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Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia

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ABSTRACT

Second-generation antipsychotics have demonstrated efficacy for patients with schizophrenia but are associated with wide-ranging side effects. Brexpiprazole, a serotonin-dopamine activity modulator, has demonstrated efficacy in adult patients with schizophrenia. This paper provides an overview of the safety and tolerability of brexpiprazole in patients with schizophrenia through examination of pooled safety data from one Phase 2 and two Phase 3 6-week, short-term studies, and two open-label, 52-week, long-term studies.

In the short-term studies, there were no reports of treatment-emergent adverse events (TEAEs) with an incidence ≥ 5% and twice that of placebo in patients treated with brexpiprazole 2–4 mg. In the long-term studies, TEAEs reported by ≥5% of patients were schizophrenia (10.7%), insomnia (8.0%), weight increase (7.7%), headache (6.0%), and agitation (5.2%). Akathisia rates were low in the short- (5.8%, pooled brexpiprazole group) and long-term studies (4.6%). Sedation rates were low in the short- (2.3%, pooled brexpiprazole group) and long-term studies (0.9%). Mean body weight increase was 1.1 kg in both short- and long-term studies.

For all studies, changes from baseline to last visit in laboratory parameters, electrocardiogram values, and vital signs were small and not clinically relevant. Changes in lipid profiles or other metabolic parameters were also small. Collectively, these studies suggest that brexpiprazole was well tolerated, with a favorable safety profile that does not exhibit significant rates of important adverse events that can be seen with existing antipsychotics (akathisia, sedation, weight gain, or QTc prolongation), and therefore may provide a useful treatment option for patients with schizophrenia.

ClinicalTrials.gov: NCT00905307; NCT01396421; NCT01393613; NCT01649557; NCT01397786.

1. Introduction

Schizophrenia is a life-long, frequently debilitating psychotic illness of positive (e.g. delusions, hallucinations) and negative (e.g. emotional withdrawal, passivity) symptoms (Volavka and Citrome, 2009). Additionally, it is associated with cognitive impairments including memory problems and attention deficits (Saha et al., 2005; Volavka and Citrome, 2009). Collectively, these symptoms significantly affect social and occupational functioning and quality of life (Browne et al., 2000; Hayhurst et al., 2014; Volavka and Citrome, 2009).

Attaining successful schizophrenia treatment outcomes remains challenging because of the heterogeneity of therapeutic and adverse responses (Citrome, 2013; Correll, 2010; De Hert et al., 2012; Leucht et al., 2013). Current second-generation antipsychotics are associated with numerous side effects: weight gain, metabolic abnormalities, hyperprolactinemia, sedation, restlessness, akathisia/other extrapyramidal symptoms (EPS), and QTc prolongation (De Hert et al., 2011; Kane et al., 2010; Leucht et al., 2013). There remains a need for antipsychotic medications offering an appropriate balance between efficacy against the core symptoms of schizophrenia and a good safety/tolerability profile, with minimal activating (e.g. akathisia, insomnia, restlessness, and anxiety) and sedating (e.g. sedation, somnolence) adverse events (AEs), and low EPS, metabolic, and cardiovascular risks (Correll, 2010; De Hert et al., 2011).

Pharmacological profiles of current second-generation antipsychotics vary in their affinity for dopamine and serotonin receptor subtypes and for adrenergic, histaminergic, and muscarinic receptors (Correll, 2010). Activity at these receptors may contribute to variation in side-effect profiles (Miller, 2004; Sharpley et al., 2005).

Brexpiprazole (OPC-34712) is a serotonin–dopamine activity modulator that was approved in the USA in July 2015 for the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the

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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 5-HT_{2A} and noradrenergic $\alpha_{1B/2C}$ receptors, all with similar potency (Maeda et al., 2014a). It has a lower intrinsic activity at the D_2 receptor and stronger antagonism at the 5-HT_{2A} receptor than aripiprazole, the first D_2 partial agonist approved for the treatment of schizophrenia (Maeda et al., 2014a). Partial agonism, with low intrinsic activity at the D_2 receptor in addition to strong 5-HT_{2A} antagonism, may reduce the potential to induce both D_2 agonist-mediated AEs such as akathisia, insomnia, restlessness, and nausea, and D_2 antagonist-like AEs such as EPS, hyperprolactinemia, and tardive dyskinesia (Kapur et al., 2000; Laoutidis and Luckhaus, 2014; Maeda et al., 2014a; Maeda et al., 2014b). Additionally, brexpiprazole has, relative to D_2/5-HT_{1A} receptors, moderate affinity for histamine H_1 receptors (Maeda et al., 2014a), often associated with sedation and weight gain. This unique pharmacological profile may provide improved tolerability, compared with other agents, without compromising efficacy.

