohr et al., 2004), which may in part be attributed to the need for higher doses of medication, leading to more severe pharmacological side effects (which also increase medical costs) (Zhang et al., 2014), and the need for combination treatment (Bolstad et al., 2011). Patients with severe symptoms may also attempt to self-medicate, as shown by an increased risk of heavy smoking and nicotine dependence (though equally this could be due to a shared vulnerability) (Krishnadas et al., 2012; Meszaros et al., 2011). More severe symptoms are associated with impaired clinical insight (Gerretsen et al., 2013; Ozzoude et al., 2019; Zhang et al., 2014), meaning that patients lack awareness or understanding of their psychiatric condition and life situation. Patients with more severe positive symptoms are also at increased risk of being homeless (Opler et al., 2001). Overall, patients with severe schizophrenia symptoms may require more complicated and costly treatment, and it is therefore important to determine whether a new drug for psychosis is efficacious among severely ill patients.

Brexpiprazole acts as a partial agonist at serotonin $(5\text{-HT})_{1A}$ and dopamine $(D)_2$ receptors, and as an antagonist at serotonin 5-HT_{2A} and noradrenaline α_{1B}/α_{2C} receptors, all with subnanomolar affinity (Maeda et al., 2014). The efficacy and safety of brexpiprazole for the treatment of adults with acute schizophrenia have been demonstrated in two pivotal 6-week, fixed-dose, placebo-controlled studies (Correll et al., 2015; Kane et al., 2015), supported by a 6-week, flexible-dose, placebo-controlled, active-referenced study (Marder et al., 2017, 2020). In two open-label extension studies, brexpiprazole was generally well

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tolerated for up to 52 weeks in patients with schizophrenia (Forbes et al., 2018; U.S. National Library of Medicine, 2017) and was associated with continued improvement in efficacy measures (Forbes et al., 2018).

The aim of this *post-hoc* analysis was to evaluate the short- and long-term effects of brexpiprazole in adult patients with schizophrenia presenting with severe symptoms, based on pooled data from three short-term, randomized, controlled studies and two open-label extension studies.

Methods

Study design and patients

The studies were conducted in compliance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline and the World Medical Association Declaration of Helsinki. The protocols were approved by independent ethics committees (listed in the Supplementary Material), and all patients provided written informed consent to participate after procedures and possible side effects were explained to them.

Short-term studies. The short-term *post-hoc* analysis included data from three randomized, double-blind, placebo-controlled studies of brexpiprazole in patients with acute schizophrenia: Vector (NCT01396421) (Correll et al., 2015), Beacon (NCT01393613) (Kane et al., 2015), and Lighthouse (NCT01810380) (Marder et al., 2017, 2020). The studies were conducted at sites across Asia, Europe, Latin America and North America between July 2011–December 2014. Descriptions of the Vector, Beacon and Lighthouse study designs and selection criteria have been published (Correll et al., 2015; Kane et al., 2015; Marder et al., 2020).

In brief, the short-term studies included patients aged 18–65 years experiencing an acute exacerbation of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria) (American Psychiatric Association, 2000), and who would benefit from hospitalization or continued hospitalization. Patients were excluded if they had a first episode of schizophrenia, treatment-resistant schizophrenia, a DSM-IV-TR Axis I diagnosis other than schizophrenia, clinically significant tardive dyskinesia, or substance abuse or dependence in the previous 180 days. The studies had similar designs, comprising a 14-day screening phase, a six-week double-blind treatment phase, and a 30-day follow-up phase. Patients were hospitalized throughout the double-blind treatment phase.

In Vector, eligible patients were randomized to placebo or fixed-dose brexpiprazole 0.25, 2, or 4 mg/day (2:1:2:2). In Beacon, eligible patients were randomized to placebo or fixed-dose brexpiprazole 1, 2, or 4 mg/day (3:2:3:3). Brexpiprazole was titrated in the 2 mg groups such that patients received 1 mg/day for the first 4 days, then 2 mg/day from the fifth day onwards. In the 4 mg group, the same pattern was followed until the eighth day, when the dose was increased to 4 mg/day. In Lighthouse, eligible patients were randomized to placebo, flexible-dose brexpiprazole 2–4 mg/day, or flexible-dose quetiapine extended-release (XR) 400–800 mg/day (an active reference) (1:1:1). Brexpiprazole was titrated such that patients received 1 mg on the first day, 2 mg on the second day, 3 mg on the third day, then 2–4 mg/day from the fourth day onwards. In all studies, brexpiprazole was administered as an oral tablet.

Long-term studies. The long-term *post-hoc* analysis included data from two open-label extension studies in schizophrenia: Zenith (NCT01397786) (Forbes et al., 2018) and Study 14644B (NCT01810783) (U.S. National Library of Medicine, 2017). The studies were conducted at sites across Asia, Europe, Latin America, and North America between September 2011–February 2016. Full descriptions of the study design and selection criteria in Zenith have been published (Forbes et al., 2018). The Study 14644B design and selection criteria are available online (https://clinicaltrials.gov/show/NCT01810783).

In brief, patients who completed Vector or Beacon were eligible to roll over into Zenith, and patients who completed Lighthouse were eligible to roll over into Study 14644B. (Zenith also enrolled *de novo* patients and those who completed a maintenance treatment study; these patients were not included in the present *post-hoc* analyses.) Patients in the long-term studies received flexibly dosed brexpiprazole 1–4 mg/day for up to 52 weeks (Zenith was amended to 26 weeks towards the end; this amendment only applied to the 11.2% of patients who enrolled after the date of the amendment). Open-label brexpiprazole was initiated at 2 mg/day and could be adjusted in 1 mg increments for reasons of efficacy or tolerability, according to the investigator's judgement.

