Brexpiprazole for the Treatment of Schizophrenia: A Review of this Novel Serotonin-Dopamine Activity Modulator

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Abstract

Brexpiprazole is an antipsychotic medication and received approval by the U.S. Food and Drug Administration for the treatment of schizophrenia in July 2015. Brexpiprazole acts as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors, and as an antagonist at serotonin 5-HT2A and at adrenergic alpha1B and alpha2C receptors. Compared with aripiprazole, brexpiprazole is more potent at 5-HT1A receptors and displays less intrinsic activity at D2 receptors. The recommended dose range of brexpiprazole for the treatment of schizophrenia is 2–4 mg/day; the recommended titration schedule is to start with 1 mg/day and increase to 2 mg/day on Day 5 to Day 7, then to 4 mg/day on Day 8. Two positive, 6-week, Phase 3 randomized controlled trials in acute schizophrenia demonstrated superiority of brexpiprazole over placebo. Pooled responder rates were 46% for brexpiprazole 2–4 mg/day vs. 31% for placebo, resulting in a number needed to treat (NNT) of 7. In a 52-week, randomized withdrawal study, significantly fewer patients relapsed in the brexpiprazole group compared with placebo (13.5% vs. 38.5%), resulting in an NNT of 4. The most commonly encountered adverse event (incidence ≥4% and at least twice the rate of placebo) is increased weight. Short-term weight gain appears modest (approximately 10% of patients receiving brexpiprazole 1–4 mg/day gained ≥7% body weight from baseline, compared with 4% for those randomized to placebo, resulting in a number needed to harm [NNH] of 17); however, more outliers with an increase of ≥7% of body weight were evident in open-label, 52-week safety studies. Effects on glucose and lipids were small. Rates of akathisia as an adverse event were 5.5% for the pooled doses of brexpiprazole 1–4 mg/day vs. 4.6% for placebo, yielding an NNH of 112. Minimal effects on prolactin were observed, and no clinically relevant effects on the ECG QTc interval were evident. Brexpiprazole is also approved as an adjunct medication for the treatment of major depressive disorder. Phase 3 trials are ongoing in patients with agitation associated with Alzheimer's disease.

Key Words: Schizophrenia, Brexpiprazole, Serotonin-Dopamine Modulator

Introduction

Brexpiprazole received approval in July 2015 for the treatment of schizophrenia and as adjunct for the treatment of major depressive disorder (MDD) (1), based on a clinical development program that included several pivotal trials (2-5). Brexpiprazole joins a crowded marketplace occupied by several other branded second-generation antipsychotics (quetiapine extended-release, lurasidone, asenapine, iloperidone, and most recently, cariprazine), and several that have lost patent exclusivity (risperidone, olanzapine, quetiapine immediate release, ziprasidone, aripiprazole, paliperidone). However, despite the apparent number of different choices of antipsychotic medications available, they differ substantially regarding their tolerability profiles (6). In addition, schizophrenia itself is heterogeneous in etiology (7). In clinical practice it is somewhat of a struggle to identify an antipsychotic medication for an individual patient that they will find works "well enough," is tolerated "well enough," and that they are willing to adhere to (8). This paper reviews the

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What are number needed to treat (NNT) and number needed to harm (NNH)?

"P-values," even as low as p<0.00001, do not necessarily mean that a result is clinically relevant. In order to determine possible clinical relevance (i.e., clinical significance), effect size needs to be evaluated. Number needed to treat (NNT) and number needed to harm (NNH) are measures of effect size that are clinically intuitive. NNT answers the question: *"How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?"* NNH answers the question: *"How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?"*

NNT (used for desired outcomes) and NNH (used for undesired outcomes) are simple to calculate:

A=frequency of outcome for Intervention A
B=frequency of outcome for Intervention B
NNT or NNH=1/(A-B)

For example, if giving a test medication results in response 50% of the time and giving placebo results in response 25% of the time, NNT for response for the test medication vs. placebo is 1/(50%-25%)=1/(0.50-0.25)=1/(0.25)=4. Thus, for every 4 persons given the test medication instead of placebo, you would expect to encounter one additional responder.

Most psychotropic medications for most indications have NNT values between 3 and 9 for clinically relevant definitions of response. The *lower* the NNT the more often desired outcomes are encountered. On the other hand, *higher* NNH values are optimal, so that adverse outcomes are seldom encountered.

NNH values 10 or greater generally denote tolerability outcomes that are not excessively problematic; however, there are always exceptions if the adverse effect is serious and/or persistent—in that case desirable NNH values could be much higher. On the other hand, a single-digit NNH (i.e., <10) may be acceptable if the adverse event is mild or moderate, does not lead to discontinuation, is temporary or causes little distress, and does not pose a serious health risk, or if a treatment has good (single-digit NNT) efficacy and there is a compelling need for efficacy that mitigates the low NNH tolerability limitation.

