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Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Cariprazine, a dopamine D_3/D_2 receptor partial agonist with preference for D_3 receptors, has demonstrated efficacy in randomized controlled trials in schizophrenia. This multinational, randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy, safety, and tolerability of cariprazine for relapse prevention in adults with schizophrenia; total study duration was up to 97 weeks. Schizophrenia symptoms were treated/stabilized with cariprazine 3–9 mg/d during 20-week open-label treatment consisting of an 8-week, flexible-dose run-in phase and a 12-week fixed-dose stabilization phase. Stable patients who completed open-label treatment could be randomized to continued cariprazine (3, 6, or 9 mg/d) or placebo for double-blind treatment (up to 72 weeks). The primary efficacy parameter was time to relapse (worsening of symptom scores, psychiatric hospitalization, aggressive/violent behavior, or suicidal risk); clinical measures were implemented to ensure safety in case of impending relapse. A total of 264/765 patients completed open-label treatment; 200 eligible patients were randomized to double-blind placebo (n = 99) or cariprazine (n = 101). Time to relapse was significantly longer in cariprazine- versus placebo-treated patients ($P = .0010$, log-rank test). Relapse occurred in 24.8% of cariprazine- and 47.5% of placebo-treated patients (hazard ratio [95% CI] = 0.45 [0.28, 0.73]). Akathisia (19.2%), insomnia (14.4%), and headache (12.0%) were reported in ≥10% of patients during open-label treatment; there were no cariprazine adverse events ≥10% during double-blind treatment. Long-term cariprazine treatment was significantly more effective than placebo for relapse prevention in patients with schizophrenia. The long-term safety profile in this study was consistent with the safety profile observed in previous cariprazine clinical trials. ClincalTrials.gov identifier: NCT01412060.

1. Introduction

Schizophrenia is a serious neuropsychiatric syndrome that often has a severe and chronic course (Emsley et al., 2013); it substantially contributes to the burden of disease attributable to mental health disorders globally (Whiteford et al., 2013). Relapses in schizophrenia are common, with each subsequent event contributing to clinical deterioration including worsening of symptoms, cognitive impairment, reduced social and vocational functioning, and diminished quality of life (Fleischhacker et al., 2014; Lehman et al., 2004; Olivares et al., 2013; Taylor et al., 2005). Although long-term antipsychotic treatment may substantially reduce relapse risk in the stable phase of schizophrenia (Kane, 2007), partial or total nonadherence to medication is a ubiquitous clinical problem (Leucht and Heres, 2006; Morken et al., 2008). Prevention of relapse is an integral component of comprehensive schizophrenia management.

Cariprazine is a dopamine D_3 and D_2 receptor partial agonist antipsychotic with preferential binding to D_3 receptors (Kiss et al., 2010). Unlike other new generation antipsychotics, which display high occupancy at D_2 receptors but low or negligible occupancy at D_3 receptors (Graff-Guerrero et al., 2009; Gyertyán et al., 2011; Mizrahi et al., 2011), cariprazine shows high and balanced occupancy of D_3 and D_2 receptors at doses effective for the treatment of psychosis (Gyertyán et al., 2011; Kiss et al., 2010). This pharmacological profile may provide benefits in treating cognitive impairment, negative symptoms, and mood

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symptoms associated with schizophrenia (Gyertyán et al., 2008; Kiss et al., 2008; Laszy et al., 2005; Schwartz et al., 2000). Cariprazine also has a unique pharmacokinetic profile, with 2 major active metabolites, desmethyl cariprazine and didesmethyl cariprazine. The effective half-life for the total active moieties, which takes into account cariprazine and the 2 major active metabolites, is approximately 1 week (Nakamura et al., 2016). This long half-life may confer some continued effect after drug discontinuation, perhaps providing protection against rapid onset of relapse in cases of nonadherence. The efficacy and safety of cariprazine in patients with schizophrenia have been supported in 3 positive randomized, placebo-controlled, phase II/III clinical studies (Durgam et al., 2014, 2015; Kane et al., 2015). The current study was designed to assess the efficacy, safety, and tolerability of long-term treatment with cariprazine for preventing symptomatic relapse in patients with schizophrenia (ClinicalTrials.gov. NCT01412060).

2. Patients and methods

This study was conducted from 2011 to 2014 in 72 centers (United States, India, Romania, Slovakia, and Ukraine) in accordance with the Declaration of Helsinki and ICH Guidance. Sites obtained institutional review board (US centers) or ethics committee/government agency (non-US centers) approval before the study. All participants provided written informed consent.

To identify early signs of relapse and ensure patient safety in the event of relapse, patients were required to have up to 2 consented caregivers who also assisted with hospitalization discharges, medication compliance, and study visits. Unscheduled study visits could be arranged in cases of potential relapse.