Results obtained from two Phase 3 short-term studies have demonstrated efficacy of brexpiprazole as a treatment for acute schizophrenia. In one trial, treatment with brexpiprazole 2 and 4 mg showed statistically significant improvements from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score, compared with placebo (Correll et al., 2015; Kane et al., 2015a). In a meta-analysis of both trials, both the 2 mg and 4 mg groups showed efficacy vs. placebo (Cohen's d effect size 0.27 and 0.33) (Correll et al., 2016). This meta-analysis presents analyses of safety and tolerability data for brexpiprazole in adult patients with schizophrenia using pooled results from one Phase 2 and two Phase 3 short-term studies, and from two long-term studies. Pooled efficacy data from the pivotal short-term studies are reported separately (Correll et al., 2016).

2. Methods

An overview of the Phase 2 and Phase 3 studies included in this safety analysis is presented in Table 1.

Written informed consent was obtained from all patients. The studies were conducted in compliance with the International Conference on Harmonization Good Clinical Practice Consolidated Guideline. The protocols were approved by independent ethics committees.

2.1. Study design

2.1.1. Short-term studies

The Phase 3 short-term studies were conducted in patients aged 18–65 years with a current diagnosis of schizophrenia as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Text Revision (DSM-IV-TR) criteria, who would benefit from hospitalization or continued hospitalization for the treatment of a current acute exacerbation of schizophrenia. Patients were excluded if it was their first episode of schizophrenia or they had a DSM-IV-TR Axis I diagnosis other than schizophrenia, clinically significant tardive dyskinesia, substance abuse/dependence in the previous 180 days, or a clinically significant medical condition. Detailed methodology of the Phase 3 studies has been described previously (Correll et al., 2015; Kane et al., 2015a).

All studies were multicenter and conducted at sites in North America (35%), Europe (50%), Asia (5%), and Latin America (10%). These randomized, double-blind, placebo-controlled studies consisted of screening (≤14 days), double-blind treatment (6 weeks), and safety follow-up (30 days) phases.

The Phase 2 study included an active reference drug (aripiprazole 10–20 mg) for demonstration of assay sensitivity only.

2.1.2. Long-term studies

The long-term studies were 52-week, flexible-dose, open-label extension studies that enrolled patients who completed the short-term studies. The Phase 2 extension study also included de novo patients who met the short-term study eligibility criteria. Study 1 (1–6 mg brexpiprazole) has been completed, and Study 2 (1–4 mg brexpiprazole) is ongoing (Table 1). Dose ranges were chosen to mirror those of the parent studies.

2.2. Safety assessments

Safety assessments comprised AEs, serious AEs (SAEs), body weight, laboratory parameters, vital signs, electrocardiograms (ECGs), Simpson–Angus Scale (SAS) (Simpson and Angus, 1970), Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), and Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). An overview of safety assessment timings can be found in Supplementary Table 1.

2.3. Statistical analysis

All analyses were performed in the safety population, comprising patients who received at least one dose of study medication.

For the short-term studies, data for brexpiprazole were pooled into integrated dose groups (<2 mg, 2–4 mg, and >4 mg), plus a pooled brexpiprazole group. Baseline was defined as the last measurement prior to the first dose of drug received.

Table 1
Phase 2/3 clinical studies in treatment of adults with acute schizophrenia.