Assessments

The primary efficacy analysis in all three short-term studies was the mean change in Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) Total score from baseline (randomization) to Week 6. The PANSS was administered at baseline and Weeks 1, 2, 3, 4, 5, and 6. In the two long-term studies, efficacy was assessed as a secondary or exploratory objective using the PANSS, which was administered at open-label Weeks 1, 2, 4, and 8, then at six-weekly intervals until Week 44, and at Week 52.

The Clinical Global Impressions–Severity of illness (CGI-S) and Improvement (CGI-I) scales (Guy, 1976) and the Personal and Social Performance scale (PSP) (Morosini et al., 2000) were also administered during the short- and long-term studies. The PSP is a clinician-rated measure of social functioning and behavior. Patients' functioning is assessed in four main domains: (a) socially useful activities; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors. Each domain is rated on a six-degree severity scale from absent to very severe. By cross-referencing the domain ratings with a descriptive table, an overall PSP score is determined from one (lack of autonomy in basic functioning leading to a survival risk) to 100 (excellent functioning in all four domains).

Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs) and change in body weight. To assess the occurrence of adverse events, investigators periodically asked patients a non-leading question, such as "How have you felt since your last visit?" All adverse events were recorded, whether observed by the investigator or spontaneously reported by the patient.

Post-hoc *categorization of 'severe' status*

Patients with more severe symptoms were defined as those with PANSS Total score greater than the median score at baseline of

the short-term studies. The median PANSS Total score at baseline in the present analysis was 95, which corresponds to a CGI-S score of five, 'markedly ill' (Leucht et al., 2005). Patients without a baseline PANSS assessment were excluded from the *post-hoc* analyses.

Statistical analyses

Short-term analysis. Data from the short-term studies were pooled for all patients allocated to placebo, and for all patients allocated to a brexpiprazole dose in the recommended dose range of 2–4 mg for schizophrenia in the USA (i.e. 2 mg, 4 mg, and 2–4 mg) (Rexulti®, 2020). The brexpiprazole 0.25 mg and 1 mg groups, intended to evaluate the lower dose range, were not included in the *post-hoc* analyses. Within these pooled subgroups, efficacy analyses were performed in the sample of patients who received at least one dose of study medication and had at least one post-baseline PANSS Total score assessment. Safety analyses were performed in the sample of patients who received at least one dose of study medication.

Baseline was defined as the randomization visit (prior to the first dose of study drug). PANSS Total, PANSS Positive and Negative subscales, PANSS Excited component, PANSS Marder factors, CGI-S, PSP, and PSP domain scores were analyzed using a mixed model for repeated measures (MMRM) analysis with fixed-effect factors of protocol, trial center within protocol, treatment, visit, and treatment-by-visit interaction, and fixed-effect covariates of baseline and baseline-by-visit interaction. A heterogeneous Toeplitz variance–covariance matrix was used for PANSS Total, PANSS Negative symptoms Marder factor, PSP Self-care, and PSP Disturbing and aggressive behaviors; a heterogeneous autoregressive of order one variance–covariance matrix was used for PANSS Positive subscale and PANSS Anxiety/depression Marder factor; a banded Toeplitz variance–covariance matrix was used for PSP Personal and social relationships; all other MMRM analyses had an unstructured variance–covariance matrix. Least squares mean differences were calculated between brexpiprazole and placebo groups, with 95% confidence limits, *p*-values, and Cohen's *d* effect sizes. Response was defined as a mean change from baseline in PANSS Total score of ⩾30% or a CGI-I score of one (very much improved) or two (much improved) at Week 6. For response rate, relative risks were derived from a Cochran–Mantel–Haenszel general association test controlling for pooled trial center and protocol, with last observations carried forward. All tests were two-sided at a 5% level. Due to the exploratory nature of the study, correction for multiple comparisons was not performed.

Long-term analysis. For the long-term analysis, data were combined from the six-week short-term studies and the 52-week open-label extension studies, so that a total of up to 58 weeks of brexpiprazole treatment could be investigated. With this treatment duration in mind, the analyses included only those patients in the long-term studies who had previously received brexpiprazole 2–4 mg in the short-term studies (i.e. patients who previously received placebo or low doses of brexpiprazole were not analyzed).

Baseline was defined as the randomization visit of the short-term studies. Mean changes from baseline in PANSS Total, PANSS Positive and Negative subscales, PANSS Excited component, PANSS Marder factors, CGI-S, PSP, and PSP domain scores were summarized using descriptive statistics. Response was defined as a mean change from baseline in PANSS Total score of ⩾30% or a CGI-I score of one (very much improved) or two (much improved), using observed cases.

Results

Patients

Short-term studies. In the short-term studies, after excluding nine patients with no baseline PANSS assessment, the randomized sample comprised 1405 patients allocated to placebo (*n*=527) or brexpiprazole 2–4 mg (*n*=878). All of these patients received at least one dose of randomized treatment and therefore the safety sample comprised 1405 patients. Excluding patients with no post-baseline PANSS measurements, the efficacy sample comprised 1385 patients.

The median baseline PANSS Total score in the randomized/safety sample was 95 (range: 46–156). Patients with baseline PANSS Total score >95 were defined as 'more severely ill', and those with score ⩽95 were defined as 'less severely ill'. Among patients allocated to brexpiprazole, completion rates were similar (69.8–70.0%) regardless of severity subgroup, and were higher than for patients allocated to placebo (Table 1). The most common reason for discontinuation among patients receiving brexpiprazole was that the patient withdrew consent (Table 1). Fewer patients receiving brexpiprazole discontinued due to adverse events or lack of efficacy than patients receiving placebo.

