Schizophrenia Research 152 (2014) 450–457

Contents lists available at ScienceDirect

Schizophrenia Research

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

An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial☆

Suresh Durgam [a,*], Anju Starace [a], Dayong Li [a], Raffaele Migliore [a], Adam Ruth [b], György Németh [c], István Laszlovszky [c]

[a] Forest Research Institute, Harborside Financial Center, Plaza V, Jersey City, NJ, USA
[b] Prescott Medical Communications Group, 205 N. Michigan Ave, Suite 3400, Chicago, IL, USA
[c] Gedeon Richter Plc, H-1103 Budapest 10, Gyomroi u. 19-21, Hungary

ARTICLE INFO

Article history:
Received 27 August 2013
Received in revised form 21 November 2013
Accepted 26 November 2013
Available online 10 January 2014

Keywords:
Cariprazine
Schizophrenia
Antipsychotic
Dopamine
D_3

ABSTRACT

Introduction: Cariprazine is an orally active and potent D_3 and D_2 partial agonist with preferential binding to D_3 receptors in development for the treatment of schizophrenia and bipolar mania. This study (NCT00694707) evaluated the efficacy and safety of cariprazine in patients with acute exacerbation of schizophrenia.
Methods: This study was a multinational, double-blind, randomized, placebo- and active-controlled, fixed-dose trial. Patients were randomized to receive placebo, cariprazine 1.5 mg/d, cariprazine 3.0 mg/d, cariprazine 4.5 mg/d, or risperidone 4.0 mg/d (for assay sensitivity) for 6 weeks of double-blind treatment and 2 weeks of safety follow-up. Primary and secondary efficacy parameters were change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total and Global Impressions-Severity of Illness (CGI-S) scores, respectively. Safety parameters included adverse events (AEs), vital signs, laboratory measures, and extrapyramidal symptom (EPS) scales.
Results: Of 732 randomized patients, 64% completed the study. PANSS total score improvement at Week 6 was statistically significant versus placebo for cariprazine 1.5 mg/d, 3.0 mg/d, and 4.5 mg/d (least squares mean difference [LSMD]: −7.6, −8.8, −10.4, respectively; $p < 0.001$; LOCF) and risperidone (−15.1, $p < 0.001$; LOCF); significant improvement on CGI-S was demonstrated for all active treatments ($p < 0.05$). The most frequent cariprazine AEs (≥5% and at least twice the rate of the placebo group) were insomnia, extrapyramidal disorder, akathisia, sedation, nausea, dizziness, and constipation. Mean changes in metabolic parameters were small and similar between groups.
Conclusion: The results of this study support the efficacy and safety of cariprazine in patients with acute exacerbation of schizophrenia.

1. Introduction

Schizophrenia is a multidimensional disorder with a heterogeneous patient population that varies considerably in symptomatology, course of illness, severity of disease, and associated medical and psychiatric comorbidities (Tandon et al., 2009). While antipsychotic medications are the cornerstone of schizophrenia treatment, effectiveness is limited by unfavorable side effects, nonresponse to medication, and modest efficacy on negative symptoms (Kirkpatrick et al., 2006) and cognitive impairment (Buchanan et al., 2005; Keefe et al., 2007). The Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE) schizophrenia study reported a 64–84% discontinuation rate with various antipsychotic treatments (Lieberman et al., 2005; Stroup et al., 2006). While patients may not adequately respond or tolerate initial treatment, they may respond to a different antipsychotic, suggesting that there may be underlying factors that influence individual outcomes with specific antipsychotic medications (Clark et al., 2011). Optimal management of schizophrenia predicates the need for new compounds with broader efficacy and better safety profiles.

Although blockade of dopamine D_2 receptors (either by a full antagonist or partial agonist) is believed to be a necessary pharmacologic property shared by all antipsychotics (Nord and Farde, 2011), affinity for other neuroreceptors varies among available agents. These pharmacological differences may help explain the variation in efficacy

* Corresponding author at: Forest Research Institute, Harborside Financial Center, Plaza V, Jersey City, NJ 07311, USA. Tel.: +1 201 427 8172; fax: +1 201 427 8538.
E-mail addresses: suresh.durgam@frx.com (S. Durgam), anju.starace@frx.com (A. Starace), dayong.li@frx.com (D. Li), raffaele.migliore@frx.com (R. Migliore), aruth@prescottmed.com (A. Ruth), gy.nemeth@richter.hu (G. Németh), i.laszlovszky@richter.hu (I. Laszlovszky).

0920-9964/$ – see front matter © 2013 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.11.041

and tolerability observed across individual patients. The dopamine D_3 receptor has emerged as an additional target for antipsychotic drug treatment. High affinity at the D_3 receptor in combination with high D_2 receptor affinity may offer the potential for augmented effect on the cognitive deficits and negative symptoms of schizophrenia (Joyce and Millan, 2005; Laszy et al., 2005; Gyertyán et al., 2008; Kiss et al., 2008).

Cariprazine is an orally active and potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors. In vitro, cariprazine has almost 10-fold greater affinity for D_3 than D_2 receptors (Kiss et al., 2010). Cariprazine showed high and balanced occupancy of both D_3 and D_2 receptors in rat brain in vivo at antipsychotic-like effective doses whereas other antipsychotics demonstrated high occupancy at D_2 and low or no occupancy at D_3 receptors (Kiss et al., 2012). Cariprazine has 2 major metabolites, desmethyl cariprazine and didesmethyl cariprazine (Citrome, 2013), which have similar pharmacological activity as the parent compound (data on file).