Study	Study design and dosage	Number of patients in safety population[a]		
		Brexpiprazole	Placebo	Aripiprazole
Short-term, double-blind studies				
Flexible dose (Phase 2)				
Study 1; NCT00905307; STEP 203	6-week, double-blind, placebo-controlled study; flexible doses of 0.25 mg to 6 mg	314	95	50
Fixed dose (Phase 3)				
Study 1; NCT01396421; VECTOR	6-week, double-blind, placebo-controlled study; 0.25 mg, 2 mg, and 4 mg fixed dose	452	184	N/A
Study 2; NCT01393613; BEACON	6-week, double-blind, placebo-controlled study; 1 mg, 2 mg, and 4 mg fixed dose	490	184	N/A
Long-term, open-label studies				
Study 1 (Phase 2); NCT01649557; STEP 210	52-week, open-label extension study; flexible doses of 1 mg to 6 mg[d]	28	N/A	N/A
Study 2 (Phase 3)[b]; NCT01397786; ZENITH	52-week, open-label extension; flexible doses of 1 mg to 4 mg	1031[c]	N/A	N/A

[a] The safety population was composed of all patients who were randomized to treatment and received ≥ 1 dose of study medication as indicated on the dosing record.
[b] Study duration was amended to 26 weeks owing to a sufficient number of patients exposed for > 52 weeks.
[c] As of cut-off date of 15 May 2015, for ongoing studies.
[d] Only a small number of patients received a brexpiprazole dose > 4 mg. This dose is not being studied further.

Data from the long-term studies (Study 2 data cut-off: 15 May 2015) were pooled. Baseline was defined according to patient cohort and study. In the open-label study, baseline was the last measurement prior to starting brexpiprazole. For patients from the short-term studies entering the long-term safety studies, baseline was the assessment from the last scheduled visit of the double-blind study prior to starting brexpiprazole. For de novo patients for whom cross-titration/washout was required in Study 2, baseline was the week 4 visit of the screening and conversion phase.

Changes from baseline to last visit (defined as the last evaluable assessment at a scheduled visit for all parameters [except body weight, where last observation carried forward was used]) were calculated for all studies. Number-needed-to-harm (NNH) estimates for discontinuations due to AEs were calculated as 100 divided by absolute risk reduction.

3. Results

3.1. Patient disposition

In the short-term studies, 1256 patients were randomized to brexpiprazole, 463 to placebo, and 50 to aripiprazole. Overall, treatment was completed by 65.4% of patients receiving brexpiprazole and 60.5% of patients receiving placebo. The most frequently reported reasons for discontinuation were withdrawal of consent (13.9%, vs. 11.9% for placebo) for the pooled brexpiprazole group and AEs for placebo (12.7%, vs. 8.1% for pooled brexpiprazole). Mean treatment duration was similar for brexpiprazole (34.3 days) and placebo (33.0 days). Mean (SD) dose for the 2–4 mg brexpiprazole group was 2.6 (0.8) mg.

In the long-term studies, 34.0% of patients completed 52 weeks of treatment; 17.6% were active in long-term Study 2 at time of data cut-off. The most frequently reported reasons for discontinuation were consent withdrawal (16.1%) and AEs (14.5%). At data cut-off, mean (SD) duration of treatment was 200.0 (136.2) days and total exposure was 584.8 patient years. Mean (SD) dose was 3.1 (1.0) mg.

In the long-term studies, patient distribution by parent study treatment was: prior placebo, 208 (19.6%); prior brexpiprazole, 625 (59.0%); prior aripiprazole, 2 (0.19%); de novo, 224 (21.2%). Patients who received brexpiprazole in the parent study had the highest incidence of discontinuations because of an AE (16.5%), while patients who had received placebo had the lowest (11.5%).

3.2. Patient demographics and baseline characteristics

Demographic and baseline characteristics were similar across the studies (Table 2). In the short-term studies, the mean age was 39.8 years, 62.9% of patients were male, and 63.1% were Caucasian. The long-term studies were similar: mean age 39.8 years, 60.7% male, 64.0% Caucasian.

In the short-term studies, a similar percentage of patients in each group (71.0–74.8%) took ≥1 concomitant medication during the study (Supplementary Table 2). In the long-term studies, 58.1% of patients took ≥1 concomitant medication (Supplementary Table 2). Lorazepam was the most frequently reported rescue medication (47.7% and 44.1% in the pooled brexpiprazole and placebo groups, respectively, from the short-term studies; 19.6% from the long-term studies).