Within a severity category, baseline demographic and clinical characteristics were similar between treatment groups (Table 2). Comparing the more severely ill and less severely ill subgroups, in addition to higher PANSS Total score (by definition), the more severely ill sample had higher CGI-S score (5.2 versus 4.6) and poorer functioning (lower PSP score) at baseline (Table 2).

The mean (standard deviation) brexpiprazole dose for the duration of the studies was 2.7 (0.9) mg in more severely ill patients, and also 2.7 (0.9) mg in less severely ill patients.

Long-term analysis. The long-term sample comprised 412 patients who rolled over from the short-term studies. Completion rates were higher among more severely ill patients (45.2%) than less severely ill patients (40.5%) (Table 1). The most common reasons for discontinuation in both subgroups were the patient withdrew consent and adverse events (Table 1).

Baseline demographic and clinical characteristics for the long-term analysis are presented in Table 2. To allow for a total of 58 weeks of brexpiprazole exposure, baseline was defined as the randomization visit of the short-term studies, and thus a similar pattern of characteristics was observed to those seen in the short-term analysis.

Over the final 52 weeks of the long-term analysis, the mean (standard deviation) brexpiprazole dose was 3.1 (0.8) mg in more severely ill patients (*n*=215), and 2.8 (0.8) mg in less severely ill patients (*n*=192).

Efficacy

Short-term studies. Among more severely ill patients, the brexpiprazole group had a greater mean reduction in PANSS

Table 1. Patient disposition and reasons for discontinuation stratified by baseline illness severity.

n (%)	Short-term studies				Long-term analysis	
	More severely ill (PANSS Total >95)		Less severely ill (PANSS Total ⩽95)		More severely ill (PANSS Total >95)	Less severely ill (PANSS Total ⩽95)
	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Brexpiprazole 1–4 mg	Brexpiprazole 1–4 mg
Randomized	254	427	273	451	217[a]	195[a]
Completed	156 (61.4)	299 (70.0)	177 (64.8)	315 (69.8)	98 (45.2)	79 (40.5)
Discontinued	98 (38.6)	128 (30.0)	96 (35.2)	136 (30.2)	119 (54.8)	116 (59.5)
Patient withdrew consent	22 (8.7)	42 (9.8)	26 (9.5)	60 (13.3)	40 (18.4)	38 (19.5)
Adverse event	31 (12.2)	40 (9.4)	34 (12.5)	30 (6.7)	40 (18.4)	42 (21.5)
Lack of efficacy	35 (13.8)	38 (8.9)	28 (10.3)	32 (7.1)	12 (5.5)	6 (3.1)
Protocol deviation	1 (0.4)	2 (0.5)	0 (0.0)	2 (0.4)	1 (0.5)	1 (0.5)
Withdrawn by investigator	3 (1.2)	1 (0.2)	1 (0.4)	1 (0.2)	3 (1.4)	3 (1.5)
Patient met withdrawal criteria	0 (0.0)	1 (0.2)	1 (0.4)	2 (0.4)	11 (5.1)	13 (6.7)
Lost to follow-up	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.7)	10 (5.1)
Other	5 (2.0)	4 (0.9)	6 (2.2)	9 (2.0)	4 (1.8)	3 (1.5)
Efficacy sample	249 (98.0)	420 (98.4)	268 (98.2)	448 (99.3)	217 (100.0)	195 (100.0)
Safety sample	254 (100.0)	427 (100.0)	273 (100.0)	451 (100.0)	217 (100.0)	195 (100.0)

PANSS: Positive and Negative Syndrome Scale.
[a]Enrolled.

Table 2. Baseline demographic and clinical characteristics stratified by baseline illness severity.

	Short-term studies (randomized sample)				Long-term analysis (enrolled sample)	
	More severely ill (PANSS Total >95)		Less severely ill (PANSS Total ⩽95)		More severely ill (PANSS Total >95)	Less severely ill (PANSS Total ⩽95)
	Placebo (*n*=254)	Brexpiprazole 2–4 mg (*n*=427)	Placebo (*n*=273)	Brexpiprazole 2–4 mg (*n*=451)	Brexpiprazole 1–4 mg (*n*=217)	Brexpiprazole 1–4 mg (*n*=195)
Demographic characteristics						
Age (years), mean (SD)	38.9 (10.8)	38.6 (10.9)	41.0 (10.5)	39.6 (10.8)	38.1 (10.5)	39.3 (10.6)
BMI (kg/m^2), mean (SD)	26.3 (5.5)	26.1 (5.5)	26.8 (5.4)	27.7 (6.3)	26.2 (5.4)	27.6 (6.0)
Male, *n* (%)	147 (57.9)	253 (59.3)	172 (63.0)	287 (63.6)	126 (58.1)	112 (57.4)
Race, *n* (%)						
White	174 (68.5)	290 (67.9)	179 (65.6)	281 (62.3)	146 (67.3)	146 (74.9)
Black/African American	52 (20.5)	77 (18.0)	72 (26.4)	131 (29.0)	26 (12.0)	30 (15.4)
Asian	15 (5.9)	32 (7.5)	13 (4.8)	23 (5.1)	21 (9.7)	8 (4.1)
Other	13 (5.1)	28 (6.6)	9 (3.3)	16 (3.5)	24 (11.1)	11 (5.6)
Clinical characteristics						
Age at first diagnosis (years), mean (SD)	26.0 (8.5)	26.1 (8.6)	27.1 (9.7)	26.8 (8.5)	26.8 (8.7)	28.0 (8.5)
Duration of current episode (weeks), mean (SD)	2.7 (2.9) (*n*=163)	2.5 (2.5) (*n*=355)	2.6 (2.6) (*n*=203)	2.5 (2.2) (*n*=373)	2.7 (2.9) (*n*=174)	2.6 (2.5) (*n*=172)
PANSS Total score, mean (SD)	105.7 (8.2)	105.8 (8.5)	87.4 (6.5)	86.6 (7.3)	106.3 (8.8)	86.0 (8.0)
CGI-S score, mean (SD)	5.2 (0.6)	5.2 (0.6)	4.6 (0.5)	4.6 (0.6)	5.1 (0.6)	4.7 (0.6)
PSP score, mean (SD)	41.9 (9.6) (*n*=251)	40.7 (9.9) (*n*=423)	46.4 (10.5) (*n*=272)	48.0 (10.6) (*n*=445)	40.5 (10.4) (*n*=215)	48.6 (11.1) (*n*=192)

