

Safety and tolerability of cariprazine in patients with acute exacerbation of schizophrenia: a pooled analysis of four phase II/III randomized, double-blind, placebo-controlled studies

Willie Earley^a, Suresh Durgam^a, Kaifeng Lu^a, István Laszlovszky^c, Marc Debelle^c and John M. Kane^b

Cariprazine, a potent dopamine D₃ and D₂ receptor partial agonist antipsychotic with preferential binding to D₃ receptors, is Food and Drug Administration approved for treating schizophrenia and manic or mixed episodes of bipolar I disorder. A post-hoc safety/tolerability analysis of data from the four acute trials in the cariprazine schizophrenia clinical development program (NCT00404573; NCT00694707; NCT01104766; NCT01104779) was carried out using the overall safety population (all patients who received ≥ 1 dose of study drug) and modal daily dose subgroups (1.5–3, 4.5–6, and 9–12 mg/day). These exploratory findings were summarized using descriptive statistics. Cariprazine was generally well tolerated. The incidence of treatment-emergent adverse events versus placebo was similar for cariprazine 1.5–3 mg/day and higher for cariprazine 4.5–6 and 9–12 mg/day; a dose–response relationship was observed for akathisia, extrapyramidal symptoms, and diastolic blood pressure. The mean changes in metabolic parameters were generally similar in cariprazine-treated

and placebo-treated patients. There was no prolactin level increase or QTc value greater than 500 ms; small increases in mean body weight (~1 to 2 kg) versus placebo were observed. Within the Food and Drug Administration-approved dose range (1.5–6 mg/day), cariprazine was generally safe and well tolerated in patients with schizophrenia. *Int Clin Psychopharmacol* 32:319–328 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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^aAllergan, Jersey City, New Jersey, ^bDepartment of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, New York, USA and ^cGedeon Richter Plc. Budapest, Hungary

Correspondence to Willie Earley, MD, Allergan, Harborside Financial Center, Jersey City, NJ 07311, USA
Tel: +1 201 427 8172; e-mail: willie.earley@allergan.com

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Introduction

Schizophrenia is a severe neuropsychiatric disorder with high rates of medical morbidity and excess mortality (Goff *et al.*, 2005). Although the introduction of first-generation typical antipsychotic medications was a significant advancement in the treatment of schizophrenia, serious acute and chronic safety and tolerability concerns, including extrapyramidal symptoms (EPS), tardive dyskinesia, and hyperprolactinemia, limited their use (Tandon, 2002). There is no consensus on what constitutes atypicality in antipsychotic medications. Clozapine was the first atypical antipsychotic approved for use in the USA and all antipsychotics introduced since have been categorized as atypical (Farah, 2005). Atypical antipsychotics have efficacy that is at least equal to typical

agents; some may offer advantages in improving negative and cognitive symptoms of schizophrenia, and they induce fewer EPS than haloperidol, a potent first-generation agent (Leucht *et al.*, 2009). Atypical antipsychotics have different pharmacological profiles, which affect the likelihood that they will cause certain treatment-induced side effects (Farah, 2005; Miyamoto *et al.*, 2005) including metabolic effects, weight gain, akathisia, and sedation (Stanniland and Taylor, 2000; Newcomer, 2007; Henderson and Doraiswamy, 2008; Kumar and Sachdev, 2010; Cha and McIntyre, 2012). Individuals with schizophrenia who experience an acute and sustained response with antipsychotic medication should continue treatment to maintain symptom relief and reduce relapse risk (Kreyenbuhl *et al.*, 2010). As such, safe and tolerable antipsychotic treatment is a medical necessity.

Cariprazine, a potent dopamine D₃ and D₂ receptor partial agonist with preferential binding to D₃ receptors, is an Food and Drug Administration (FDA)-approved treatment for schizophrenia (1.5–6 mg/day) and manic or mixed episodes associated with bipolar I disorder (3–6 mg/day). Cariprazine shows high and balanced occupancy

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of D₃ and D₂ receptors at doses effective for the treatment of psychosis (Kiss *et al.*, 2010; Gyertyan *et al.*, 2011; Girgis *et al.*, 2016), which may provide benefits in treating cognitive impairment, negative symptoms, and mood symptoms associated with schizophrenia (Schwartz *et al.*, 2000; Laszy *et al.*, 2005; Gyertyan *et al.*, 2008; Kiss *et al.*, 2008). The efficacy and safety of cariprazine in schizophrenia has been supported in three positive randomized, placebo-controlled, phase II/III clinical studies (Durgam *et al.*, 2014; Durgam *et al.*, 2015; Kane *et al.*, 2015). In this investigation, pooled data from these studies and one additional exploratory study (Durgam *et al.*, 2016) were analyzed to characterize the safety and tolerability of cariprazine in patients with schizophrenia. This exploratory reanalysis of the original database of safety information from the phase II/III controlled studies in schizophrenia was based on the overall pooled safety population and cariprazine modal daily doses (most frequent dose taken by a patient during double-blind treatment); it was carried out to better characterize potential dose–response relationships for various safety parameters.