An additional tutorial for the use of NNT and NNH that is free to access can be found at www.ncbi.nlm.nih.gov/pmc/articles/PMC4140623/

pharmacology of brexpiprazole and the evidence supporting its use in persons with schizophrenia. A literature search was conducted using the U.S. National Library of Medicine's PubMed.gov resource, as well as querying the ClinicalTrials.gov registry for completed Phase 2 or 3 studies of brexpiprazole for the treatment of schizophrenia. Other sources of information included product labeling (1) and prior reviews published in the biomedical literature (9-12).

Pharmacodynamics

Brexpiprazole is a dopamine D2 receptor partial agonist, with similar binding affinities to serotonin 5-HT1A (partial agonist) and 5-HT2A (antagonist) receptors, and to adrenergic α1B (antagonist) and α2C (antagonist) receptors (1, 13). These affinities are at the subnanomolar level (Ki <1 nM). Compared with aripiprazole—the first dopamine receptor partial agonist to be commercialized—brexpiprazole is more potent at 5-HT1A receptors and displays less intrinsic activity at D2 receptors (9, 13). In animal models this pharmacodynamic profile of serotonin and dopamine modulation has shown robust activity, suggesting antipsychotic, antidepressant, anxiolytic, and pro-cognitive effects, with limited extrapyramidal symptom liability (9).

Brexpiprazole also has high affinity (Ki <5 nM) for dopamine D3 (partial agonist), serotonin 5-HT2B (antagonist), and 5-HT7 (antagonist), and at adrenergic α1A (antagonist) and α1D (antagonist) receptors (1, 9, 13). Brexpiprazole has moderate affinity for histamine H1 receptors (Ki=19 nM, antagonist), and low affinity for muscarinic M1 receptors (Ki >1,000 nM, antagonist) (13). The latter two attributes of brexpiprazole predict a relatively low propensity for sedation and anticholinergic adverse effects (14).

Pharmacokinetics and Dosing

Elimination half-lives of brexpiprazole and its major metabolite, DM-3411 (inactive), are 91 hours and 86 hours, respectively. In the Phase 3 clinical trials, brexpiprazole was titrated to target dosages, and thus the product label recom-

mends the same: for schizophrenia the recommended titration schedule is to start with 1 mg/day and increase to 2 mg/day on Day 5 to Day 7, then to 4 mg/day on Day 8 based on the patient's clinical response and tolerability, with a target dose range of 2–4 mg/day (1). Brexpiprazole can be administered with or without food. Exposure, as measured by maximum concentration and area under the concentration curve, is dose proportional.

Because the metabolism of brexpiprazole is mediated principally by cytochrome P450 (CYP) 3A4 and CYP2D6, there is the potential for drug-drug interactions with agents that are strong CYP2D6 or CYP3A4 inhibitors (administer one-half the usual dosage in the presence of one of these agents, or a one-quarter of the usual dosage in the presence of both a strong/moderate CYP2D6 inhibitor and a strong/moderate CYP3A4 inhibitor) (1). For known CYP2D6 poor metabolizers, administer one-half the usual dosage; for known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors, administer a quarter of the usual dose (1). In the presence of strong CYP3A4 inducers, double the usual dosage over 1 to 2 weeks and further adjust based on clinical response (1).

For patients with moderate to severe hepatic impairment, or moderate, severe, or end-stage renal impairment, the maximum recommended dosage is 3 mg/day for patients with schizophrenia (1).

No dosage adjustment for brexpiprazole is required on the basis of sex, race or ethnicity, or smoking status (1). Although clinical studies did not include patients with age ≥65 years, the product label recommends that, in general, dose selection for a geriatric patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of somatic comorbidities (1).

Efficacy of Brexpiprazole in Schizophrenia

Tables 1–3 outline the Phase 2 and 3 clinical trials of brexpiprazole completed among patients with schizophrenia. Two of these studies are the 6-week, double-blind, placebo-controlled trials in persons with acute schizophrenia that are described in product labeling (1) and have been

Table 1 Completed Randomized, Phase 2/3, Double-Blind, Controlled Clinical Trials Of Brexpiprazole for Schizophrenia, as Registered at ClinicalTrials.gov

ClinicalTrials.gov Identifier	Length (weeks)	Phase	N	Brexpiprazole Dose (mg/day) (and dose of active control if applicable)	Comments
NCT00905307	6	2	459	0.25, 1, 2.5, 5 (dose of aripiprazole 15)	This was a failed study for the acute treatment of schizophrenia. No initial titration to the assigned dose took place but afterwards dose adjustments were permitted. Although improvement in PANSS scores was clinically meaningful for all dose groups, this was also the case for placebo and the improvements in the brexpiprazole- (1, 2.5, and 5 mg) and aripiprazole-treatment groups were numerically greater, but not significantly different from placebo. Results are available at https://www.clinicaltrials.gov/ct2/show/results/NCT00905307.
NCT01396421	6	3	636	0.25, 2, 4	This was a positive study for brexpiprazole 2 and 4 mg/day for the acute treatment of schizophrenia and is noted in product labeling. Results published in Correll et al. (2).
NCT01393613	6	3	674	1, 2, 4	This was a positive study for brexpiprazole 4 mg/day for the acute treatment of schizophrenia and is noted in product labeling. Results published in Kane et al. (3).
NCT01810380	6	3	465	Up to 4 (quetiapine XR up to 800)	This is a study for the acute treatment of schizophrenia. Results not publicly available at this time.
NCT01668797	52	3	202 randomized	1–4	This is a randomized, double-blind, placebo-controlled withdrawal study demonstrating a longer time to exacerbation of psychotic symptoms or impending relapse for brexpiprazole vs. placebo. Results have been presented as a poster (15).