BMI: body mass index; CGI-S: Clinical Global Impressions–Severity of illness; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance scale; SD: standard deviation.

Total score compared with the placebo group at Week 6 ($p<0.0001$) (Figure 1(a); Table 3). Benefits over placebo ($p<0.05$) were seen at all weekly visits (Figure 1(a)). Brexpiprazole was also superior to placebo at Week 6 among patients who were less severely ill ($p=0.0004$) (Figure 1(a); Table 3). The Cohen's *d* effect size versus placebo at Week 6 was

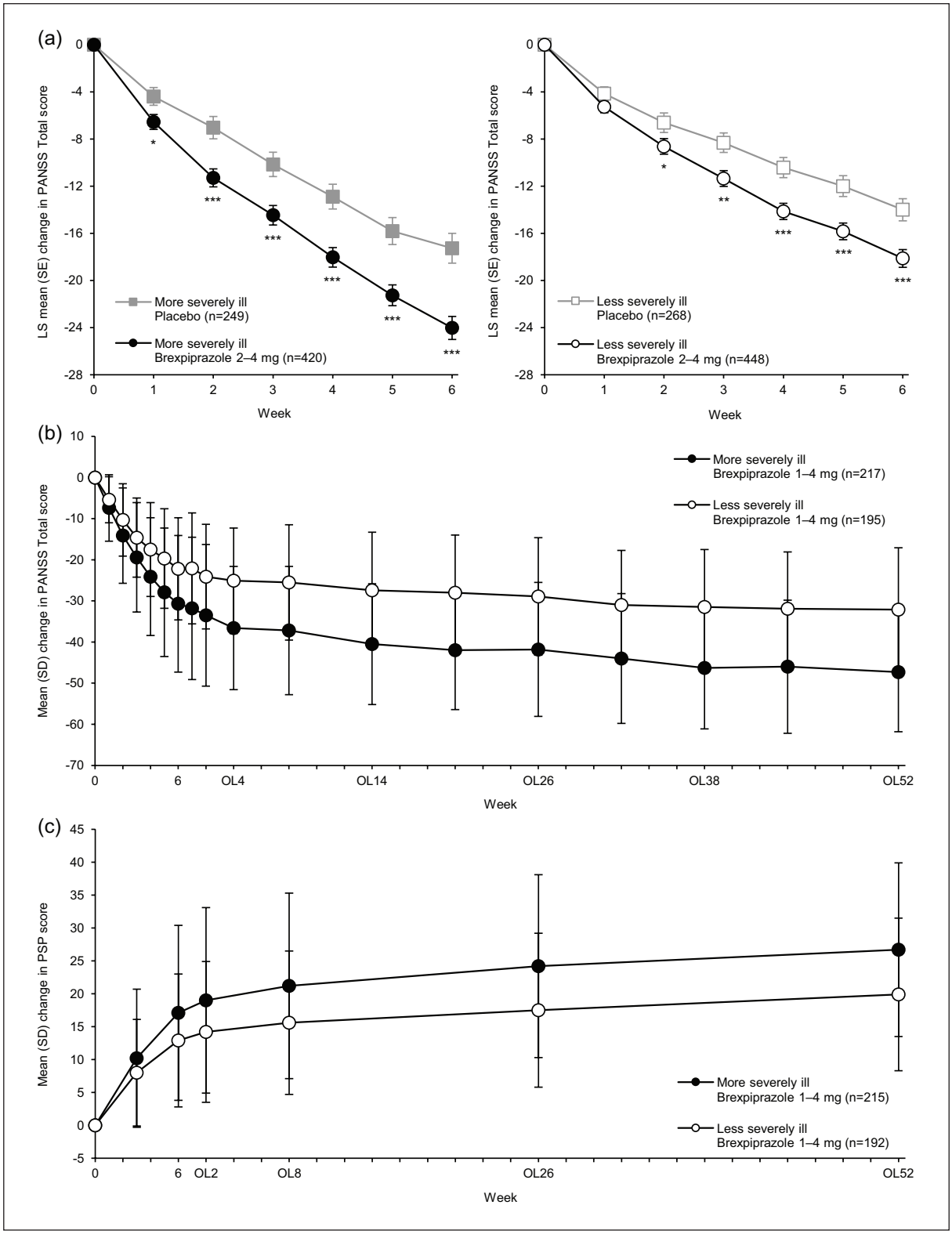

Figure 1. Positive and Negative Syndrome Scale (PANSS) Total score change during (a) short-term and (b) long-term treatment with brexpiprazole, and (c) Personal and Social Performance scale (PSP) score change during long-term treatment, stratified by baseline illness severity (efficacy sample). Baseline PANSS Total score: (a) more severely ill placebo, 105.6; more severely ill brexpiprazole, 105.8; less severely ill placebo, 87.4; less severely ill brexpiprazole, 86.6; (b) more severely ill, 106.3; less severely ill, 86.0. Baseline PSP score: (c) more severely ill, 40.5; less severely ill, 48.6. LS: least squares; MMRM: mixed model for repeated measures; OL: open-label; SD: standard deviation; SE: standard error. *$p<0.05$, **$p<0.01$, ***$p<0.001$ versus placebo; MMRM (short-term); observed cases (long-term).

greater in more severely ill patients (0.43) than in less severely ill patients (0.33).