Participants and methods

The constituent study protocols were approved by the institutional review board (US sites) or the ethics committee (non-US sites); ICH-E6 Good Clinical Practice guidelines were followed and written informed consent was obtained from all participants.

Study design and patient population

The detailed methods of the included studies have been published previously; studies were similarly designed and included a 6-week double-blind treatment period (Supplementary Table 1, Supplemental digital content 1, <http://links.lww.com/ICP/A28>). In RGH-MD-03 (NCT00404573) (Durgam *et al.*, 2016), patients were randomized to placebo or cariprazine 1.5–4.5 or 6–12 mg/day. In RGH-MD-16 (NCT00694707) (Durgam *et al.*, 2014), patients were randomized to placebo, cariprazine 1.5, 3, or 4.5 mg/day, or risperidone 4 mg/day. In RGH-MD-04 (Durgam *et al.*, 2015) (NCT01104766), patients were randomized to placebo, cariprazine 3 or 6 mg/day, or aripiprazole 10 mg/day. Risperidone and aripiprazole were included in these studies for assay sensitivity. In RGH-MD-05 (NCT01104779) (Kane *et al.*, 2015), patients were randomized to placebo or cariprazine 3–6 or 6–9 mg/day.

The patients included (18–60 years, inclusive [18–65 years for RGH-MD-03]) had a *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) (American Psychiatric Association, 2000) diagnosis of schizophrenia for 1 year or more and a current exacerbation less than 2 weeks in duration (<4 weeks for RGH-MD-03). Patients were required to fulfill the clinical criteria for inclusion: Clinical Global Impressions-Severity (Guy, 1976b) baseline score of at least 4 (moderately ill or worse), Positive and Negative Syndrome Scale (Kay *et al.*, 1987) total score of at least 80 and less than or equal to 120, and a score of at least 4

(moderate or higher) on at least two specified Positive and Negative Syndrome Scale items (delusions, hallucinatory behavior, suspiciousness/persecution, and conceptual disorganization).

Exclusion criteria were typical of clinical studies in schizophrenia and included the presence of various other DSM-IV-TR diagnoses (e.g. schizoaffective disorder, bipolar disorders), treatment-resistant schizophrenia, substance abuse, and active suicidal intent or past attempt within 2 years. Concurrent medical conditions that could interfere with the conduct of the study, confound the interpretation of results, or endanger the patient's well-being were exclusionary. Drugs with psychotropic activity were not allowed, except for lorazepam for agitation, hostility, and restlessness; eszopiclone, zolpidem, chloral hydrate, or zaleplon for insomnia; and diphenhydramine, benztropine, or propranolol for EPS.

Safety assessments

Safety was assessed by adverse event (AE) recordings (all study weeks), clinical laboratory tests (screening, weeks 2, 4, 6), vital sign parameters (screening, baseline, all study weeks), weight change (baseline, all study weeks), ECGs (screening, weeks 2, 4, 6), and EPS scales (baseline, all study weeks). An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not it was considered related to the use of the product. The mean changes in EPS and treatment-emergent EPS were evaluated using the Abnormal Involuntary Movement Scale (Guy, 1976a), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970). In some of the studies, ophthalmologic parameters (RGH-MD-03, RGH-MD-04, RGH-MD-05 at screening, week 6) and suicidality (RGH-MD-04, RGH-MD-05 at screening, baseline, all study weeks) were also evaluated; suicidal ideation and behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner *et al.*, 2011). The schedule of some safety assessments differed slightly among studies (Supplementary Table 2, Supplemental digital content 2, <http://links.lww.com/ICP/A29>).

Statistical evaluation

Safety was evaluated in the overall safety population (all patients who received ≥ 1 dose of study drug) and in cariprazine subgroups stratified by modal daily dose. Modal daily dose was used to assess dose response as some of the studies included in the analyses used a flexible-dose design, which makes dose response difficult to evaluate. Three modal daily dose groups were analyzed: 1.5–3, 4.5–6, and 9–12 mg/day. The safety baseline was the last nonmissing value before the first dose of the study drug; end of treatment was the last nonmissing value during double-blind treatment. Because of the exploratory nature of these analyses, all safety parameters were summarized using descriptive

statistics; between-group inferential statistical analyses were not carried out. A treatment-emergent adverse event (TEAE) was an AE that started during double-blind treatment or safety follow-up and was not present before the first dose of double-blind study drug or an AE that was present before the first dose of double-blind study drug, but increased in severity during the double-blind treatment phase or the safety follow-up phase. Treatment-emergent parkinsonism was defined as an SAS score less than or equal to 3 at baseline and greater than 3 postbaseline; treatment-emergent akathisia was defined as a BARS score less than or equal to 2 at baseline and greater than 2 postbaseline.

Results

The pooled safety population included 2193 patients. Completion rates were slightly higher in cariprazine-treated patients than in placebo-treated patients, with the exception of the cariprazine 1.5–3 mg/day group, which had higher rates of withdrawn consent (Table 1). Discontinuations because of AEs and insufficient therapeutic response were greater for the placebo group than for any of the cariprazine-dose groups; withdrawal of consent was greater in the cariprazine-dose groups than in the placebo group. Baseline demographics and patient characteristics are presented in Table 2.

