Abstract

Background. Patients with major depressive disorder (MDD) often do not respond to antidepressant (ADT) monotherapy; adjunctive treatment is often used to address this unmet need. Cariprazine (CAR), a dopamine D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist approved to treat adults with manic, mixed, or depressive episodes of bipolar I disorder, is under investigation as adjunctive therapy for patients with MDD.
Methods. This randomized, double-blind, phase 3 placebo (PBO)-controlled study assessed the efficacy, safety, and tolerability of CAR 1.5 and 3 mg/d as an adjunct to ADT in adult patients with MDD (18–65 years) and inadequate response to ADT alone (NCT03738215). The primary endpoint was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Hamilton Depression Rating Scale (HAMD-17), Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impressions (CGI) were also assessed. Treatment response was defined as at least 50% decrease in MADRS total score at week 6.
Results. Patients (n=751) in the modified intent-to-treat population were randomly assigned to CAR 1.5 mg/d+ADT (n=250), CAR 3 mg/d+ADT (n=252), or PBO+ADT (n=249). Mean age was 44.8 years and 73.4% were female; mean baseline total scores were: MADRS=32.5, HAMD-17=25.9, HAM-A= 21.4. Overall, 89.7% of patients completed the study; rates of discontinuation due to adverse events (AEs) and lack of efficacy were 3.6% and 0.5%, respectively. The difference in MADRS total score change from baseline to week 6 was statistically significant after multiplicity adjustment for CAR 1.5 mg/d vs PBO (-14.1 vs -11.5; adjusted *P*=.0050), but not for CAR 3 mg/d (-13.1; *P*=.0727). Differences for CAR 1.5 mg/d vs PBO were observed by week 2 (nominal *P*=.0453) and maintained at weeks 4 (nominal *P*<.0001) and 6 (nominal *P*=.0025). At week 6, more CAR 1.5 mg/d patients (44%) than PBO patients (34.9%) responded to treatment (nominal *P*=.0446). Greater improvement in the CGI-I scores was observed for CAR 1.5 (nominal *P*=.0026) and 3 mg/d (nominal *P*=.0076) vs PBO. At week 6, improvement in HAMD-17 total score reached nominal significance for CAR 1.5 mg/d vs PBO (-13.1 vs -11.1; nominal *P*=.0017), but not for CAR 3 mg/day (-12.2; *P*=.0783). HAM-A improvement was greater for CAR 1.5 mg/d vs PBO (nominal *P*=.0370). There were no deaths; 2 serious AEs occurred in each group (CAR: kidney infection, social stay hospitalization; PBO: depression, multiple sclerosis). The most common CAR AEs (≥5% and twice PBO) were akathisia and nausea.
Conclusion. Cariprazine 1.5 mg/d was effective as adjunctive treatment in adults with MDD and inadequate response to ADT. Cariprazine was generally well tolerated, with a safety profile that was consistent with other indications. Together with results from a prior flex-dose study, these results suggest that adjunctive cariprazine may be an effective option for patients with inadequate response to ADT alone.
Funding. AbbVie

Safety and Tolerability of Cariprazine for the Adjunctive Treatment of Major Depressive Disorder: A Pooled Analysis of Phase 2B and 3 Clinical Trials

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Abstract

Background. Cariprazine has been shown to be efficacious in placebo-controlled clinical trials. In this pooled analysis, the safety of cariprazine in patients with major depressive disorder (MDD) with inadequate response to antidepressants was evaluated using data from placebo-controlled studies of up to 8 weeks' duration and a long-term open-label safety study.
Methods. The safety, tolerability, and efficacy of cariprazine as an adjunctive treatment for patients with MDD with inadequate response to antidepressant alone was assessed in five placebo-controlled studies (two 6-week fixed-dose studies [NCT03738215; NCT03739203] and three 8-week flexible-dose studies [NCT00854100; NCT01715805; NCT01469377]) and one 26-week open-label flexible-dose study (NCT01838876). Fixed doses of cariprazine 1.5 and 3 mg/d and flexible doses of 0.1-4.5 mg/d were evaluated. Safety assessments included adverse event (AE) reporting, clinical laboratory tests, weight and other vital signs, and suicide evaluation with Columbia-Suicide Severity Rating Scale (C-SSRS). Pooled analyses of the incidence of safety endpoints overall and within each treatment arm were performed using the most frequent (modal) daily dose taken by patients during the study.
Results. A total of 2,222 MDD patients with an ongoing antidepressant received treatment with cariprazine, representing 370 patient-years of exposure in placebo-controlled and open-label studies. In the placebo-controlled studies, 1,969 patients were randomized to cariprazine (dose range, 0.1–4.5 mg/d) and 1,108 patients were randomized to placebo. Overall, treatment-emergent AEs occurred in 61% of cariprazine- and 48% of placebo-treated patients; discontinuation due to an AE occurred with 6% of cariprazine- and 2% of placebo-treated patients. The 2 AEs that occurred in at least 5% of cariprazine-treated patients and at a rate at least twice the rate in placebo-treated patients were akathisia (cariprazine=11%; placebo=2%) and restlessness (cariprazine=6%; placebo=2%). Changes in metabolic parameters, including shifts in fasting glucose and lipid parameters, were similar in cariprazine- and placebo-treated patients. In the long-term safety study, mean weight change was 1.6 kg over 6 months. In the placebo-controlled and long-term studies, other safety endpoints including laboratory and C-SSRS assessments of suicidality were generally consistent with the safety profile of cariprazine in approved indications of bipolar disorder and schizophrenia.