In patients who were more severely ill, brexpiprazole showed greater improvement than placebo ($p<0.01$) on the PANSS Positive and Negative subscales, PANSS Excited component, all PANSS Marder factors, and the CGI-S (Table 3). Response rates were also higher with brexpiprazole than placebo (relative risk: 1.74; $p<0.0001$). Similarly, in patients who were less severely ill, brexpiprazole showed greater improvement than placebo ($p<0.05$) on the PANSS Positive and Negative subscales, PANSS Excited component, all PANSS Marder factors except for Anxiety/depression ($p=0.078$), and the CGI-S (Table 3). Again, response rates were higher with brexpiprazole than placebo (relative risk: 1.33; $p=0.0052$). For each of these outcomes, Cohen's *d* effect sizes (brexpiprazole versus placebo) were greater in more severely ill patients than in less severely ill patients.

Among more severely ill patients, the brexpiprazole group had a greater mean increase (improvement) in PSP score compared with the placebo group at Week 6 ($p=0.0001$) (Table 3). Greater improvement than placebo ($p<0.05$) was also observed on all four PSP domains. Among patients who were less severely ill, benefits over placebo ($p<0.05$) were observed for the PSP and all its domains except Disturbing and aggressive behaviors ($p=0.85$) (Table 3).

Long-term analysis. More severely ill patients receiving brexpiprazole showed an improvement in PANSS Total score that was maintained over 58 weeks (Figure 1(b); Table 4). Less severely ill patients also had a maintained improvement in PANSS Total score (Figure 1(b); Table 4), though the magnitude of the improvement was less. In both subgroups, the majority of the improvement occurred over the first half of the study (Figure 1(b)).

Improvement from baseline was also observed for all other outcomes over 58 weeks, in the more severely ill and less severely ill subgroups (Table 4). Improvement in PSP score mirrored the improvement in PANSS Total score, with the majority of improvement occurring over the first half of the study (Figure 1(c)).

Safety and tolerability

Short-term studies. The incidence of TEAEs was similar across the placebo and brexpiprazole treatment subgroups, regardless of illness severity (brexpiprazole range: 57.4–59.2%; placebo range: 52.0–62.6%) (Table 5). The most common TEAEs (⩾5% in any subgroup) were insomnia, headache, agitation, schizophrenia, akathisia, and weight increase (Table 5). The incidences of sedation and somnolence were low (each <5%) in all treatment subgroups, regardless of illness severity. Worsening of schizophrenia as a side effect was more common in the placebo subgroups than in the brexpiprazole subgroups. The mean (standard deviation) increase in body weight over 6 weeks among more severely ill and less severely ill patients, respectively, was 1.5 (3.5) and 1.5 (3.3) kg for brexpiprazole, and 0.4 (3.2) and 0.4 (2.6) kg for placebo.

Long-term analysis. In the long-term, the incidence of TEAEs was comparable between the more severely ill and less severely ill subgroups (Table 5). Worsening of schizophrenia as a side effect and weight increase had a higher incidence over the long-term than in the short-term. The mean (standard deviation) increase in body weight over 58 weeks was 2.7 (6.8) kg among more severely ill patients, and 4.4 (7.8) kg among less severely ill patients.

Discussion

In this analysis of pooled data from five clinical trials in schizophrenia, brexpiprazole demonstrated robust efficacy in the treatment of the subgroup of patients experiencing more severe symptoms at baseline. Over 6 weeks, among more severely ill patients, brexpiprazole 2–4 mg had a clinically meaningful, small-to-medium benefit over placebo (Cohen, 1988) on PANSS Total, Positive and Negative subscales, Excited component and Marder factors, and the CGI-S, and greater responder rates than placebo. Effect sizes for these outcomes fell in the range of 0.27–0.43; a recent network meta-analysis comparing 32 drugs for psychosis found mean effect sizes on overall symptoms ranging from 0.03–0.89, though differences between most individual drugs were not significant (Huhn et al., 2019). Of the Marder factors, brexpiprazole had the greatest effect on 'Disorganized thought.' These results in more severely ill patients are consistent with the robust improvements seen with brexpiprazole 2 mg and 4 mg across all symptomatic outcomes in the total sample of the Vector and Beacon studies (Correll et al., 2016). In the present analysis, though potentially biased by the observed cases approach which did not account for dropouts, symptomatic improvement with brexpiprazole was maintained over 58 weeks among patients with more severe symptoms, consistent with the maintenance of improvement seen in the total sample of the Zenith study (Forbes et al., 2018). More than three-quarters of severely ill patients who remained in the study were responders after 32 and 58 weeks of brexpiprazole treatment.