Safety and tolerability findings

Extent of exposure

The mean treatment duration was similar for placebo-treated and cariprazine-treated patients (32 and 33 days, respectively); the mean treatment duration in the cariprazine 1.5–3, 4.5–6, and 9–12 mg/day dose groups was 31, 33, and 36 days, respectively. The overall cariprazine exposure was 117.9 patient-years.

Adverse events

TEAEs were reported in slightly more cariprazine-treated than placebo-treated patients, and showed a dose–response relationship, with the highest rates of TEAEs observed in the 9–12 mg/day group (Table 3). Discontinuation because of AEs was higher in the placebo group (12.2%) than in the cariprazine-dose groups (1.5–3 mg/day = 10.8%; 4.5–6 mg/day = 9.2%; 9–12 mg/day = 3.4%); the only AE leading to discontinuation in 2% of patients or greater in any treatment group was exacerbated schizophrenia. There was no observed cariprazine dose response for discontinuations because of AEs.

Individual TEAEs occurring at an incidence of 5% or greater in any group are presented in Table 3; many of the TEAEs showed a dose–response relationship. AEs that occurred in the overall cariprazine group at an incidence of at least 5% and twice the rate of placebo were EPS (grouped terms) and akathisia; the risk of these TEAEs was lower at doses less than or equal to 6 mg/day. A dose response was observed for the grouped term for somnolence, with similar rates observed for cariprazine 1.5–3 mg/day (5.2%) and placebo (5.5%) and higher rates for cariprazine 4.5–6 mg/day (8.0%) and 9–12 mg/day (10.3%). The majority of TEAEs were considered mild or moderate in severity; some severe TEAEs were reported in all treatment groups (placebo = 8.7%; cariprazine: 1.5–3 mg/day = 6.1%, 4.5–6 mg/day = 5.4%, 9–12 mg/day = 3.9%; risperidone = 8.6%; aripiprazole = 3.9%). Most TEAEs were considered to be related to treatment in all groups. A complete listing of patients in the pooled population with a TEAE is presented in Supplementary Table 3 (Supplemental digital content 3, <http://links.lww.com/ICP/A30>); the occurrence of a TEAE may or may not be related to the study drug.

Serious adverse events (SAEs) occurred in 4.9% of cariprazine-treated and 7.2% of placebo-treated patients, with no dose response observed for the incidence of

Table 1 Patient disposition (safety population)

	Cariprazine modal daily dose and overall						
	Placebo (n = 584)	1.5–3 mg ^a (n = 539)	4.5–6 mg ^a (n = 575)	9–12 mg (n = 203)	Overall ^b (n = 1317)	RISP 4 mg/day (n = 140)	ARI 10 mg/day (n = 152)
Completed [n (%)]	334 (57.2)	310 (57.5)	360 (62.6)	142 (70.0)	812 (61.7)	101 (72.1)	114 (75.0)
Reasons for discontinuation [n (%)]							
Did not fulfill inclusion/ exclusion criteria	2 (0.3)	1 (0.2)	1 (0.2)	0	2 (0.2)	0	0
Adverse event	71 (12.2)	58 (10.8)	53 (9.2)	7 (3.4)	118 (9.0)	13 (9.3)	14 (9.2)
Insufficient therapeutic response	100 (17.1)	59 (10.9)	67 (11.7)	25 (12.3)	151 (11.5)	10 (7.1)	8 (5.3)
Protocol violation	5 (0.9)	6 (1.1)	6 (1.0)	1 (0.5)	13 (1.0)	1 (0.7)	0
Withdrawal of consent	64 (11.0)	96 (17.8)	78 (13.6)	24 (11.8)	198 (15.0)	15 (10.7)	15 (9.9)
Lost to follow-up	6 (1.0)	5 (0.9)	7 (1.2)	3 (1.5)	15 (1.1)	0	1 (0.7)
Other reasons	2 (0.3)	4 (0.7)	3 (0.5)	1 (0.5)	8 (0.6)	0	0
Entered safety follow-up ^c	374 (64.0)	334 (62.0)	333 (57.9)	134 (66.0)	801 (60.8)	93 (66.4)	72 (47.4)

ARI, aripiprazole; RISP, risperidone.

^aIndicates Food and Drug Administration-recommended dose range.

^bAll dose groups combined.

^cIncludes all patients who had any scheduled assessment in the safety follow-up period.