Table 2 Completed Open-Label, Phase 2/3 Uncontrolled Clinical Trials of Brexpiprazole for Schizophrenia, as Registered at ClinicalTrials.gov

ClinicalTrials.gov Identifier	Length (weeks)	Phase	N	Brexpiprazole Dose (mg/day) (and dose of active control if applicable)	Comments
NCT01649557	52	2	28	**1–6**	This is an open-label, 52-week, flexible-dose safety and tolerability study that enrolled patients who had completed NCT00905307. Results presented in a poster (18) included 785 additional subjects from an ongoing study (NCT01397786), based on a data cut from January 31, 2014.

Table 3 Completed Open-Label, Phase 3 Exploratory Clinical Trials of Brexpiprazole for Schizophrenia, as Registered At ClinicalTrials.gov

ClinicalTrials.gov Identifier	Length (weeks)	N	Brexpiprazole Dose (mg/day) (and dose of active control if applicable)	Comments
NCT02054702	6	97	1–4 (aripiprazole study arm 10–20)	Patients with an acute relapse of schizophrenia were randomized 2:1 to receive brexpiprazole (3 mg/day target dose) or aripiprazole (15 mg/day target dose). Presented as a poster (16).
NCT02013622	16	49	1–4	Enrolled were patients 18- to 35-years old with early-episode schizophrenia. Presented as a poster (17).

published (2, 3). In each of these two trials, adults with an acute exacerbation of schizophrenia were hospitalized and remained so during the entire duration of the study. Subjects were randomized to receive placebo, brexpiprazole 4 mg/day, 2 mg/day, or 0.25 mg/day or 1 mg/day in the Correll (2) and Kane (3) studies, respectively. Study medication was administered once daily. Subjects were titrated to their assigned dose so that patients randomized to 4 mg/day received 1 mg/day for 4 days, 2 mg/day for 3 days, and then 4 mg/day on the 8th day after randomization. Patients randomized to 2 mg/day received 1 mg/day for 4 days and then 2 mg/day on the 5th day after randomization. Subjects randomized to 0.25 mg/day (2) or 1 mg/day (3) were not titrated. Patients were assessed weekly using the Positive and Negative Syndrome Scale (PANSS), which was the primary efficacy measure. Patients were also assessed weekly using the Clinical Global Impressions (CGI) Scale-severity score (CGI-S), which was the key secondary endpoint measure.

In addition, the Personal and Social Performance (PSP) scale was administered at the baseline, Week 3, and Week 6 visits.

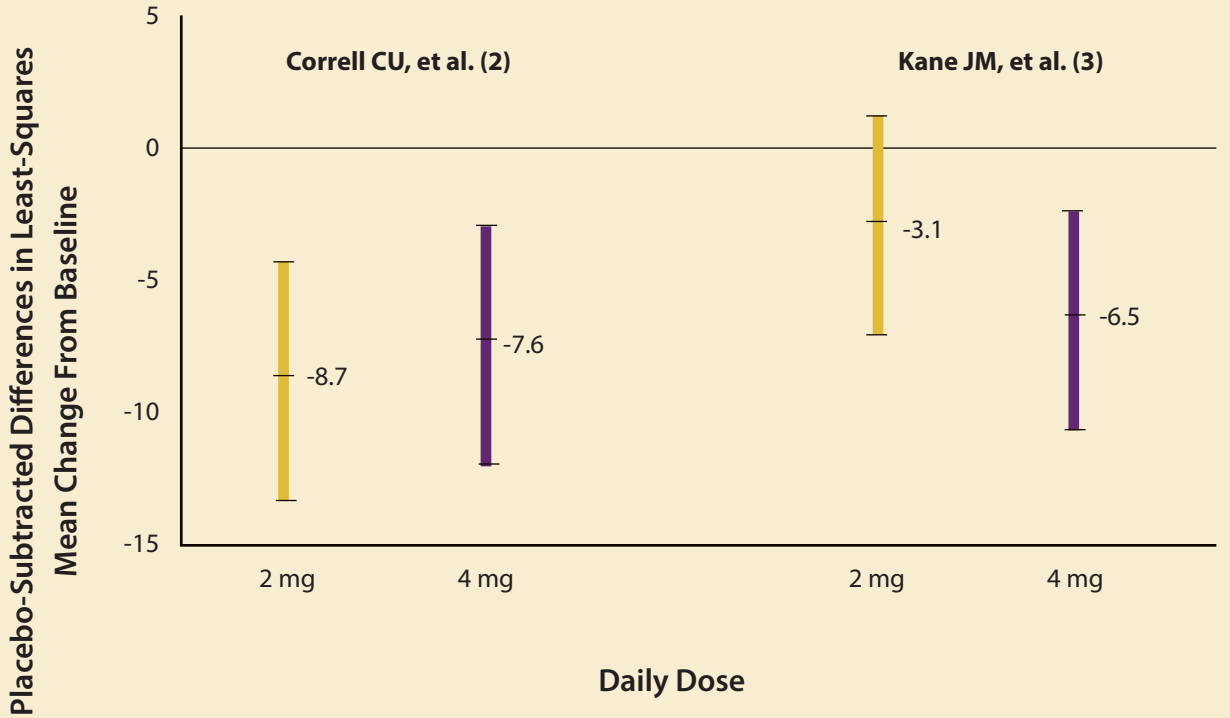
Although the primary efficacy measure was change from baseline at Week 6 in PANSS total score, other analyses of substantial clinical interest included the rate of response at Week 6, defined as achieving a change from baseline ≥30% in PANSS total score or CGI-improvement (CGI-I) score of 1 (very much improved) or 2 (much improved).