Brexpiprazole also improved functioning in the subgroup of patients with more severe symptoms at baseline, as measured by the PSP. Improvement was evident after 6 weeks, continued to increase over the next 26 weeks, and then plateaued over the final 26 weeks. Over 6 weeks, brexpiprazole had the greatest effect in the domains of 'Personal and social relationships' and 'Self-care.' The mean improvement in PSP score over 58 weeks among more severely ill patients was 26.7 points, well above the 10-point category change that is thought to be a conservative threshold for clinically meaningful response (Nasrallah et al., 2008). Whereas psychotic symptoms can quickly respond to treatment, improvements in functioning are thought to take longer (Harvey and Bellack, 2009). However, in the present analysis, improvement in functioning occurred simultaneously with improvement in PANSS Total score. This may be because the PSP includes a 'Disturbing and aggressive behaviors' domain, which is not necessarily independent of psychosis, and might therefore be expected to improve acutely and in parallel with PANSS Total score. Deficits in social functioning are a core feature of schizophrenia and are increasingly recognized as a key target for new therapeutic agents, beyond improvement of symptoms (Burns and Patrick, 2007).

Benefits for brexpiprazole were also observed across a range of PANSS, CGI-S, and PSP outcomes for patients who were less severely ill, albeit with slightly lower effect sizes than in the more severely ill patients. For PANSS Total and subscale scores,

Table 3. Efficacy outcomes at Week 6 of treatment with brexpiprazole, stratified by baseline illness severity (efficacy sample).

Short-term studies	Placebo		Brexpiprazole 2–4 mg				
	Mean (SD) at baseline	LS mean (SE) change from baseline	Mean (SD) at baseline	LS mean (SE) change from baseline	Difference from placebo		
					LS mean (95% CLs)	*p*-Value	Cohen's *d*
More severely ill (PANSS Total >95)	(*n*=249)		(*n*=420)				
PANSS Total	105.6 (8.2)	−17.3 (1.3)	105.8 (8.5)	−24.0 (1.0)	−6.76 (−9.80, −3.72)	<0.0001	0.43
Positive subscale	27.3 (3.8)	−5.8 (0.4)	27.4 (3.8)	−7.8 (0.3)	−2.00 (−3.02, −0.99)	0.0001	0.38
Negative subscale	26.4 (4.0)	−3.0 (0.4)	26.5 (4.1)	−4.5 (0.3)	−1.44 (−2.31, −0.57)	0.0012	0.32
Excited component	14.7 (3.4)	−2.5 (0.3)	14.8 (3.5)	−3.8 (0.3)	−1.25 (−2.02, −0.48)	0.0015	0.31
Positive symptoms MF	31.8 (4.2)	−5.7 (0.5)	32.0 (3.9)	−7.8 (0.4)	−2.08 (−3.27, −0.88)	0.0007	0.34
Negative symptoms MF	25.3 (4.4)	−3.7 (0.3)	25.1 (4.3)	−5.0 (0.3)	−1.28 (−2.06, −0.51)	0.0012	0.32
Disorganized thought MF	24.8 (3.6)	−3.0 (0.4)	24.9 (3.7)	−4.5 (0.3)	−1.54 (−2.40, −0.68)	0.0005	0.35
Uncontrolled hostility/ excitement MF	11.1 (3.1)	−1.7 (0.3)	11.3 (3.1)	−2.7 (0.2)	−1.06 (−1.71, −0.40)	0.0016	0.31
Anxiety/depression MF	12.5 (3.1)	−3.4 (0.2)	12.4 (2.9)	−4.1 (0.2)	−0.68 (−1.17, −0.19)	0.0066	0.27
Response rate	– (*n*=250)	68/249 (27.3)[a]	– (*n*=420)	197/420 (46.9)[a]	1.74 (1.38, 2.20)[b]	<0.0001	–
CGI-S	5.2 (0.6) (*n*=227)	−0.9 (0.1)	5.2 (0.6) (*n*=399)	−1.2 (0.1)	−0.34 (−0.53, −0.15)	0.0005	0.35
PSP[c]	42.0 (9.8)	8.9 (1.0)	40.5 (10.0)	13.3 (0.7)	4.38 (2.14, 6.62)	0.0001	0.38
Socially useful activities	3.6 (0.9)	−0.5 (0.1)	3.5 (0.7)	−0.7 (0.1)	−0.19 (−0.34, −0.04)	0.016	0.24
Personal and social relationships	3.3 (0.8)	−0.5 (0.1)	3.2 (0.7)	−0.7 (0.0)	−0.22 (−0.36, −0.09)	0.0014	0.32
Self-care	2.2 (1.1)	−0.5 (0.1)	2.1 (1.0)	−0.8 (0.1)	−0.30 (−0.45, −0.14)	0.0003	0.37
Disturbing and aggressive behaviors	1.4 (1.0)	−0.3 (0.1)	1.3 (1.1)	−0.5 (0.1)	−0.22 (−0.37, −0.07)	0.0034	0.29
Less severely ill (PANSS Total ⩽95)	(*n*=268)		(*n*=448)				
PANSS Total	87.4 (6.5)	−14.0 (0.9)	86.6 (7.2)	−18.1 (0.8)	−4.13 (−6.40, −1.86)	0.0004	0.33
Positive subscale	23.2 (3.4)	−5.2 (0.3)	22.9 (3.4)	−6.3 (0.3)	−1.16 (−1.98, −0.35)	0.0052	0.26
Negative subscale	21.8 (4.1)	−2.0 (0.3)	21.4 (4.1)	−2.9 (0.2)	−0.88 (−1.56, −0.20)	0.012	0.24
Excited component	11.3 (3.1)	−1.4 (0.3)	11.2 (3.0)	−2.2 (0.2)	−0.81 (−1.46, −0.15)	0.017	0.22
Positive symptoms MF	27.5 (3.6)	−5.5 (0.4)	27.3 (3.7)	−6.6 (0.3)	−1.11 (−2.06, −0.16)	0.022	0.21
Negative symptoms MF	20.7 (4.4)	−2.6 (0.3)	20.6 (4.3)	−3.6 (0.2)	−0.96 (−1.55, −0.37)	0.0015	0.30
Disorganized thought MF	20.0 (3.6)	−2.1 (0.3)	19.6 (3.7)	−3.2 (0.2)	−1.04 (−1.67, −0.41)	0.0013	0.30
Uncontrolled hostility/ excitement MF	8.4 (2.9)	−0.6 (0.2)	8.3 (2.8)	−1.3 (0.2)	−0.67 (−1.23, −0.12)	0.018	0.22
Anxiety/depression MF	10.8 (2.8)	−2.9 (0.2)	10.8 (2.8)	−3.3 (0.2)	−0.42 (−0.89, 0.05)	0.078	0.16
Response rate	– (*n*=271)	94/268 (35.1)[a]	– (*n*=452)	203/448 (45.3)[a]	1.33 (1.08, 1.63)[b]	0.0052	–
CGI-S	4.6 (0.5) (*n*=245)	−0.8 (0.1)	4.7 (0.6) (*n*=419)	−1.1 (0.1)	−0.26 (−0.42, −0.11)	0.0011	0.30
PSP[c]	46.0 (10.0)	9.2 (0.8)	48.0 (10.5)	11.9 (0.6)	2.77 (0.93, 4.62)	0.0032	0.28
Socially useful activities	3.4 (0.8)	−0.5 (0.1)	3.2 (0.8)	−0.7 (0.1)	−0.25 (−0.38, −0.11)	0.0003	0.34
Personal and social relationships	3.0 (0.8)	−0.6 (0.1)	2.8 (0.8)	−0.7 (0.0)	−0.13 (−0.26, 0.00)	0.042	0.19
Self-care	1.5 (1.0)	−0.3 (0.1)	1.3 (1.0)	−0.5 (0.0)	−0.16 (−0.28, −0.03)	0.016	0.23
Disturbing and aggressive behaviors	1.0 (1.0)	−0.2 (0.1)	0.8 (0.9)	−0.2 (0.0)	−0.01 (−0.13, 0.10)	0.85	0.02