3.3. Adverse events

Treatment-emergent adverse events (TEAEs) reported by ≥5% of patients are displayed in Table 3. Most TEAEs were mild or moderate in severity, based on investigator assessment.

In the short-term studies of brexpiprazole up to 4 mg, no TEAEs with an incidence ≥ 5% and twice that of placebo were reported. Overall, the incidence of akathisia was generally low (5.8% vs. 4.5% for the pooled brexpiprazole and placebo groups, respectively) and increased with doses > 4 mg (15.1%); this observation, which was in the Phase 2 study, was the primary reason why doses > 4 mg were not tested in Phase 3. Sedation TEAEs were reported by 2.3% of patients in both the brexpiprazole 2–4 mg and pooled brexpiprazole groups, and 0.6% in the placebo group. Somnolence TEAEs were reported by 2.6% and 2.5% in the brexpiprazole 2–4 mg and pooled brexpiprazole groups, respectively, and 2.6% in the placebo group. The NNH estimates for akathisia, sedation, and weight gain in the short-term studies were 84, 60 (sedation rates were 2.3% for the brexpiprazole 2–4 mg group vs. 0.6% for the placebo group), and 40, respectively, for the brexpiprazole 2–4 mg group. The most frequently reported SAEs were associated with underlying disease; schizophrenia (1.2% and 2.4%, respectively) and psychotic disorder (0.6% and 0.9%, respectively).

In the long-term studies, 58.6% of patients reported ≥1 TEAE, the most frequent being insomnia and schizophrenia (Table 3). Sedation and somnolence TEAEs were reported by 0.9% and 2.4% of patients, respectively. The most frequently reported SAEs were associated with underlying disease, including schizophrenia (7.9%) and psychotic disorder (1.3%).

There were six deaths overall: one in the short-term controlled study (cause of death not specified) and five in the completed long-term study (peritonitis, septic shock, cardiac failure, coronary artery disease, and completed suicide). In the short-term studies, 30 (8.8%), 61 (7.4%), 11 (11.8%), 102 (8.1%), and 59 (12.7%) patients in the < 2 mg, 2–4 mg, > 4 mg, pooled brexpiprazole, and placebo groups, respectively, discontinued because of an AE, as did 154 patients (14.5%) in the long-term studies. Most subjects with AEs resulting in discontinuation had events in the psychiatric disorders system organ class.

3.4. Extrapyramidal-symptoms-associated adverse events

Across all studies, the majority of EPS-associated TEAEs were mild or moderate in severity, based on investigator assessment. In the short-term studies, EPS-associated TEAEs (Supplementary Table 3) did not indicate dose-related tolerability issues. Four patients discontinued because of an EPS-related TEAE (three from the pooled brexpiprazole group [severe psychomotor hyperactivity (brexpiprazole 4 mg group), tremor and akathisia (both brexpiprazole 5.0 ± 1.0 mg group)] and

Table 2
Summary of demographic and baseline characteristics (safety population).

Assessment	Short-term					Long-term
	Brexpiprazole					
	< 2 mg (n = 341)	2–4 mg (n = 822)	> 4 mg (n = 93)	Pooled (n = 1256)	Placebo (n = 463)	Brexpiprazole (1–6 mg) (n = 1059)
Age, years, mean (SD)	39.7 (11.0)	38.8 (10.8)	39.5 (11.1)	39.1 (10.9)	39.4 (10.9)	39.8 (11.1)
Female, n (%)	123 (36.1)	305 (37.1)	38 (40.9)	466 (37.1)	176 (38.0)	416 (39.3)
Caucasian, n (%)	215 (63.0)	517 (62.9)	60 (64.5)	792 (63.1)	291 (62.9)	678 (64.0)
Weight, kg, mean (SD)	77.8 (20.3)	78.5 (19.5)	72.1 (18.4)	77.8 (19.7)	77.4 (18.4)	81.2 (21.0)
BMI, kg/m^2, mean (SD)	26.7 (6.4)	26.8 (6.0)	25.3 (6.3)	26.7 (6.2)	26.5 (5.5)	27.8 (6.6)
Age at first diagnosis, years, mean (SD)	26.7 (8.9)	26.3 (8.4)	26.9 (9.6)	26.5 (8.6)	26.3 (8.9)	N/A
Duration of current episode, estimated weeks, mean (SD)	2.5 (2.2)	2.6 (2.4)	2.3 (1.6)	2.5 (2.3)	2.7 (2.8)	N/A

BMI, body mass index; N/A, not applicable; SD, standard deviation.