In both studies, the average age of the participants was approximately 40 years, and between 60–68% of the participants were men, depending on the study and the assigned treatment group. Mean body mass index ranged from about 26 kg/m^2 to about 27 kg/m^2 in these two international studies. Mean baseline PANSS scores were approximately 95.

Brexpiprazole at doses of 0.25 mg/day or 1 mg/day failed to demonstrate statistically significant differences from placebo on the primary outcome measure. In one study (2), both the 2 mg/day dose and the 4 mg/day dose evidenced superiority over placebo on improvement in the total PANSS score (see Figure 1). The difference between brexpiprazole and placebo in mean change from baseline reached statistical significance at Week 1 in the 2 mg/day group and at Week 2 in the 4 mg/day group, and the effect was maintained throughout the remainder of the study. In addition, the mean change from baseline at Week 6 on the CGI-S was statistically significantly greater in both the 2 mg/day and 4 mg/day brexpiprazole groups than for placebo. Responder rates were also higher for the 2 mg/day (48%) and 4 mg/day (46%) brexpiprazole groups compared to placebo (30%) (see Figure 2); this resulted in a number needed to treat (NNT) versus placebo of 6 for 2 mg/day, and 7 for 4 mg/day in this study (for an explanation of NNT see Box).

Mean change from baseline at Week 6 on the PSP was statistically significantly greater than that for placebo for the 2 mg/day brexpiprazole group but not for the 4 mg/

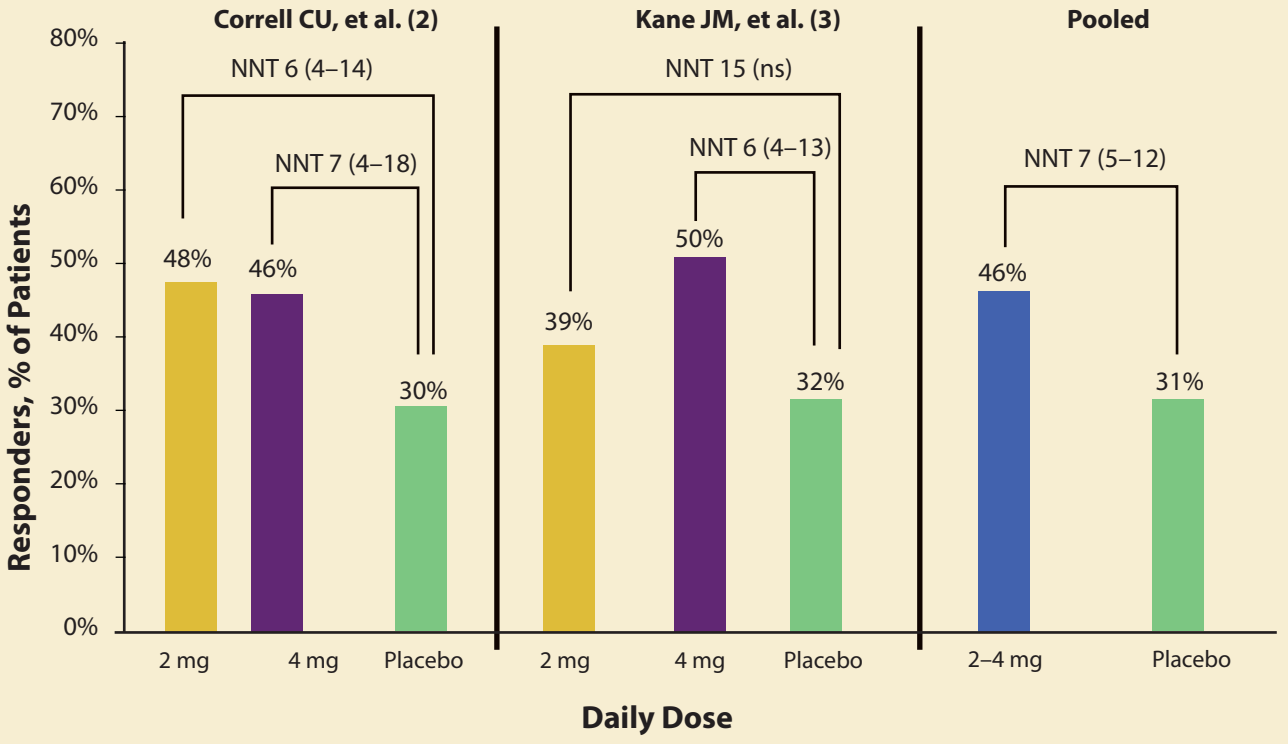
Figure 1 Placebo-Subtracted Differences in Least-Squares Mean Change from Baseline and 95% Confidence Intervals on the Positive and Negative Syndrome Scale in the Phase 3 Pivotal Trials for Schizophrenia