Table 2 Patient demographic characteristics and schizophrenia history (safety population)

Characteristics	Cariprazine modal daily dose and overall						
	Placebo (n = 584)	1.5–3 mg ^a (n = 539)	4.5–6 mg ^a (n = 575)	9–12 mg (n = 203)	Overall ^b (n = 1317)	RISP 4 mg/day (n = 140)	ARI 10 mg/day (n = 152)
Age [mean (SD)] (years)	37.8 (11.0)	37.3 (10.1)	37.6 (10.7)	39.9 (9.8)	37.8 (10.4)	36.5 (11.1)	39.3 (10.8)
Men [n (%)]	415 (71.1)	372 (69.0)	422 (73.4)	151 (74.4)	945 (71.8)	98 (70.0)	94 (61.8)
Race [n (%)]							
White	237 (40.6)	278 (51.6)	247 (43.0)	49 (24.1)	574 (43.6)	67 (47.9)	99 (65.1)
Black/African American	215 (36.8)	141 (26.2)	191 (33.2)	108 (53.2)	440 (33.4)	35 (25.0)	33 (21.7)
Asian	96 (16.4)	90 (16.7)	104 (18.1)	38 (18.7)	232 (17.6)	37 (26.4)	2 (1.3)
Other	24 (4.1)	13 (2.4)	16 (2.8)	8 (3.9)	37 (2.8)	1 (0.7)	2 (1.3)
Missing ^c	12 (2.1)	17 (3.2)	17 (3.0)	NA	34 (2.6)	NA	16 (10.5)
Weight [mean (SD)] (kg)	77.9 (19.8)	75.2 (17.7)	76.7 (18.7)	81.3 (20.3)	76.8 (18.6)	75.1 (18.2)	79.5 (17.1)
BMI [mean (SD)] (kg/m ²)	26.4 (5.4)	25.7 (5.0)	26.0 (5.3)	27.4 (5.8)	26.1 (5.3)	25.8 (4.8)	26.9 (5.5)
Duration of schizophrenia [mean (SD)] (years)	13.0 (10.4)	11.8 (8.9)	12.5 (10.1)	14.5 (10.3)	12.5 (9.7)	12.3 (9.9)	12.4 (8.9)
Age at onset [mean (SD)] (years)	24.9 (8.9)	25.5 (8.2)	25.1 (8.6)	25.4 (9.5)	25.3 (8.6)	24.3 (7.8)	26.9 (9.2)

ARI, aripiprazole; RISP, risperidone.

^aIndicates Food and Drug Administration-recommended dose range.^bAll dose groups combined.^cRace data were not collected for patients enrolled at Romanian study centers in RGH-MD-04 per local regulations.**Table 3 Treatment-emergent adverse events during double-blind treatment (safety population)**

Preferred terms	Cariprazine modal daily dose and overall						
	Placebo (n = 584)	1.5–3 mg ^a (n = 539)	4.5–6 mg ^a (n = 575)	9–12 mg (n = 203)	Overall (n = 1317)	RISP 4 mg/day (n = 140)	ARI 10 mg/day (n = 152)
Summary [n (%)]							
Patients with ≥ 1 TEAE	403 (69.0)	370 (68.6)	442 (76.9)	172 (84.7)	984 (74.7)	95 (67.9)	100 (65.8)
Patients with ≥ 1 SAE	42 (7.2)	28 (5.2)	26 (4.5)	11 (5.4)	65 (4.9)	5 (3.6)	4 (2.6)
Deaths	0	0	2 (0.3) ^b	0	2 (0.2)	0	0
Discontinuations because of AE	71 (12.2)	58 (10.8)	53 (9.2)	7 (3.4)	118 (9.0)	13 (9.3)	14 (9.2)
Incidence of common AEs leading to study discontinuation (≥1% in any group) [n (%)]							
Schizophrenia	29 (5.0)	17 (3.2)	17 (3.0)	3 (1.5)	37 (2.8)	2 (1.4)	7 (4.6)
Psychotic disorder	11 (1.9)	10 (1.9)	5 (0.9)	0	15 (1.1)	1 (0.7)	1 (0.7)
Akathisia	1 (0.2)	1 (0.2)	4 (0.7)	2 (1.0)	7 (0.5)	0	0
Blood creatine phosphokinase	1 (0.2)	0	1 (0.2)	0	1 (0.1)	2 (1.4)	0
Oromandibular dystonia	0	0	0	0	0	2 (1.4)	0
Incidence of common TEAEs (≥ 5% in any group) [n (%)]							
Extrapyramidal symptoms ^c	45 (7.7)	80 (14.8)	108 (18.8)	41 (20.2)	229 (17.4)	38 (27.1)	9 (5.9)
Headache ^d	74 (12.7)	46 (8.5)	65 (11.3)	37 (18.2)	148 (11.2)	13 (9.3)	15 (9.9)
Insomnia ^e	64 (11.0)	65 (12.1)	74 (12.9)	23 (11.3)	162 (12.3)	22 (15.7)	16 (10.5)
Somnolence ^f	32 (5.5)	28 (5.2)	46 (8.0)	21 (10.3)	95 (7.2)	22 (15.7)	4 (2.6)
Akathisia	21 (3.6)	49 (9.1)	72 (12.5)	28 (13.8)	149 (11.3)	12 (8.6)	11 (7.2)
Constipation	29 (5.0)	31 (5.8)	39 (6.8)	20 (9.9)	90 (6.8)	13 (9.3)	7 (4.6)
Abdominal pain ^g	28 (4.8)	17 (3.2)	25 (4.3)	15 (7.4)	57 (4.3)	4 (2.9)	13 (8.6)
Schizophrenia	47 (8.0)	24 (4.5)	24 (4.2)	6 (3.0)	54 (4.1)	1 (0.7)	8 (5.3)
Nausea	29 (5.0)	29 (5.4)	38 (6.6)	16 (7.9)	83 (6.3)	8 (5.7)	11 (7.2)
Restlessness	18 (3.1)	21 (3.9)	33 (5.7)	11 (5.4)	65 (4.9)	4 (2.9)	5 (3.3)
Anxiety	24 (4.1)	31 (5.8)	27 (4.7)	6 (3.0)	64 (4.9)	3 (2.1)	12 (7.9)
Hypertension ^h	6 (1.0)	13 (2.4)	15 (2.6)	13 (6.4)	41 (3.1)	2 (1.4)	1 (0.7)
Vomiting	20 (3.4)	22 (4.1)	29 (5.0)	11 (5.4)	62 (4.7)	5 (3.6)	3 (2.0)
Dizziness	12 (2.1)	17 (3.2)	28 (4.9)	11 (5.4)	56 (4.3)	8 (5.7)	6 (3.9)
Toothache	21 (3.6)	14 (2.6)	20 (3.5)	12 (5.9)	46 (3.5)	4 (2.9)	6 (3.9)
Weight increased	8 (1.4)	17 (3.2)	14 (2.4)	6 (3.0)	37 (2.8)	7 (5.0)	6 (3.9)