Table 3
Summary of adverse events (safety population).

	Short-term					Long-term
	Brexpiprazole					
	< 2 mg (n = 341)	2–4 mg (n = 822)	> 4 mg (n = 93)	Pooled (n = 1256)	Placebo (n = 463)	Brexpiprazole (1–6 mg) (n = 1059)
Any TEAE, n (%)	204 (59.8)	487 (59.2)	70 (75.3)	761 (60.6)	283 (61.1)	621 (58.6)
Death, n (%)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.1)	0 (0.0)	5 (0.5)
Any SAE, n (%)	10 (2.9)	19 (2.3)	4 (4.3)	33 (2.6)	20 (4.3)	126 (11.9)
Any AE leading to discontinuation of study drug, n (%)	30 (8.8)	61 (7.4)	11 (11.8)	102 (8.1)	59 (12.7)	147 (13.9)
Incidence of TEAEs reported by ≥5% patients in any group						
Insomnia, n (%)	39 (11.4)	93 (11.3)	9 (9.7)	141 (11.2)	61 (13.2)	85 (8.0)
Headache, n (%)	32 (9.4)	91 (11.1)	7 (7.5)	130 (10.4)	52 (11.2)	64 (6.0)
Agitation, n (%)	22 (6.5)	57 (6.9)	7 (7.5)	86 (6.8)	36 (7.8)	55 (5.2)
Akathisia, n (%)	12 (3.5)	47 (5.7)	14 (15.1)	73 (5.8)	21 (4.5)	49 (4.6)
Schizophrenia, n (%)	16 (4.7)	41 (5.0)	3 (3.2)	60 (4.8)	43 (9.3)	113 (10.7)
Weight gain, n (%)	15 (4.4)	38 (4.6)	6 (6.5)	59 (4.7)	9 (1.9)	82 (7.7)
Constipation, n (%)	12 (3.5)	33 (4.0)	6 (6.5)	51 (4.1)	24 (5.2)	8 (0.8)
Nausea, n (%)	8 (2.3)	30 (3.6)	6 (6.5)	44 (3.5)	16 (3.5)	17 (1.6)
Anxiety, n (%)	13 (3.8)	15 (1.8)	10 (10.8)	38 (3.0)	14 (3.0)	22 (2.1)
Somnolence, n (%)	5 (1.5)	21 (2.6)	5 (5.4)	31 (2.5)	12 (2.6)	25 (2.4)
Dizziness, n (%)	8 (2.3)	16 (1.9)	5 (5.4)	29 (2.3)	8 (1.7)	13 (1.2)
Blood CPK increased, n (%)	6 (1.8)	17 (2.1)	5 (5.4)	28 (2.2)	5 (1.1)	13 (1.2)
Extrapyramidal disorder, n (%)	4 (1.2)	15 (1.8)	6 (6.5)	25 (2.0)	10 (2.2)	14 (1.3)

AE, adverse event; CPK, creatine phosphokinase; EPS, extrapyramidal symptoms; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

one with placebo). In the long-term studies, eight patients discontinued because of an EPS-related TEAE (four with akathisia [two prior brexpiprazole, one de novo, one prior placebo], one with severe tremor [prior brexpiprazole], one with parkinsonism [prior brexpiprazole], one with dyskinesia [de novo], and one with muscle rigidity [prior brexpiprazole]).

In the long-term studies, 9.3% of patients reported an EPS-related TEAE (Supplementary Table 3). The incidence of EPS-related TEAEs was higher in the prior placebo (13.0%) and de novo groups (11.2%) than in the prior brexpiprazole group (7.4%).