day group. In the second study (3), although brexpiprazole 4 mg/day was statistically significantly superior to placebo, 2 mg/day was not (as seen in Figure 1 by inspecting the 95% confidence interval where the upper bound is >0 for the 2 mg/day-dose group). Brexpiprazole 4 mg/day in the second study also demonstrated improvements compared with placebo on the CGI-S and PSP. Responder rates in the second study were 39% for brexpiprazole 2 mg/day, 50% for brexpiprazole 4 mg/day, and 32% for placebo, yielding NNT values of 15 for the 2 mg/day group and 6 for the 4 mg/day group (see Figure 2). Pooling together the 2 mg/day and 4 mg/day dose groups from both studies resulted in a responder rate of 46% compared with 31% for the pooled placebo groups, with an NNT of 7 (11).

The results of a Phase 3, 52-week, maintenance study that demonstrated the effectiveness of brexpiprazole in preventing exacerbation of psychotic symptoms/impending relapse in patients with schizophrenia have been presented as a poster (15). Patients with schizophrenia who were experiencing an acute exacerbation (PANSS total score >80) were eligible to participate. Patients were cross-titrated from their current antipsychotic treatment(s) to brexpiprazole over a period of 1–4 weeks and then entered a 12- to 36-week, single-blind, stabilization phase on brexpiprazole 1–4 mg/day. Stability criteria included having a PANSS total score ≤70 and scores of ≤4 on key PANSS items as well as a CGI-S score ≤4, and the absence of current suicidal, violent or aggressive behavior. A pre-specified interim analysis was planned for after 45 events of impending relapse. Because efficacy was demonstrated at a significance level of <0.003 at the interim analysis, the study was terminated early. A total of 464 patients entered the study and 202 (44%) subjects with stable symptoms for 12 consecutive weeks and on stable dose of brexpiprazole for at least the last 4 weeks were randomized as outpatients to brexpiprazole (n=97) or placebo (n=105) for up to 52 weeks (maintenance phase). Similar to the acute pivotal trials (2, 3), mean age of the randomized participants was approximately 40 years and approximately 61% were male. Mean baseline body mass index was approximately 29 kg/m^2 in this international study. The mean PANSS total score of all subjects at study entry was 91.1 and at randomization (i.e., after stabilization) was approximately 57 points. Time from randomization to exacerbation of psychotic symptoms or impending relapse was longer for brexpiprazole than for placebo, with a hazard ratio of 0.292. Significantly fewer patients relapsed in the brexpiprazole group compared with placebo (13.5% vs. 38.5%), resulting in an NNT of 4 (95% CI 3–8).

Figure 2 **Response, as Defined by ≥30% Decrease in the Positive and Negative Syndrome Scale Total Score or a Clinical Global Impressions-Improvement Score of 1 (Very Much Improved) or 2 (Much Improved), as Observed in the Phase 3 Pivotal Trials for Schizophrenia**



NNT=number needed to treat (with 95% confidence interval); ns=not significant.

Additional exploratory studies have been conducted and have been presented thus far as posters at scientific meetings. These include a study conducted in the U.S. where adult patients with acute schizophrenia were randomized to open-label brexpiprazole (3 mg/day target dose) or aripiprazole (15 mg/day target dose) (16). Reduction in the symptoms of schizophrenia as assessed by the PANSS total score was observed in both treatment groups (-22.9 and -19.4 for brexpiprazole and aripiprazole, respectively). Also available is a study conducted in the U.S. where open-label brexpiprazole (target dose 3 mg/day) was given to adult outpatients aged 18 to 35 years with early-episode schizophrenia (start of first schizophrenia episode ≤5 years before the time of study) (17). About half (51%) of the participants completed 16 weeks of treatment. The most common reasons for discontinuation were lost to follow-up (20%) and withdrawal of consent (12%). Improvements were observed in PANSS total score from baseline (mean 70.6) to Week 16 endpoint (-10.2), and in the PSP and Specific Level of Functioning in Schizophrenia scales.