Version 14.1 of MedDRA was used to code adverse events.

AE, adverse event; ARI, aripiprazole; RISP, risperidone; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

^aIndicates Food and Drug Administration-recommended dose range.^bIn study RGH-MD-04, 2 deaths occurred in the cariprazine 6 mg/day group [suicide one patient], ischemic stroke/myocardial infarction (one patient)]; neither death was considered related to treatment.^cExtrapyramidal symptoms grouped terms = bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, and tremor.^dHeadache grouped terms: headache and tension headache.^eInsomnia grouped term: initial insomnia, insomnia, and middle insomnia.^fSomnolence grouped terms: somnolence, sedation, and hypersomnia.^gAbdominal pain grouped terms: abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal tenderness.^hHypertension grouped terms: blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension.

SAEs. Schizophrenia exacerbation and worsening of psychotic disorder were the most commonly reported SAEs (placebo = 2.9 and 1.5%; cariprazine = 1.4 and 0.8%, respectively).

Metabolic, laboratory, ECG, and additional safety parameters

A summary of safety parameters is presented in Table 4.

Metabolic parameters

Overall, cariprazine-treated patients showed a decrease in mean total cholesterol, fasting low-density lipoprotein cholesterol, and triglyceride levels, whereas placebo-treated patients showed increases from baseline in these parameters. The decrease in high-density lipoprotein cholesterol was similar for cariprazine and placebo, as was the increase in the mean fasting blood glucose. Clinically relevant shifts in lipid and glucose parameters were similar for cariprazine and placebo. The percentage of patients with a fasting glucose increase 10 mg/dl or more was higher in the cariprazine group than in the placebo group; no clear dose response was observed.

Greater mean increases in weight occurred in the cariprazine-treatment groups versus the placebo group. The overall cariprazine weight increase was 1.1 kg for cariprazine-treated patients compared with 0.3 kg for placebo-treated patients; weight increase of 7% or more occurred in 9.2% of cariprazine-treated patients and 4.7% of placebo-treated patients. Both mean weight change and shifts in weight of 7% or more were larger in the 9–12 mg/day dose group. Within the recommended cariprazine-dose range (1.5–6 mg/day), weight gain was 0.8–1.0 kg for cariprazine; the proportion of patients with weight increase of 7% or more was 7.6 and 7.7% for the 1.5–3 and 4.5–6 mg/day groups, respectively.

Clinical laboratory values

Small increases occurred in alanine aminotransferase and aspartate aminotransferase levels with cariprazine relative to placebo; there were no mean increases in bilirubin levels with cariprazine or placebo, and alkaline phosphatase levels decreased slightly in both groups. No cariprazine patient fulfilled Hy's Law criteria [alanine aminotransferase or aspartate aminotransferase $\geq 3 \times$ upper limit of normal (ULN) with concurrent total bilirubin $\geq 2 \times$ ULN and alkaline phosphatase $< 2 \times$ ULN]. The mean prolactin levels decreased in all treatment groups, except for risperidone; decreases were greater for cariprazine-treated women (-26.0) than for cariprazine-treated men (-8.1).

There was a modest dose-related increase in the mean creatine phosphokinase (CPK) level with cariprazine. However, large fluctuations in CPK levels occurred over time as evidenced by large SDs and a relatively high percentage of patients entered the studies with elevated CPK levels. Treatment-emergent CPK levels more than 1000 U/l were similar for placebo (3.5%), overall

cariprazine (4.7%), and risperidone (4.5%) and lower for aripiprazole (2.0%); $\sim 60\%$ of events resolved during the study for patients in all treatment groups. Elevations greater than $1.5 \times$ ULN occurred in patients in all treatment groups (placebo = 14.2%, cariprazine = 22.7%, risperidone = 23.0%, aripiprazole = 18.9%). Most elevations greater than $1.5 \times$ ULN did not resolve during treatment, but data should be interpreted with caution as laboratory tests were not scheduled after the end of treatment. CPK elevations were not associated with altered renal function or renal failure.

