Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia ☆

John M. Kane [a,*], Aleksandar Skuban [b], John Ouyang [b], Mary Hobart [b], Stephanie Pfister [b], Robert D. McQuade [b], Margaretta Nyilas [b], William H. Carson [b], Raymond Sanchez [b], Hans Eriksson [c]

[a] The Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd Street, Glen Oaks, NY 11004, USA
[b] Otsuka Pharmaceutical Development & Commercialization, Inc., 1 University Square Drive, Princeton, NJ 08540, USA
[c] H. Lundbeck A/S, Valby, Denmark

ARTICLE INFO

Article history:
Received 20 November 2014
Received in revised form 23 January 2015
Accepted 25 January 2015
Available online xxxx

Keywords:
Schizophrenia
Phase 3 trial
Brexpiprazole
Efficacy
Safety
Acute

ABSTRACT

The objective of this study was to evaluate the efficacy, safety and tolerability of brexpiprazole versus placebo in adults with acute schizophrenia. This was a 6-week, multicenter, placebo-controlled double-blind phase 3 study. Patients with acute schizophrenia were randomized to brexpiprazole 1, 2 or 4 mg, or placebo (2:3:3:3) once daily. The primary endpoint was changed from baseline at week 6 in Positive and Negative Syndrome Scale (PANSS) total score; the key secondary endpoint was Clinical Global Impressions—Severity (CGI-S) at week 6. Brexpiprazole 4 mg showed statistically significant improvement versus placebo (treatment difference: −6.47, $p = 0.0022$) for the primary endpoint. Improvement compared with placebo was also seen for the key secondary endpoint (treatment difference: −0.38, $p = 0.0015$), and on multiple secondary efficacy outcomes. Brexpiprazole 1 and 2 mg also showed numerical improvements versus placebo, although $p > 0.05$. The most common treatment-emergent adverse events were headache, insomnia and agitation; incidences of akathisia were lower in the brexpiprazole treatment groups (4.2%–6.5%) versus placebo (7.1%). Brexpiprazole treatment was associated with moderate weight gain at week 6 (1.23–1.89 kg versus 0.35 kg for placebo); there were no clinically relevant changes in laboratory parameters and vital signs. In conclusion, brexpiprazole 4 mg is an efficacious and well-tolerated treatment for acute schizophrenia in adults.
Clinical Trials.gov NCT01393613; BEACON trial.

1. Introduction

Schizophrenia is a chronic, severe, progressive and debilitating mental illness (Messias et al., 2007; McGrath et al., 2008) that substantially contributes to disability (Whiteford et al., 2013). In the Global Burden of Disease Study 2010, schizophrenia ranked sixteenth world-wide (ninth in North America), regarding Years Lived with Disability (Vos et al., 2012) and, of 289 studied diseases and injuries, was the illness with the highest disability weighting (Salomon et al., 2012).

Individuals with schizophrenia experience striking and well-known positive symptoms (hallucinations, delusions, thought disorders) but also typically experience negative symptoms (e.g. social withdrawal and lack of emotion, energy and motivation), cognitive symptoms and behavioral changes. Symptoms experienced by patients with schizophrenia can negatively impact their ability to maintain personal relationships, engage productively in work and care for themselves (Lieberman et al., 2001; Bobes et al., 2007; Stip and Tourjman, 2010). Current second-generation antipsychotic treatments for schizophrenia are efficacious for positive symptoms with low propensity to cause extrapyramidal symptoms (EPS) (Kane and Correll, 2010). While these drugs have represented an important advance in treating schizophrenia, it is still important to develop and offer new drugs with pharmacologies that differ from those of currently available drugs, as physicians and patients seek additions to the current armamentarium. The pharmacological profiles of current second-generation antipsychotics vary with respect to affinity for dopamine and/or serotonin receptor subtypes, and adrenergic, histamine and/or muscarinic receptors (Correll, 2010). The different receptor-binding profiles of current antipsychotics may contribute to variance in associated side effects (Correll, 2010), including

☆ Funding: Funding for this study was provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, USA) and H. Lundbeck A/S (Valby, Denmark) (Clinical Trials.gov NCT01393613).