2.1. Study design

This study consisted of 5 phases (screening, open-label run-in, open-label stabilization, double-blind treatment, safety follow-up) with a total duration up to 97 weeks; dosing was flexible (cariprazine 3–9 mg/d) or fixed (cariprazine 3, 6, or 9 mg/d) depending on the study phase (Fig. 1). Patients were required to complete the prior study phase and meet all of the following eligibility criteria to progress from open-label run-in to open-label stabilization (end of week 8) and from open-label stabilization to double-blind treatment (end of week 20): Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score ≤ 60; at least 20% decrease in PANSS total score from baseline; Clinical Global Impressions-Severity of Illness (CGI-S) (Guy, 1976b) score ≤ 4; score ≤ 4 on each of 7 PANSS items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control); and no significant tolerability issues (investigator judged). Patients who did not meet eligibility criteria at the end of each open-label phase were discontinued from the study and seen for a final/early termination visit.

Patients were hospitalized during screening and for the first 2 weeks of the run-in phase; they were then either discharged and followed-up as outpatients, or hospitalized for 2 additional weeks (investigator discretion). Patients unable to be discharged after 4 weeks were discontinued due to insufficient therapeutic response or unavailability of a caregiver.

Patients were randomized (1:1) to fixed-dose cariprazine or placebo for double-blind treatment of variable duration (26–72 weeks or until early termination including a relapse event) (Fig. 1). Per protocol, double-blind treatment for all active patients was stopped when the last randomized patient completed 26 weeks of treatment regardless of the number of relapse events. Investigators and patients were blinded to the double-blind treatment assignment through an interactive web response system; identically appearing treatments were used. Breaking the randomization code disqualified the patient from further participation.

2.2. Patients

To be included, male or female inpatients (18–60 years of age, inclusive) were required to have a current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) (American Psychiatric Association, 2000) diagnosis of schizophrenia (minimum 1 year) and a current psychotic episode < 4 weeks' duration. Patients additionally had a PANSS total score ≥ 70 and ≤120, and a score ≥ 4 (moderately severe) on at least 2 PANSS positive symptoms (delusions, hallucinatory behavior, conceptual disorganization, suspiciousness/persecution). Patients in their first psychotic episode were excluded; various psychiatric conditions other than schizophrenia or concurrent medical conditions that could interfere with study conduct, confound interpretation of results, or endanger patient well-being were also exclusionary. Additional exclusion criteria are presented in Table S1.

2.3. Efficacy assessments

The primary efficacy parameter was time to first relapse during double-blind treatment (number of days from randomization to the relapse date); patients who did not meet relapse criteria were considered censored at the time of completion or discontinuation from the study.

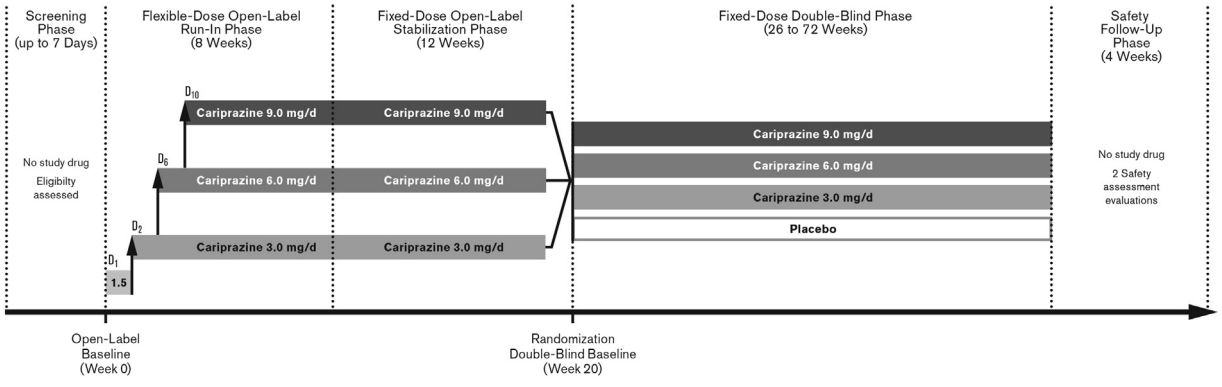

Fig. 1. Study design. Patients were assessed for eligibility to enter the open-label run-in phase during a no-drug screening period. To progress through open-label treatment, patients had to meet eligibility criteria at the end of the run-in phase (week 8) and at the end of the stabilization phase (week 20) (see Section 2.1). Patients who completed open-label treatment and met eligibility criteria after each phase were randomized (1:1) to double-blind treatment. Cariprazine was initiated at 1.5 mg/d and increased to 3.0 mg/d on day 2; for patients with inadequate response and no significant tolerability issues (investigator judged), dosage increases were allowed on day 6 (6.0 mg/d [interim increase to 4.5 mg/d on day 4]) and day 10 (9.0 mg/d) if needed. Flexible-dose cariprazine 3–9 mg/d was continued through week 6 of the run-in phase; fixed-dose cariprazine 3, 6, or 9 mg/d (no adjustments allowed) was administered for weeks 7 and 8. During the open-label stabilization phase, cariprazine was continued at the same fixed dose as in the last 2 weeks of the run-in phase; dose decreases to 3 or 6 mg/d were allowed for significant tolerability issues. During double-blind treatment, cariprazine was administered at the same fixed dose as in the stabilization phase but no adjustments were allowed. During the safety follow-up, patients continued as outpatients and received treatment as usual at the discretion of the investigator; patients did not receive study drug.

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