Cardiac measures

Overall, no clinically significant changes in pulse or blood pressure were observed in cariprazine-treated patients, with the exception of patients in the 9–12 mg/day dose group, where the mean increase in diastolic blood pressure was 3.4 mmHg and five (6.8%) patients shifted from baseline normotensive values to stage I hypertension. No mean increases were observed in the overall cariprazine group versus the placebo group on ECG parameters; no cariprazine patient had a QTc interval greater than 500 ms (Bazett or Fridericia formula).

Orthostatic hypotension

The incidence of orthostatic hypotension (reduction of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure while changing from a supine position to standing) was similar for placebo (12.3%) and cariprazine (13.4%). No syncopal episodes were reported in the controlled schizophrenia studies.

Extrapyramidal symptoms

A dose-response relationship was observed for the incidence of akathisia and EPS AEs (excluding akathisia and restlessness). Most events of akathisia and EPS were considered mild or moderate in severity; AEs of akathisia that were considered severe occurred in one (4.8%) of 21 placebo-treated patients and four (2.7%) of 149 cariprazine-treated patients (1.5–3 and 9–12 mg/day = one patient each; 4.5–6 mg = two patients). Severe EPS-related AEs (excluding akathisia and restlessness) were reported in one (2.2%) of 45 placebo-treated patients and three (1.3%) of 229 cariprazine-treated patients (4.5–6 mg/day = two patients; 9–12 mg/day = one patient). Rates of discontinuation for EPS TEAEs, including akathisia and restlessness, were less than or equal to 2% among cariprazine-treated patients and no akathisia, restlessness, or EPS SAEs were reported. EPS was assessed by rating scales and TEAEs (Table 5); a greater percentage of cariprazine-treated than placebo-treated patients had treatment-emergent parkinsonism (SAS total score ≤ 3 at baseline and > 3 postbaseline) and akathisia (BARS total score ≤ 2 at baseline and > 2 postbaseline).

During double-blind treatment, the mean duration of akathisia was 24 days for cariprazine-treated and 29 days

Table 4 Safety parameters: change from baseline to the end of the double-blind treatment (safety population)

Parameters	Cariprazine modal daily dose and overall				
	Placebo (n = 584)	1.5–3 mg ^a (n = 539)	4.5–6 mg ^a (n = 575)	9–12 mg (n = 203)	Overall (n = 1317)
Metabolic parameters [mean change (SD)]^b					
Total cholesterol (mg/dl)	2.0 (32.6)	-1.2 (32.2)	-2.7 (31.4)	-5.1 (31.6)	-2.5 (31.7)
Fasting LDL cholesterol (mg/dl)	2.7 (28.3)	-1.8 (26.1)	-1.8 (26.0)	-4.4 (27.4)	-2.2 (26.3)
HDL cholesterol (mg/dl)	-1.3 (10.3)	-0.2 (11.2)	-0.4 (10.5)	-1.8 (10.2)	-0.6 (10.7)
Fasting triglycerides (mg/dl)	2.6 (63.7)	-0.8 (76.7)	-3.9 (67.5)	6.4 (66.5)	-1.1 (71.2)
Fasting glucose (mg/dl)	4.9 (26.8)	2.2 (16.8)	7.6 (22.1)	3.8 (17.4)	4.9 (19.6)
Clinically relevant shifts in lipid levels and glucose [n (%)]					
Total cholesterol, normal/borderline (< 240 mg/dl) to high (> 240 mg/dl)	53/515 (10.3)	34/440 (7.7)	37/514 (7.2)	8/181 (4.4)	79/1135 (7.0)
Fasting LDL cholesterol, normal/borderline (< 160 mg/dl) to high (> 160 mg/dl)	45/457 (9.8)	27/405 (6.7)	27/451 (6.0)	7/155 (4.5)	61/1011 (6.0)
HDL cholesterol, normal (> 40 mg/dl) to low (< 40 mg/dl)	98/412 (23.8)	58/343 (16.9)	72/407 (17.7)	30/164 (18.3)	160/914 (17.5)
Fasting triglycerides, normal/borderline (< 200 mg/dl) to high (> 200 mg/dl)	61/429 (14.2)	46/386 (11.9)	46/424 (10.8)	18/152 (11.8)	110/962 (11.4)
Fasting glucose, normal (< 100 mg/dl) to high (> 126 mg/dl)	27/402 (6.7)	27/365 (7.4)	41/417 (9.8)	4/149 (2.7)	72/931 (7.7)
Fasting glucose, increase ≥ 10 mg/dl	182/517 (35.2)	184/446 (41.3)	254/510 (49.8)	100/199 (50.3)	538/1155 (46.6)
Body weight					
Body weight change [mean (SD)] (kg) ^b	0.3 (3.0)	0.8 (3.0)	1.0 (2.8)	2.0 (3.3)	1.1 (3.0)
≥ 7% increase from baseline (%) ^c	4.7	7.6	7.7	17.2	9.2
≥ 7% decrease from baseline (%) ^c	3.1	1.8	1.1	2.0	1.5
Clinical laboratory parameters [mean change (SD)]^b					
Prolactin (ng/ml)	-9.3 (28.7)	-13.4 (30.2)	-14.1 (37.9)	-9.9 (23.7)	-13.1 (33.0)
Alanine aminotransferase (U/l)	1.0 (18.1)	3.7 (31.0)	6.0 (28.7)	9.4 (24.0)	5.6 (29.0)
Aspartate aminotransferase (U/l)	0.3 (11.1)	1.2 (13.6)	2.5 (15.3)	3.9 (14.3)	2.2 (14.5)
Alkaline phosphatase (U/l)	-1.5 (27.8)	-0.7 (17.4)	-1.6 (14.1)	-2.0 (14.9)	-1.3 (15.6)
Total bilirubin (mg/dl)	0.0 (0.3)	0.0 (0.2)	0.0 (0.3)	-0.0 (0.2)	0.0 (0.3)
Creatine phosphokinase (U/l)	29.0 (401.6)	51.6 (335.4)	73.2 (409.4)	76.3 (320.9)	65.2 (367.9)
Changes in blood pressure and pulse					
Systolic blood pressure [mean (SD)] (mmHg)	0.9 (10.4)	0.6 (9.7)	1.3 (11.0)	2.1 (12.3)	1.2 (10.8)
Diastolic blood pressure [mean (SD)] (mmHg)	0.4 (8.0)	0.2 (7.6)	1.6 (8.3)	3.4 (9.6)	1.3 (8.3)
Pulse [mean (SD)] (bpm)	-0.1 (12.6)	-0.2 (11.1)	1.1 (11.8)	1.5 (12.1)	0.7 (11.6)
Shift from normotensive to stage I hypertension [n (%)] ^d	4/205 (2.0)	2/182 (1.1)	6/213 (2.8)	5/74 (6.8)	13/469 (2.8)
ECG findings [mean change (SD)]^b					
Ventricular heart rate (bpm)	0.5 (15.2)	1.5 (15.1)	4.5 (15.7)	4.6 (14.7)	3.3 (15.3)
QRS interval (ms)	0.5 (7.6)	0.5 (7.5)	0.2 (6.9)	-0.7 (6.7)	0.1 (7.1)
PR interval (ms)	-0.4 (13.5)	-0.6 (14.4)	-1.1 (13.7)	-0.9 (13.1)	-0.9 (13.9)
QT interval (ms)	-2.3 (30.4)	-5.1 (29.3)	-10.1 (30.7)	-10.7 (30.1)	-8.2 (30.2)
QTcB interval (ms)	-1.7 (22.3)	-1.4 (21.8)	0.9 (22.2)	1.3 (20.6)	0.1 (21.8)
QTcF interval (ms)	-1.9 (17.8)	-2.6 (17.2)	-3.0 (17.9)	-3.0 (18.0)	-2.9 (17.6)