Side Effects, Safety and Tolerability in Patients with Schizophrenia

Safety and tolerability data collected during the two 6-week, acute pivotal trials in schizophrenia (2, 3) included the incidence of spontaneously reported adverse events (AEs), body weight, laboratory measurements, vital signs, electrocardiogram, movement disorder scales (Barnes Akathisia Rating Scale, Simpson-Angus Scale/Drug-Induced Extrapyramidal Symptom Scale, Abnormal Involuntary Movement Scale), and the Columbia-Suicide Severity Rating Scale. For brexpiprazole doses of 1–4 mg/day, the rates of discontinuation because of an adverse event were overall lower for patients receiving brexpiprazole vs. placebo (5.9% to 9.4% vs. 12.0% to 17.4% for brexpiprazole vs. placebo, respectively). Table 4 provides a list of the spontaneously reported adverse events associated with the use of brexpiprazole 1–4 mg/day (incidence of ≥2% and brexpiprazole incidence greater than placebo) as observed in the Phase 3 pivotal trials for schizophrenia and reported in product labeling (1), together with their respective values for number

Table 4 Adverse Events Associated with the Use of Brexpiprazole (Incidence of ≥2% and Brexpiprazole Incidence Greater than Placebo) as Observed in the Phase 3 Pivotal Trials For Schizophrenia, Number and Percentage of Subjects, and Number Needed To Harm vs. Placebo and 95% Confidence Intervals*

	Placebo (N=368)	Brexpiprazole							
		1 mg/day (N=120)		2 mg/day (N=368)		4 mg/day (N=364)		All (N=852)	
Adverse Event	%	%	NNH (95% CI)	%	NNH (95% CI)	%	NNH (95% CI)	%	NNH (95% CI)
Akathisia	4.6	4.2	-221 (ns)†	4.6	ND	6.9	45 (ns)	5.5	112 (ns)
Weight increase	2	3	100 (ns)	4	50 (ns)	4	50 (ns)	4	50 (26–1,773)
Dyspepsia	1.9	5.8	26 (ns)	2.4	184 (ns)	3.0	90 (ns)	3.2	79 (ns)
Tremor	1	2	100 (ns)	2	100 (ns)	3	50 (ns)	3	50 (29–214)
Diarrhea	1.9	0.8	-94 (ns)†	3.3	74 (ns)	3.3	72 (ns)	2.9	97 (ns)
Sedation	0.8	1.7	118 (ns)	1.6	123 (ns)	2.7	52 (26–5,580)	2.1	78 (ns)
Blood creatine phosphokinase increase	1	4	34 (ns)	2	100 (ns)	2	100 (ns)	2	100 (ns)

*The adverse events are taken from product labeling (1) and are from the two pivotal acute Phase 3 clinical trials (2, 3); where possible, fractions are provided based on data presented in the published reports (2, 3).
†A "negative" NNH results from when the rate of the adverse event is higher for placebo than for brexpiprazole. In both these instances, the results were not statistically significant.
CI=confidence interval; ND=no difference; NNH=number needed to harm; ns=not significant at the $p<0.05$ threshold and, thus, the 95% CI is not shown.

needed to harm (NNH) vs. placebo (11). Of interest are the rates of akathisia: 5.5% for the pooled doses of brexpiprazole 1–4 mg/day vs. 4.6% for placebo, yielding a nonstatistically significant NNH of 112, and is consistent with what was observed on the Barnes Akathisia Rating Scale for both studies (2, 3). The lowest (most problematic) NNH values were observed for weight increase and tremor; however, the actual NNH values are 50, and thus reassuring.

Short-term comparative data regarding akathisia are available from a 6-week exploratory study (16) where the incidence of extrapyramidal symptom (EPS)-related AEs including akathisia was lower in the patients treated with brexpiprazole (14.1%) compared with the patients treated with aripiprazole (30.3%), for an NNT advantage for brexpiprazole of 7 (but not statistically significant).

Short-term mean weight changes with brexpiprazole were observed to be small (1.0 kg with 1 mg/day, and 1.2 kg with 2 mg/day or 4 mg/day, vs. 0.2 kg with placebo); however, approximately 10% of patients receiving brexpiprazole 1–4 mg/day gained ≥7% body weight from baseline, compared with 4% for those randomized to placebo (1), resulting in an NNH of 17 (95% CI 11–31) (11). In the short-term Phase 3 studies, the increases in body weight were not accompanied by clinically relevant changes in lipid profiles or other metabolic parameters (2, 3). The proportions of patients with shifts in fasting glucose from normal to high or borderline to high were similar in patients treated with brexpiprazole and placebo; changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in brexpiprazole- and placebo-treated patients (1). Shifts from normal to high levels of triglycerides were observed in 6% of patients receiving placebo and in 8–10% of those receiving brexpiprazole 1-4 mg/day; one patient receiving brexpiprazole 4 mg/day experienced a shift from normal/borderline levels to very high levels (1).