* Corresponding author at: The Zucker Hillside Hospital, Psychiatry Research, 75-79 263rd Street, Glen Oaks, NY 11004, USA. Tel.: +1 718 470 8141; fax: +1 718 343 7739.
E-mail addresses: JKane2@NSHS.edu (J.M. Kane), Aleksandar.Skuban@otsuka-us.com (A. Skuban), John.Ouyang@otsuka-us.com (J. Ouyang), Mary.Hobart@otsuka-us.com (M. Hobart), Stephanie.Pfister@otsuka-us.com (S. Pfister), Robert.McQuade@otsuka-us.com (R.D. McQuade), Margaretta.Nyilas@otsuka-us.com (M. Nyilas), William.Carson@otsuka-us.com (W.H. Carson), Raymond.Sanchez@otsuka-us.com (R. Sanchez), HERI@lundbeck.com (H. Eriksson).

http://dx.doi.org/10.1016/j.schres.2015.01.038
0920-9964/

hyperprolactinemia (and associated sexual effects), sedation, weight gain and other metabolic effects (De Hert et al., 2012; Leucht et al., 2013). The movement disorder akathisia is another common side effect associated with dopamine receptor antagonists, and may be associated with subjective distress in patients (Kane et al., 2009).

Side effects associated with current schizophrenia treatments can affect the ability of the patient to function and interact with others, potentially affecting their subjective well-being and quality of life (Correll, 2010). Treatment choice among currently available antipsychotics for patients with schizophrenia requires trade-offs between different activating and sedating adverse effects; additional, safe treatment options to compensate for the highly heterogeneous responses between individuals are needed (Correll, 2010). There is a need for better tolerated antipsychotics with broad-based symptom control (positive and negative, as well as cognitive and behavioral) that improve patient functioning by having minimal sedating or activating effects, negligible impacts upon prolactin/sexual functioning and inconsequential neuromotor or cardiovascular adverse effects.

Brexpiprazole, a rationally designed serotonin-dopamine activity modulator, acts as a partial agonist with similar potency at serotonin 5-HT_{1A} and dopamine D_2 receptors, and a potent antagonist at serotonin 5-HT_{2A} and noradrenaline α_{1B} and α_{2C} receptors (Maeda et al., 2014b). Brexpiprazole's D_2 receptor partial agonism with lower intrinsic activity than the only currently available D_2 partial agonist, aripiprazole (Maeda et al., 2014b), suggests a low potential to induce D_2 agonist-mediated adverse effects such as akathisia, insomnia, restlessness and nausea (Fleischhacker, 2005). Brexpiprazole's potential to induce D_2 antagonist-like adverse effects, such as EPS, hyperprolactinemia and tardive dyskinesia, is also considered to be lower than that of D_2 antagonists (Maeda et al., 2014a). In addition, the balanced binding ratio of brexpiprazole to 5-HT_{2A}, and 5-HT_{1A}, relative to D_2, may translate into low incidences of both activation-like and antipsychotic-like adverse effects. Finally, brexpiprazole has moderate affinity, relative to D_2/5-HT_{1A} receptor affinity, for histamine H_1 (Maeda et al., 2014b), which may result in low levels of sedation.

The objective of this study was to evaluate the efficacy, safety and tolerability of three fixed doses of brexpiprazole (1, 2 and 4 mg) compared with placebo in the treatment of acute schizophrenia in adults. The 1 mg group was included to explore the lower efficacious dose of brexpiprazole.

2. Methods

2.1. Patients

Male and female patients were recruited from 64 study centers from Colombia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan and the USA. Eligible subjects were 18–65 years of age with a current diagnosis of schizophrenia (defined by DSM-IV-TR and confirmed by Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies) who were experiencing an acute exacerbation of psychotic symptoms and marked deterioration of usual function, as demonstrated by meeting all of the following criteria at screening and baseline visits: Total Brief Psychiatric Rating Scale (BPRS) score ≥40; score of ≥4 on two or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization or suspiciousness); and CGI-S score ≥4. Patients were eligible if they would benefit from hospitalization or continued hospitalization for an acute relapse at trial entry, and had a history of relapse and/or symptom exacerbation when they were not receiving antipsychotic treatments. Patients presenting with their first episode of schizophrenia, a current DSM-IV-TR Axis I diagnosis other than schizophrenia, clinically significant tardive dyskinesia, severe akathisia, or a history of substance abuse within the past 180 days were excluded from the study.