CGI-S: Clinical Global Impressions–Severity of illness; CL: confidence limit; LS: least squares; MF: Marder factor; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance scale; SD: standard deviation; SE: standard error.

[a]Number of responders/number of patients with an assessment (%).

[b]Relative risk (95% CLs).

[c]PSP domains were scored from 0 (absent) to 5 (very severe), where a decrease in score signifies improvement; overall PSP score ranges from 1 (worst functioning) to 100 (best functioning), where an increase in score signifies improvement.

Table 4 Efficacy outcomes at open-label Week 52 of treatment with brexpiprazole, stratified by baseline illness severity (efficacy sample).

Long-term analysis	More severely ill (PANSS Total >95)			Less severely ill (PANSS Total ⩽95)		
	Mean (SD) at baseline	Mean (SD) change from baseline to OL Week 26	Mean (SD) change from baseline to OL Week 52	Mean (SD) at baseline	Mean (SD) change from baseline to OL Week 26	Mean (SD) change from baseline to OL Week 52
	(*n*=217)	(*n*=126)	(*n*=98)	(*n*=195)	(*n*=112)	(*n*=80)
PANSS Total	106.3 (8.8)	−41.8 (16.3)	−47.3 (14.5)	86.0 (8.0)	−28.9 (14.3)	−32.1 (15.0)
Positive subscale	27.0 (3.8)	−13.3 (5.8)	−14.9 (5.3)	22.6 (3.5)	−9.6 (5.3)	−10.7 (4.8)
Negative subscale	26.9 (4.2)	−8.2 (4.9)	−9.5 (5.0)	21.2 (4.1)	−4.8 (4.4)	−5.5 (5.6)
Excited component	14.6 (3.4)	−6.7 (4.2)	−7.5 (3.7)	11.0 (2.9)	−4.0 (3.6)	−4.2 (3.3)
Positive symptoms MF	31.9 (3.8)	−14.3 (6.3)	−16.2 (5.7)	27.2 (3.9)	−11.0 (5.9)	−12.2 (5.4)
Negative symptoms MF	25.7 (4.3)	−8.6 (5.1)	−10.0 (5.1)	20.3 (4.2)	−5.6 (4.8)	−6.3 (5.5)
Disorganized thought MF	25.2 (3.9)	−8.4 (4.4)	−9.7 (4.3)	19.8 (3.6)	−5.4 (3.5)	−6.5 (4.0)
Uncontrolled hostility/ excitement MF	11.1 (3.1)	−5.0 (3.6)	−5.6 (3.3)	8.1 (2.7)	−2.6 (3.2)	−2.6 (3.0)
Anxiety/depression MF	12.3 (3.1)	−5.5 (3.3)	−5.7 (3.2)	10.6 (2.7)	−4.3 (3.1)	−4.6 (2.8)
Response rate	–	105/136 (77.2)[a]	88/115 (76.5)[a]	–	73/121 (60.3)[a]	58/93 (62.4)[a]
	(*n*=216)	(*n*=93)	(*n*=72)	(*n*=193)	(*n*=100)	(*n*=72)
CGI-S	5.1 (0.6)	−2.1 (1.1)	−2.3 (0.9)	4.7 (0.6)	−1.6 (1.0)	−1.8 (0.9)
	(*n*=215)	(*n*=124)	(*n*=97)	(*n*=192)	(*n*=109)	(*n*=80)
PSP[b]	40.5 (10.4)	24.2 (13.9)	26.7 (13.2)	48.6 (11.1)	17.5 (11.7)	19.9 (11.6)
Socially useful activities	3.6 (0.7)	−1.5 (1.0)	−1.7 (1.0)	3.1 (0.8)	−1.2 (0.9)	−1.3 (0.9)
Personal and social relationships	3.2 (0.8)	−1.4 (1.0)	−1.6 (0.9)	2.7 (0.8)	−1.0 (1.0)	−1.2 (1.0)
Self-care	2.1 (1.0)	−1.2 (0.9)	−1.3 (1.0)	1.3 (0.9)	−0.9 (0.9)	−0.9 (0.8)
Disturbing and aggressive behaviors	1.2 (1.1)	−0.8 (1.2)	−0.9 (1.1)	0.7 (0.8)	−0.4 (0.8)	−0.3 (0.7)