Effects on prolactin concentrations due to brexpiprazole appear minimal. In one of the Phase 3 acute pivotal studies (2), shifts to abnormal prolactin values were similar in the placebo and brexpiprazole groups. In the other Phase 3 acute pivotal study (3), the incidence of potentially clinically relevant prolactin values were highest in the brexpiprazole 4 mg/day group (19.1%) compared with brexpiprazole 1 mg/day (10.5%), brexpiprazole 2 mg/day (16.4%) and placebo groups (13.9%); most of these increases were small, falling between 1 and 2 times the upper limit of normal and the incidence of increases greater than two times the upper limit of normal was similar for all treatment groups.

In the 52-week relapse prevention/maintenance study, the discontinuation rate due to adverse events was 8.8% in the stabilization phase. During the maintenance-treatment phase the withdrawal rates because of adverse events were 5.2% and 11.5% for the brexpiprazole and placebo groups, respectively. Rates for akathisia were 9.1% in the stabilization phase and 1% each for the brexpiprazole and the pla-

cebo groups in the randomized maintenance phase (15).

Also available are safety data from two 52-week, flexible-dose, international, open-label studies of brexpiprazole in persons with schizophrenia. A total of 813 patients entered the studies and, of these, approximately 26% completed 52 weeks of treatment (18). The most commonly encountered adverse events (incidence of ≥5%) included symptoms of schizophrenia (12.2%), insomnia (9.1%), weight increased (7.4%), headache (5.8%), agitation (5.3%) and akathisia (5.0%). Among the observed cases, mean weight gain was 1.3 kg at Week 26 and 2.0 kg at Week 52. An increase of ≥7% of body weight was observed in 19.6% of patients; however, a decrease of ≥7% of body weight was observed in 9.7% of patients. Of the patients who were treated for 52 weeks, 6.6% gained >15 kg. Few subjects (0.6%) discontinued because of adverse events associated with weight increase. The increases in body weight were generally not accompanied by clinically meaningful changes in lipid profiles or glycemic parameters.

In the long-term, open-label schizophrenia studies, 8% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking brexpiprazole; 17% of subjects with borderline fasting glucose experienced shifts from borderline to high (1). Shifts in baseline fasting cholesterol from normal to abnormal were reported in 6, 2, and 17% for total cholesterol, LDL cholesterol, and HDL cholesterol, respectively. Of patients with normal baseline triglycerides, 13% experienced shifts to high, and 0.4% experienced shifts to very high triglycerides (1). Prolactin changes were minimal with mean prolactin concentrations increasing from 17.7 ng/mL at baseline to 19.9 ng/mL at the last visit in women (normal range 2–29 ng/mL) and from 9.4 ng/mL at baseline to 10.2 ng/mL at the last visit in men (normal range 2–20 ng/mL) (18). Brexpiprazole dose was reduced due to prolactin increase in one patient and no patients were discontinued due to hyperprolactinemia.

Brexpiprazole does not appear to lengthen the ECG QTc interval (1-3).

As reported for one of the pivotal acute studies (2), the occurrence of suicidal ideation or behavior, as recorded on the Columbia-Suicide Severity Rating Scale, was low; one patient in the 2 mg/day brexpiprazole group reported suicidal behavior and serious active suicidal ideation at Week 1, a different patient in the 2 mg/day brexpiprazole group had active suicidal ideation at Week 1, and one patient randomized to placebo reported suicidal behavior. In the second pivotal acute study (3), the incidence of suicidality was also low and similar across all treatment groups.

The product label for brexpiprazole includes class-level warnings for increased mortality in elderly patients with dementia-related psychosis, and suicidal thoughts and behaviors in patients aged 24 years and under; these bolded boxed warnings are in the product labels of all antipsychotics and all antidepressants, respectively. There are no contraindications to brexpiprazole other than known hypersensitivity to the product. Other warnings and precautions include cerebrovascular adverse reactions including stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, leukopenia/neutropenia/agranulocytosis, orthostatic hypotension/syncope, seizures, body temperature dysregulation, dysphagia and potential for cognitive and motor impairment; these warnings and precautions are found in all antipsychotic drug labels (19), as is standard language regarding caution for women who are pregnant or nursing. Warnings about metabolic changes are also present, as for all second-generation antipsychotic medication labels, and details regarding the metabolic profile of brexpiprazole are as previously described above.

How Does Brexpiprazole Compare With Other Antipsychotics?