Prohibited concomitant medications used prior to randomization included oral/immediate release intramuscular antipsychotics, depot/long-acting injectable antipsychotics, antidepressants, mood stabilizers and benzodiazepines. Required washout periods ranged from 3 to 28 days; patients were to have washed out of all antipsychotic and other prohibited concomitant medications prior to initial dosing of double-blind treatment on day 1. Exclusions included patients who had received electroconvulsive therapy 60 days prior to screening or study drug in any other previous trial. All psychotropic agents, ramelteon, non-benzodiazepine sleep aids (except for limited treatment of insomnia), antihistamines (excluding cetirizine and loratadine), varenicline, vitamins/nutritional supplements/herbal preparations (unless approved in advance by medical monitor), CYP2D6 inhibitors, CYP3A4 inhibitors/inducers and investigational agents were prohibited during the trial.

This study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice Consolidated Guidelines. The protocol was approved by independent ethics committees and all participating patients provided informed consent.

2.2. Study design

This was a randomized, double-blind, placebo-controlled phase 3 study (Clinical Trials.gov NCT01393613; BEACON trial) conducted between 15 July 2011 and 29 January 2014 to evaluate the efficacy and safety of three doses of brexpiprazole. There was a pre-treatment screening phase of ≤14 days, a 6-week double-blind treatment period, and a 30-day follow-up phase (Fig. 1A). Screening began when the patient provided informed consent; patients were hospitalized for the duration of the screening and treatment period.

Eligible patients were randomized (2:3:3:3) into one of four treatment groups (1, 2 or 4 mg brexpiprazole, or placebo) using an interactive voice response system (IVRS) or interactive web response system (IWRS). Blocks of randomization numbers based on a permuted-block randomization schedule pre-generated by the sponsor were assigned to trial sites by the IVRS/IWRS. Blinding was assured by restricting access of sponsor personnel to the treatment code and providing identical tablets and packaging for the brexpiprazole and placebo treatments. All doses of trial medication were administered orally, once daily. Patients were assessed weekly, and followed up for safety for 30 days after the last dose of trial medication.

2.3. Assessments

2.3.1. Efficacy

The primary endpoint for this study was change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score (Kay et al., 1999).

The key secondary endpoint was changed from baseline at week 6 in Clinical Global Impressions—Severity (CGI-S) (Guy, 1976). Additional secondary outcomes were changes from baseline at week 6 in Personal and Social Performance scale (PSP) (Morosini et al., 2000; Gharabawi et al., 2007), PANSS positive and negative subscales (Kay et al., 1999), PANSS excited component (PEC) (Montoya et al., 2011) and Marder Factor (Lindenmayer et al., 1995; von Knorring and Lindstrom, 1995; Marder et al., 1997; Nakaya et al., 1999; van der Gaag et al., 2006) scores, Clinical Global Impressions—Improvement (CGI-I) score at week 6, response rate, and discontinuation rate for lack of efficacy. Response was defined as mean reduction from baseline in PANSS total score ≥30%, or CGI-I score of 1 (very much improved) or 2 (much improved) at week 6; additional post-hoc exploratory analyses were conducted based on reductions of ≥20%, ≥40% and ≥50% in PANSS total score.

2.3.2. Safety and tolerability

Safety variables examined during this clinical trial included adverse events (AE), physical examinations, vital signs, body weight, laboratory measurements (hematology, serum chemistry [including prolactin], urinalysis and pregnancy tests), vital signs, electrocardiograms (ECGs),

Please cite this article as: Kane, J.M., et al., A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia, Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.01.038