CGI-S: Clinical Global Impressions–severity of illness; CL: confidence limit; LS: least squares; MF: Marder factor; OL: open-label; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance scale; SD: standard deviation; SE: standard error.

[a]Number of responders/number of patients with an assessment (%).

[b]PSP domains were scored from 0 (absent) to 5 (very severe), where a decrease in score signifies improvement; overall PSP score ranges from 1 (worst functioning) to 100 (best functioning), where an increase in score signifies improvement.

Table 5. Treatment-emergent adverse events (TEAEs) stratified by baseline illness severity (safety sample).

n (%)	Short-term studies				Long-term analysis	
	More severely ill (PANSS Total >95)		Less severely ill (PANSS Total ⩽95)		More severely ill (PANSS Total >95)	Less severely ill (PANSS Total ⩽95)
	Placebo (*n*=254)	Brexpiprazole 2–4 mg (*n*=427)	Placebo (*n*=273)	Brexpiprazole 2–4 mg (*n*=451)	Brexpiprazole 1–4 mg (*n*=217)	Brexpiprazole 1–4 mg (*n*=195)
At least one TEAE	132 (52.0)	245 (57.4)	171 (62.6)	267 (59.2)	105 (48.4)	108 (55.4)
TEAEs occurring in ⩾5% of patients in any subgroup						
Insomnia	27 (10.6)	54 (12.6)	25 (9.2)	43 (9.5)	14 (6.5)	18 (9.2)
Headache	20 (7.9)	39 (9.1)	34 (12.5)	46 (10.2)	12 (5.5)	13 (6.7)
Agitation	19 (7.5)	31 (7.3)	20 (7.3)	28 (6.2)	10 (4.6)	9 (4.6)
Schizophrenia	27 (10.6)	27 (6.3)	27 (9.9)	21 (4.7)	26 (12.0)	29 (14.9)
Akathisia	10 (3.9)	20 (4.7)	11 (4.0)	31 (6.9)	7 (3.2)	8 (4.1)
Weight increase	4 (1.6)	20 (4.7)	8 (2.9)	18 (4.0)	15 (6.9)	16 (8.2)
Other TEAEs of interest						
Sedation	3 (1.2)	9 (2.1)	5 (1.8)	11 (2.4)	2 (0.9)	1 (0.5)
Somnolence	6 (2.4)	8 (1.9)	12 (4.4)	16 (3.5)	1 (0.5)	7 (3.6)
Restlessness	1 (0.4)	6 (1.4)	2 (0.7)	5 (1.1)	1 (0.5)	1 (0.5)
Anxiety	5 (2.0)	6 (1.4)	5 (1.8)	9 (2.0)	5 (2.3)	6 (3.1)
Fatigue	1 (0.4)	2 (0.5)	4 (1.5)	8 (1.8)	2 (0.9)	0 (0.0)

PANSS: Positive and Negative Syndrome Scale.

effect sizes versus placebo were generally around 0.1 lower among less severely ill patients. A meta-analysis examining the influence of baseline schizophrenia severity on the efficacy of drugs for psychosis found that the greater the baseline severity, the greater the difference between active treatment and placebo after treatment (Furukawa et al., 2015). Thus, while drugs for psychosis can provide benefits for the full spectrum of patients with schizophrenia, benefits of such drugs (including brexpiprazole) appear to be greatest among the most severely ill patients. Although the 'law of initial values' suggests that a greater response might be expected among patients with a higher baseline value (Wilder, 1957), this does not explain the greater difference between brexpiprazole and placebo observed among patients who were more severe at baseline.

Brexpiprazole was safe and well-tolerated in patients with more severe symptoms. There was no indication of activating adverse effects, which are associated with lurasidone, cariprazine, and risperidone, or sedating adverse effects, which are associated with olanzapine, quetiapine XR, and risperidone (Citrome, 2017). Illness severity did not appear to influence the incidence of TEAEs with brexpiprazole.

This study is limited by its *post-hoc* nature and the lack of an active comparator. As an exploratory analysis, no correction was made for multiple comparisons. The definition of severe symptoms was based on the median total score within the dataset, and did not consider the specific symptoms that increased the overall severity score. Finally, while the results of this investigation show benefits for brexpiprazole among patients with severe symptoms, the enrolled patient sample–notably, the exclusion of patients at risk of committing suicide–mean that results may not be generalizable to the real-world population.

In conclusion, the results of this analysis in a large sample of 1405 patients suggest that brexpiprazole 2–4 mg is an efficacious and well-tolerated treatment for schizophrenia in patients with more severe, and less severe, symptoms. Furthermore, brexpiprazole 1–4 mg appears to show a sustained benefit for over a year in patients with more severe, and less severe, symptoms. Finally, brexpiprazole was observed to improve functioning, with the strongest effect among patients with more severe symptoms in the domain of self-care, and also with meaningful improvements in personal and social relationships and socially useful activities.

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Supplemental material

Supplemental material for this article is available online.

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