Incidence of akathisia was similar in the brexpiprazole 2–4 mg, pooled brexpiprazole, and placebo groups in the short-term studies and the brexpiprazole group in the long-term studies. Akathisia occurred early during treatment (peak incidence between days 8 and 11 of treatment), coincided with treatment initiation, and was related to dose and dose increases. Discontinuation rates for akathisia were <1% in both short-term (0.1%) and long-term (0.4%) studies. There were no reports of tardive dyskinesia in brexpiprazole-treated patients in any of the studies. One patient (de novo) in the long-term studies discontinued because of dyskinesia.

There were minimal changes from baseline to last visit in all SAS, BARS, and AIMS mean scores for all studies, and no dose-related tolerability issues in the short-term studies (Supplementary Table 4).

3.5. Body weight

In the short-term (6-week) studies, mean increase in body weight was 1.1 kg and 0.2 kg in the pooled brexpiprazole and placebo groups, respectively. Overall, 10.4% in the brexpiprazole 2–4 mg group, 9.9% in the pooled brexpiprazole group, and 4.8% in the placebo group had clinically relevant weight increases (≥7%). No patients discontinued because of a TEAE associated with weight gain.

In the long-term studies, the overall mean increase in body weight was 1.1 kg for brexpiprazole treated patients. For patients exposed for ≥52 weeks the mean increase in body weight was 2.2 kg. Overall, 18.2% of patients had ≥7% weight increase. A total of 7.8% of patients reported a TEAE associated with weight increase, and 0.5% discontinued for this reason. For patients exposed for ≥52 weeks, 5.6% gained ≥15 kg. Patients who had been exposed to brexpiprazole in a parent study had more stable mean weight and less weight gain over time than patients previously exposed to placebo (Supplementary Fig. 1).

3.6. Metabolic parameters

Mean changes from baseline to last visit in all metabolic parameters were similar for all studies (Table 4). A detailed description of shifts in fasting lipids and glucose in the short- and long-term studies can be found in Supplementary Table 5.

The incidence of new diagnosis of metabolic syndrome was 1.2% and 0.8% in the pooled brexpiprazole and placebo groups, respectively, in the short-term studies, and 3.1% in the long-term studies. Metabolic syndrome was recorded for 7 of the 213 patients treated with brexpiprazole for ≥52 weeks.

3.7. Prolactin

Prolactin changes were small and similar across all studies (Table 4). TEAEs potentially related to prolactin were mild or moderate, based on investigator assessment, and were reported in six patients (0.5%) in the brexpiprazole-treated groups and two (0.4%) in the placebo group. In all the brexpiprazole groups, 18 women (5.5%) and 15 men (2.7%) had an elevation >2× upper limit of normal (ULN), and 3 (0.9%) women and 5 men (0.9%) had >3× ULN, reported at one visit. All were asymptomatic.

In the long-term studies, mean changes in prolactin levels from baseline were not clinically meaningful. TEAEs related to prolactin were reported in five patients (0.5%); one had their dose reduced, and none discontinued. Overall, 40 female (10.2%) and 38 male (6.3%) patients had a post-baseline value > 2× ULN, including 21 female (5.4%) and 14 male (2.3%) patients with a post-baseline value > 3× ULN. No patients discontinued because of hyperprolactinemia.

3.8. Other measures

In the short-term studies, mean (SD) change from baseline in creatine phosphokinase (CPK) showed an increase of 72.81 (534.38) U/L and 65.28 (1213.54) U/L in the pooled brexpiprazole and placebo groups, respectively. In the brexpiprazole groups, three patients had a TEAE of rhabdomyolysis; all were SAEs and two patients discontinued. However, classification of rhabdomyolysis was based on blood CPK levels only. Other than the increased CPK levels, no patient had symptoms characteristic of rhabdomyolysis.

Table 4
Mean change (SD) in fasting metabolic parameters and prolactin from baseline to last visit (safety population).