ARI, aripiprazole; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RISP, risperidone.

^aIndicates Food and Drug Administration-recommended dose range.

^bMean change from the baseline to the end of double-blind treatment.

^cAt any time during the double-blind treatment.

^dNormotensive = systolic blood pressure < 120 mmHg and diastolic blood pressure 80–89 mmHg, stage I hypertension = systolic blood pressure 140–159 mmHg and diastolic blood pressure 90–99 mmHg.

Table 5 Extrapyramidal symptoms (safety population)

	Cariprazine modal daily dose and overall						
	Placebo (n = 584)	1.5–3 mg ^a (n = 539)	4.5–6 mg ^a (n = 575)	9–12 mg (n = 203)	Overall (n = 1317)	RISP 4 mg/day (n = 140)	ARI 10 mg/day (n = 152)
EPS Rating Scales [mean change (SD)] ^b							
AIMS total score	−0.1 (1.1)	−0.0 (1.0)	−0.0 (1.1)	−0.1 (1.1)	−0.0 (1.1)	−0.0 (1.4)	−0.1 (1.0)
BARS total score	−0.1 (0.9)	0.2 (1.2)	0.2 (1.2)	0.0 (1.4)	0.2 (1.2)	0.1 (1.3)	0.1 (1.2)
SAS total score	−0.2 (1.6)	0.0 (1.6)	0.2 (1.8)	0.2 (2.0)	0.1 (1.8)	−0.1 (1.5)	−0.1 (2.1)
Percentage of patients with treatment-emergent akathisia or parkinsonism ^c							
Akathisia (BARS baseline ≤ 2 and postbaseline > 2)	5.8	14.7	15.8	14.8	15.2	10.1	10.7
Parkinsonism (SAS baseline ≤ 3 and postbaseline > 3)	4.2	8.2	11.2	12.9	10.3	10.1	5.3
Percentage of patients with EPS-related TEAEs ^d							
EPS-related TEAEs (excluding akathisia and restlessness) ^e	7.7	14.8	18.8	20.2	17.4	27.1	5.9
Akathisia	3.6	9.1	12.5	13.8	11.3	8.6	7.2
Restlessness	3.1	3.9	5.7	5.4	4.9	2.9	3.3

AIMS, Abnormal Involuntary Movement Scale; ARI, aripiprazole; BARS, Barnes Akathisia Rating Scale; EPS, extrapyramidal symptoms; RISP, risperidone; SAS, Simpson–Angus Scale; TEAE, treatment-emergent adverse event.