Cariprazine can be administered with or without food and is well absorbed with peak plasma concentrations in 3–4 h (Citrome, 2013). Elimination of cariprazine and its 2 major active metabolites is mainly by hepatic metabolism via CYP3A4 (Citrome, 2013). Cariprazine and its active metabolites show dose-proportional kinetics over the therapeutic dose range (Citrome, 2013). At steady state, didesmethyl cariprazine is the prominent moiety, with exposure (AUC) about 3-fold higher than cariprazine (data on file). Steady-state exposure of desmethyl cariprazine is about 30 to 40% of cariprazine (Citrome, 2013). Steady state is reached in about 1 week for cariprazine and desmethyl cariprazine (Citrome, 2013) and 4 weeks for didesmethyl cariprazine (data on file). Upon dosing discontinuation, about 50% reduction in plasma exposure of total active moieties occurs in about 1 week (data on file).

This Phase IIb trial (NCT00694707) was designed to explore the dose range of cariprazine in the treatment of patients with acute exacerbation of schizophrenia.

2. Methods

2.1. Study design

A 9-week, multinational, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose study was conducted from June 2008 to August 2009 in patients with acute exacerbation of schizophrenia. Patients were screened at 65 study centers in the United States, India, Russia, Ukraine, and Malaysia. The study was conducted in compliance with the ICH-E6 Good Clinical Practice guidelines.

After a washout period of up to 7 days, patients were randomized (1:1:1:1:1) to placebo, cariprazine 1.5 mg/d, cariprazine 3.0 mg/d, cariprazine 4.5 mg/d, or risperidone 4.0 mg/d (included for assay sensitivity) for 6 weeks of double-blind treatment. A 2-week safety period followed during which patients were cross-titrated and stabilized on appropriate medication as deemed necessary by the investigator. Cariprazine was initiated at 1.5 mg/d and increased by 1.5 mg until the target dose was reached (Day 2 or 3); risperidone was initiated at 2.0 mg/d and increased to 4.0 mg/d on Day 3.

Patients were hospitalized at screening and for at least 4 weeks of double-blind treatment. Starting on Day 28, discharge was allowed for patients with Clinical Global Impressions-Severity of Illness (CGI-S) (Guy, 1976b) scores of 3 (mildly ill) or less, no significant risk of suicide or violent behavior, and were ready for discharge in the opinion of the investigator; patients could be rehospitalized if their condition worsened.

2.2. Patients

Patients (18 to 60 years) met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) (APA, 2000) criteria for schizophrenia (paranoid, disorganized, catatonic, or undifferentiated type). Patients had the diagnosis for at least 1 year, current exacerbation less than 2 weeks' duration, and at least 1 psychotic episode requiring hospitalization/antipsychotic medication change/intervention during the preceding year. Patients experiencing a first episode of psychosis were excluded. Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987, 1991) total score between 80 and 120, a score ≥ 4 (moderate) on at least 2 of 4 PANSS positive symptoms (delusions, hallucinatory behavior, conceptual disorganization, suspiciousness/persecution), and CGI-S rating ≥ 4 were required. Body mass index (BMI) between 18 and 35 was also required.

Exclusion criteria included diagnosis of various DSM-IV-TR disorders (e.g., schizoaffective, schizophreniform, bipolar I and II); alcohol/substance abuse/dependence (within 3 months) was prohibited. Patients with treatment-resistant schizophrenia (poor response to ≥ 2 antipsychotics of adequate dose and duration) or suicidal or homicidal attempt/intent (active or preceding 2 years) were excluded. Typical treatment-related, concomitant medication, and medical/physical exclusions were applied.

2.3. Concomitant medications

The use of psychotropic drugs (e.g., antipsychotics, neuroleptics, antidepressants, stimulants, mood stabilizers, sedatives/hypnotics/anxiolytics, dopamine-releasing drugs or dopamine agonists) was not allowed. Zolpidem, zaleplon, chloral hydrate, or eszopiclone for insomnia were permitted. Diphenhydramine, benztropine, or propranolol was permitted as rescue medication for extrapyramidal (EPS) symptoms; lorazepam was permitted to control agitation, restlessness, irritability, and hostility.

2.4. Outcome assessments

PANSS and CGI-S were administered at screening, baseline, and at each visit (Weeks 1–6). Additionally, the 16-item Negative Symptom Assessment (NSA-16) (Axelrod et al., 1993) (baseline and Weeks 2, 4, and 6) and the Clinical Global Impressions-Improvement (CGI-I) (Guy, 1976b) (Weeks 1–6) were administered.

Treatment-emergent adverse events (TEAEs) were recorded at all visits. Additional safety assessments included physical examination, laboratory evaluations, vital signs, weight, and 12-lead ECG. EPS was monitored by the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976a), Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and Simpson-Angus Scale (SAS) (Simpson and Angus, 1970) at each visit.

2.5. Statistical analysis

The Safety Population comprised all randomized patients who received double-blind study medication. The Intent-to-Treat (ITT) Population comprised patients in the Safety Population with a postbaseline PANSS assessment; efficacy analyses were based on the ITT Population.

The percentage of patients who prematurely discontinued was compared between each active treatment group and placebo using Fisher's exact test. Between-group differences for demographic parameters and baseline characteristics were analyzed using 2-way analysis of variance (ANOVA) with treatment group and study center as factors for continuous variables; the Cochran–Mantel–Haenszel (CMH) test, controlling for study center, was used for categorical variables.

The primary efficacy parameter was change from baseline to Week 6 in PANSS total score using the last observation carried forward (LOCF) approach to impute missing postbaseline values. Between-group comparisons were conducted using an analysis of covariance model (ANCOVA) with treatment group and study center as factors and baseline PANSS total score as a covariate. To control overall type I error rate, a sequential, stepwise, multiple-comparison procedure was used.