Despite the availability of many antipsychotics for the treatment of schizophrenia, this disorder is complex and often difficult to treat. Antipsychotics vary in terms of tolerability and safety concerns (6), and patients themselves differ in terms of pre-existing risk factors and comorbidities that make drug selection challenging (20). Brexpiprazole appears to have comparable efficacy to aripiprazole for the treatment of schizophrenia, with similar NNT values for response (12), and aripiprazole itself is similar in efficacy to other first-line antipsychotics (6). Thus, when comparing groups of patients in clinical trials, the biggest differences appear to be regarding tolerability. Table 5 contains a summary of NNH values vs. placebo for weight gain ≥7% from baseline, the incidence of somnolence as an adverse event, and the incidence of akathisia as an adverse event for approved first-line, oral, second-generation antipsychotics in adults with schizophrenia. Brexpiprazole appears to have favorable (i.e., higher) NNH values than some of the other agents and, of particular interest, are the NNH values for akathisia when comparing brexpiprazole vs. aripiprazole where higher (more favorable) values for NNH are observed for brexpiprazole. When contrasting the three available dopamine receptor partial agonists, the rank order for propensity for weight gain appears to be brexpiprazole>aripiprazole>cariprazine, the propensity for somnolence aripiprazole>brexpiprazole>cariprazine, and the propensity for akathisia cariprazine>aripiprazole>brexpiprazole; these indirect comparisons will need to be confirmed by appropriately designed head-to-head clinical trials (12).

Table 5 Number Needed to Harm vs. Placebo for Approved First-Line, Oral, Second-Generation Antipsychotics in Adults for Weight Gain, Somnolence, and Akathisia, as Observed in Acute Short-Term Studies for Schizophrenia as Calculated from Product Labeling*

Antipsychotic	NNH for Weight Gain ≥7%	NNH for Somnolence Adverse Events	NNH for Akathisia Adverse Events
Brexpiprazole	17	50‡	112
Aripiprazole	21	20†	25
Cariprazine (to 6 mg/day)	34	100	15
Risperidone (to 8 mg/day)	18†	13	15
Olanzapine	6†	7†	25
Quetiapine Immediate Release	6	10†	ND
Quetiapine Extended Release	22	7	188
Ziprasidone	16	15	100
Paliperidone	35	42	39
Iloperidone	10	16	ND
Asenapine	35	17	34
Lurasidone	67	11	10

*Adapted from (12).
†Reported in product labeling for schizophrenia and bipolar mania pooled together.
‡Data for somnolence for brexpiprazole are taken from the section regarding potential for cognitive and motor impairment and includes sedation and hypersomnia, and differs from that presented in the tables for commonly occurring adverse events.
ND=no difference or rate with medication is lower than rate with placebo; NNH=number needed to harm.

Other Indications

As noted, brexpiprazole is also approved as an adjunct for the treatment of major depressive disorder (1), as supported by two Phase 3 randomized clinical trials where patients with a history of inadequate response to 1 to 3 treatment trials of standard antidepressants for their current depressive episode were enrolled (4, 5). Patients entered the 6-week randomized phase only if they had an inadequate response to antidepressant therapy during an 8-week prospective treatment trial of standard antidepressant treatment plus single-blind placebo. Dosing for brexpiprazole for major depressive disorder differs from that for schizophrenia: the recommended starting dosage for brexpiprazole as adjunctive treatment for major depressive disorder is 0.5 mg or 1 mg/day. Brexpiprazole is titrated to the target dosage of 2 mg/day, with dosage increases occurring at weekly intervals based on the patient's clinical response and ability to tolerate the agent, with a maximum recommended dosage of 3 mg/day (1). Additional details can be found elsewhere (11, 12).

Two placebo-controlled Phase 3 studies of brexpiprazole for agitation associated with Alzheimer's disease are ongoing (NCT01862640, NCT01922258). A placebo-controlled Phase 3 study of adjunctive treatment for posttraumatic stress disorder was terminated because of "challenges with patient eligibility; the decision to terminate was not based on any safety concerns" (NCT01987960). A placebo-controlled Phase 2 study of adjunctive brexpiprazole for adult attention deficit hyperactivity disorder was completed (NCT01074294); there are no Phase 3 studies registered for this indication.

Summary

Brexpiprazole is a new antipsychotic medication approved for the treatment of schizophrenia and for adjunctive use in the treatment of MDD. Although brexpiprazole is a dopamine D2 partial agonist, it differs from aripiprazole in terms of having more potent receptor binding affinities at serotonin 5-HT1A (partial agonist), 5-HT2A (antagonist), and adrenergic α1B (antagonist) and α2C (antagonist) receptors, and functionally exhibits lower intrinsic activity at the dopamine D2 receptor. Controlled randomized clinical trials support the efficacy of brexpiprazole at the recommended target dose of 2–4 mg/day for the treatment of schizophrenia. Overall tolerability is promising, with the

rate of discontinuation due to adverse events lower than that observed for placebo in the two published, 6-week, Phase 3, acute pivotal trials for schizophrenia. The absolute risk increase for akathisia for brexpiprazole vs. placebo in patients with schizophrenia is small. Brexpiprazole requires titration, and although the recommended titration schedule is to start with 1 mg/day and increase to 2 mg/day on Day 5 to Day 7, then to 4 mg/day on Day 8, real-world clinical experience will be necessary to validate this, including as it relates to the potential occurrence of akathisia. Short-term weight gain appears modest; however, there may be persons who gain weight upon long-term exposure. Effects on glucose and lipids appear small. Minimal effects on prolactin were observed, and no clinically relevant effects on the ECG QTc interval were evident.

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