Assessment	Short-term					Long-term
	Brexpiprazole					
	< 2 mg (n = 341)	2–4 mg (n = 822)	> 4 mg (n = 93)	Pooled (n = 1256)	Placebo (n = 463)	Brexpiprazole (1–6 mg) (n = 1059)
Fasting metabolic parameters						
Cholesterol, mg/dL	−3.75 (29.44) (n = 311)	2.26 (29.88) (n = 752)	−6.52 (31.61) (n = 88)	−0.03 (30.04) (n = 1151)	−3.48 (29.39) (n = 415)	0.24 (33.50) (n = 939)
HDL cholesterol, mg/dL	−0.98 (12.34) (n = 185)	1.15 (9.93) (n = 752)	0.08 (8.51) (n = 88)	0.49 (10.57) (n = 1151)	−1.55 (8.62) (n = 415)	0.47 (11.31) (n = 939)
LDL cholesterol mg/dL	−0.29 (26.26) (n = 311)	1.33 (24.96) (n = 660)	−24.50 (16.26) (n = 2)	0.91 (25.25) (n = 847)	−1.82 (25.64) (n = 325)	−0.53 (28.13) (n = 900)
Triglycerides, mg/dL	−5.84 (71.41) (n = 311)	0.06 (76.21) (n = 752)	−2.90 (75.92) (n = 88)	−1.76 (74.90) (n = 1151)	−3.34 (64.27) (n = 415)	1.66 (72.85) (n = 939)
Glucose, mg/dL	1.38 (16.38) (n = 308)	1.09 (15.92) (n = 748)	3.69 (14.07) (n = 88)	1.37 (15.91) (n = 1144)	0.46 (14.49) (n = 414)	2.59 (21.62) (n = 936)
HbA1C, %	−0.00 (0.29) (n = 280)	0.02 (0.33) (n = 730)	0.03 (0.25) (n = 73)	0.01 (0.31) (n = 1083)	0.01 (0.31) (n = 388)	0.06 (0.44) (n = 996)
Prolactin						
Females, ng/mL	−7.24 (36.45) (n = 117)	−1.21 (27.14) (n = 291)	−10.30 (44.80) (n = 37)	−3.55 (31.65) (n = 445)	−10.54 (36.80) (n = 164)	2.78 (0.50) (n = 392)
Males, ng/mL	−3.01 (13.26) (n = 210)	−1.16 (10.25) (n = 488)	−3.54 (11.87) (n = 55)	−1.85 (11.31) (n = 753)	−1.60 (9.94) (n = 262)	0.60 (0.09) (n = 607)

HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

In the long-term studies, mean (SD) change from baseline for CPK was −5.97 U/L (852.82). No patient developed rhabdomyolysis. Changes from baseline to last visit in laboratory/ECG parameters (Supplementary Table 6) and vital signs were negligible for all studies. No dose-related tolerability issues were apparent in the short-term studies.

3.9. Suicidality

The incidence of TEAEs associated with suicidality was low. In the short-term studies, three patients (0.2%) in the pooled brexpiprazole group and one (0.2%) in the placebo group reported a TEAE related to suicidality. None discontinued. Treatment-emergent suicidal behavior as assessed by C-SSRS was reported by two patients (2 mg brexpiprazole group and placebo group).

In the long-term studies, eight patients (0.8%) reported a TEAE related to suicidality: six patients reported suicidal ideation, one attempted suicide, and one completed suicide. C-SSRS assessment identified two patients (0.19%) with treatment-emergent suicidal behavior.

4. Discussion

Results from these five studies in patients with schizophrenia suggest that brexpiprazole 2–4 mg is well tolerated, as confirmed by relatively high completion rates in the short-term studies and low TEAE-related discontinuation rates across all studies. The incidence of SAEs and discontinuations because of TEAEs were higher for placebo than brexpiprazole in the short-term studies; most were indicative of worsening schizophrenia symptoms. For all studies, there were low rates of activating and sedating AEs in brexpiprazole-treated patients, confirming the pharmacology-predicted safety profile of brexpiprazole.

Akathisia is a common side effect of some antipsychotic treatments (Kane et al., 2009; Kane et al., 2015b; Rummel-Kluge et al., 2012); brexpiprazole possesses a pharmacological binding profile that provides low intrinsic activity at D_2 receptors alongside strong antagonistic activity at 5-HT_{2A} receptors, which may minimize akathisia and other activating side effects (Kapur et al., 2000; Laoutidis and Luckhaus, 2014; Maeda et al., 2014a). In the short-term studies, akathisia was reported at a slightly higher incidence in patients treated with brexpiprazole (5.8% [pooled brexpiprazole group]) and placebo (4.5%), with only one patient, in the > 4 mg group, discontinuing. The long-term studies support this promising tolerability profile: <1% patients discontinued because of akathisia, and there was a relatively low incidence of EPS-related TEAEs (predominantly in the prior placebo and de novo groups).