https://doi.org/10.1017/S1092852923001992 Published online by Cambridge University Press

Conclusion. Cariprazine is generally safe and well-tolerated in MDD patients with inadequate response to antidepressant monotherapy. Safety analysis of 2,222 cariprazine-treated patients with MDD revealed no new safety signals, and the data is consistent with the currently approved prescribing information.
Funding. AbbVie

Pharmacokinetic Profile of Aripiprazole 2-Month Ready-to-Use 960 mg in Adult Patients With Schizophrenia or Bipolar I Disorder

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Abstract

Introduction. Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a new long-acting injectable (LAI) antipsychotic formulation for gluteal administration every 2 months, intended for the treatment of schizophrenia and maintenance monotherapy treatment of bipolar I disorder (BP-I). This 32-week trial evaluated the safety, tolerability, and pharmacokinetic profile of multiple-dose administration of Ari 2MRTU 960 in clinically stable adult patients with a diagnosis of schizophrenia or BP-I, versus that of aripiprazole once-monthly 400 mg (AOM 400; an LAI indicated for the treatment of schizophrenia and maintenance monotherapy treatment of BP-I).
Methods. This was an open-label, multiple-dose, randomized, parallel-arm trial conducted at 16 sites in the US. Patients were randomized to receive Ari 2MRTU 960 every 56±2 days (n=132) or AOM 400 every 28±2 days (n=134). The primary objective was to establish the similarity of aripiprazole concentrations on the last day of the dosing interval, as well as exposure during the dosing interval (area under the concentration-time curve [AUC]), between Ari 2MRTU 960 and AOM 400 following multiple doses. It was pre-specified that the lower bound of the 90% confidence interval (CI) of the geometric means ratio (GMR) for these parameters must be >0.8.
Results. In the Ari 2MRTU 960 group, 102 patients (77.3%) completed the study; in the AOM 400 group, 92 patients (68.7%) completed the study. The GMR of C_{56} for Ari 2MRTU 960 to C_{28} for AOM 400 was 1.011 (90% CI: 0.893, 1.145). The GMR (90% CI) of AUC_{0-56} for Ari 2MRTU 960 to AUC_{0-28} for AOM 400 was 1.006 (90% CI: 0.851, 1.190). Mean (standard deviation) maximum aripiprazole plasma concentration was 342 (157) ng/ml after the fourth Ari 2MRTU 960 dose and 344 (212) ng/ml after the eighth AOM 400 dose.
Conclusion. Pharmacokinetic parameters were similar between Ari 2MRTU 960 and AOM 400.
Funding. Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark).

Prevention in Practice: Improving Communication on the Benefits of Treatments for Schizophrenia

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Abstract

Introduction. Antipsychotic treatment can help improve outcomes in schizophrenia by reducing the risk of relapse and psychiatric hospitalization, and increasing rates of remission and recovery, particularly when used early in the disease course. However, adherence to oral antipsychotics is often poor. Long-acting injectable (LAI) antipsychotic formulations are associated with significant improvements in treatment adherence compared with oral medications, but LAIs are not widely used in early-phase schizophrenia.
Methods. An educational training program, called "Prevention in Practice," was developed to offer clinicians a range of innovative, web-based, patient-centered resources, including virtual role-play and educational films, that aim to improve communication between clinicians and patients and help progress care for patients with early-phase schizophrenia. The program was based on findings from the PRELAPSE study, in which clinicians received training to improve communication with patients. The PRELAPSE trial was a cluster randomized study conducted in 39 mental health centers across 19 US states. Sites were randomized to encourage treatment with the LAI aripiprazole once-monthly 400 mg (AOM 400) or to provide treatment as usual. Eligible patients had a diagnosis of schizophrenia, <5 years of lifetime antipsychotic use, and were aged 18–35 years. The objective was to evaluate whether use of the LAI delayed time to first hospitalization in early-phase schizophrenia, compared with usual care. Clinicians received training on the rationale for LAI use in early psychosis, transitioning to LAIs, and discussing LAIs with patients and families. Communication training included the principles of shared decision-making, suggested responses to frequently asked questions, and role-playing.
Results. In PRELAPSE, the sites randomized to encourage LAI treatment enrolled 234 patients and the sites randomized to usual care enrolled 255 patients. Training clinicians to improve their communication with patients made a difference—91% of patients with early-phase schizophrenia were willing to use LAI treatment at least once in the first 3 months of the study. Furthermore, the results showed that AOM 400 significantly prolonged time to first psychiatric hospitalization compared with usual care (hazard ratio: 0.56 [95% confidence interval: 0.34, 0.92]; p=0.02).
Conclusions. Offering clinicians training to improve their communication with patients, through techniques such as shared decision-making and motivational interviewing, may increase LAI use in early-phase schizophrenia. "Prevention in Practice" is now available in in different countries and languages.
Funding. Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark).

https://doi.org/10.1017/S1092852923001992 Published online by Cambridge University Press