Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 6 April 2016
Accepted 11 April 2016
Available online xxxx

Keywords:
Brexpiprazole
Schizophrenia
Safety
Akathisia
Sedation
D2 partial agonist

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 treatment of major depressive disorder. It acts as a partial agonist at

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http://dx.doi.org/10.1016/j.schres.2016.04.013
0920-9964/

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.

Please cite this article as: Kane, J.M., et al., Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.04.013