Sedation and somnolence rates were low for both short- and long-term studies, with no events leading to discontinuation.

Antipsychotic medications are associated with increases in body weight (De Hert et al., 2011; De Hert et al., 2012; Leucht et al., 2013). In this analysis, changes in body weight were moderate for all groups in the short-term studies and not markedly different between studies. Our results showed that more patients had clinically relevant weight gain (≥7%) following long-term (18.2%) compared with short-term (9.9%) treatment, and that patients exposed to brexpiprazole in a parent study tended to have less weight gain over time compared with patients exposed to placebo. Although comparisons with other studies should be made with caution, clinically significant weight gain in long-term studies has been observed in 10–14% of patients taking aripiprazole (Chrzanowski et al., 2006; McQuade et al., 2004) and 37% taking quetiapine (Brecher et al., 2007).

For the short-term studies, NNH estimates were calculated for the 2–4 mg brexpiprazole group, a dose range with demonstrated efficacy in acute schizophrenia (Correll et al., 2015; Kane et al., 2015a). The high NNH values for akathisia (84), sedation (60), and weight gain ≥7% (40) are encouraging as previous studies have reported NNH values for akathisia of 34, 15, and 25 for aripiprazole, risperidone, and olanzapine, respectively (Belgamwar and El-Sayeh, 2011; Citrome, 2013), NNH values for sedation of 23, 20, and 3 for aripiprazole, risperidone, and quetiapine, respectively (Belgamwar and El-Sayeh, 2011; Komossa et al., 2010), and NNH values for weight gain ≥7% of 20, 12, 6, and 6 for aripiprazole, risperidone, olanzapine, and quetiapine, respectively (Citrome, 2013; De Hert et al., 2012).

Metabolic side effects, such as hyperglycemia, dyslipidemia, and metabolic syndrome, have been associated with second-generation antipsychotics (e.g. olanzapine and quetiapine) (De Hert et al., 2011; De Hert et al., 2012). However, we observed only small changes in metabolic parameters in brexpiprazole-treated patients across the studies and only one case of metabolic syndrome, suggesting that brexpiprazole has a good metabolic profile. No clinically significant differences between brexpiprazole and placebo were observed for other safety and tolerability parameters, and no new safety issues associated with long-term use were identified.

With current second-generation antipsychotics being associated with an array of side effects, there is a need for efficacious antipsychotics

with a more favorable safety profile. Based on the current analyses, brexpiprazole appears to be a suitable treatment for patients with schizophrenia, with good overall tolerability in both short- and long-term settings. Together with the demonstrated efficacy (Correll et al., 2016), the favorable long-term tolerability profile provides reason to anticipate that brexpiprazole will provide a valuable therapeutic option for treating patients with schizophrenia.

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Contributors

Drs Kane, Skuban, and Hobart designed the studies and wrote the protocol; Drs Kane, Skuban, Hobart, Correll, Weiller, and Weiss contributed to interpretation of the data; and Dr Ouyang performed the statistical analysis. All authors contributed to and have approved the final manuscript.

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Conflict of interest

Dr Kane has been a consultant for Amgen, Alkermes, Bristol-Meyers Squibb, Eli Lilly, EnVivo Pharmaceuticals (Forum) Genentech, H. Lundbeck. Intracellular Therapeutics, Janssen Pharmaceutica, Johnson and Johnson, Merck, Novartis, Otsuka, Pierre Fabre, Proteus, Reviva, Roche, and Sunovion. Dr Kane has been on the Speakers' Bureaus for Bristol-Meyers Squibb, Eli Lilly, Janssen, Genentech, and Otsuka, and is a shareholder in MedAvante, Inc. Drs Skuban, Hobart, Ouyang, Weiss are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Dr Weiller is an employee of H. Lundbeck A/S. Dr Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Actavis, Alkermes, Eli Lilly, Forum, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, MedAvante, Medscape, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, and Teva; and has received grant support from Bristol-Myers Squibb, Otsuka, and Takeda.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.04.013.

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