^aIndicates Food and Drug Administration-recommended dose range.

^bMean change from the baseline to the end of double-blind treatment.

^cAt any time during the double-blind treatment.

^dEPS-related TEAEs include akathisia, bradykinesia, cogwheel rigidity, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, musculoskeletal stiffness, oculogyric crisis, oromandibular dystonia, parkinsonism, restlessness, salivary hypersecretion, tardive dyskinesia, tongue spasm, tremor, trismus, and torticollis.

for placebo-treated patients; the peak onset of akathisia generally occurred within 2–3 weeks of initiation of cariprazine treatment. A greater percentage of cariprazine-treated patients (21.9%) than placebo-treated patients (8.7%) received EPS medication. In accordance with the constituent study protocols, investigators used beta-blocking agents (e.g. propranolol) and antiparkinson medications (e.g. benzotropine and trihexyphenidyl) to manage symptoms of akathisia and EPS. Among active-treatment groups, the use of any EPS medication was the highest for risperidone (39/140, 27.9%) and the lowest for aripiprazole (18/152, 11.8%); EPS medications were used by 21.9% (288/1317) of cariprazine-treated patients. A lower rate of medication use for EPS-related AEs (excluding akathisia and restlessness) was observed in patients with mild AEs (96/158; 60.8%) than in patients with moderate (58/68; 85.3%) or severe (3/3; 100%) AEs. Antiparkinson drugs were used to control EPS in 25.0% (35/140) of risperidone-treated patients, 17.3% (228/1317) of cariprazine-treated patients, and 7.9% (12/152) of aripiprazole-treated patients.

Suicidal behavior

Per C-SSRS assessment, suicidal ideation was reported in 4.7% of placebo-treated and 3.6% of cariprazine-treated patients, with the majority of instances in the least severe category. No suicidal behavior was recorded by the C-SSRS in the placebo-treatment or the cariprazine-treatment groups, including patients who had akathisia or restlessness. The incidence of suicidality TEAEs for cariprazine (0.4%) was low and similar to placebo (0.2%); suicidal ideation was reported as a TEAE in one placebo-treated patient and four cariprazine-treated patients.

There were two suicidality SAEs in the cariprazine group, including one completed suicide that was not considered to be treatment related.

Ophthalmologic parameters

Change from baseline in ophthalmologic parameters is presented in Supplementary Table 4 (Supplemental digital content 4, <http://links.lww.com/ICP/A31>). The most commonly reported ocular TEAE was blurred vision (placebo = 0.3%; cariprazine = 1.5%; risperidone = 2.1%, aripiprazole = 1.3%); all other ocular AEs were reported in less than 1% of patients in any group. No AEs of cataract or lens opacity were reported.

Discussion

In this pooled analysis of safety data from 4 short-term randomized, controlled studies in adult patients with acute exacerbation of schizophrenia, cariprazine at doses up to 12 mg/day was generally safe and well tolerated; patients receiving doses above 6 mg/day showed higher likelihood for AEs, EPS, akathisia, and blood pressure changes. The most frequent TEAEs in cariprazine overall (reported in ≥ 5% of cariprazine-treated patients and at least twice the rate of placebo) were EPS reported by grouped terms and akathisia. A dose–response relationship was observed for akathisia and EPS in cariprazine-treated patients. No cariprazine dose response was observed for SAEs and discontinuations because of AEs. The most commonly reported SAEs and discontinuations because of AEs were associated with worsening of schizophrenia or psychotic symptoms.

Of the distinct TEAEs associated with atypical antipsychotics, those that increase the risk for cardiometabolic disease are among the most important (Hennekens, 2007). Cardiovascular disease is the second leading cause of premature death for patients with schizophrenia, surpassed only by suicide (Goff *et al.*, 2005). Compared with the general population, the prevalence of several modifiable risk factors associated with cardiovascular disease, including obesity, smoking, diabetes, and hypertension, is high in patients with schizophrenia (Newcomer, 2007). The propensity for medication-induced metabolic and weight TEAEs in this at-risk population varies among atypical antipsychotics (Newcomer, 2007; Riordan *et al.*, 2011). For example, the incidence of clinically significant weight gain ($\geq 7\%$) associated with atypical antipsychotics has been reported to range from 8.1% for aripiprazole (Abilify, 2014) to 22.2% for olanzapine (Zyprexa, 2011).

As such, the cardiometabolic profile of cariprazine is important to patients with schizophrenia. In our analyses, the mean changes and clinically relevant shifts in lipid parameters and fasting glucose were generally similar for placebo and cariprazine, suggesting that short-term cariprazine exposure had minimal effects on these parameters; glucose increase of more than 10 dl was greater in cariprazine than in the other treatment groups. No QTc values greater than 500 ms were observed; overall, there were no clinically significant changes in pulse or blood pressure in cariprazine-treated patients, however dose-related increases in blood pressure were observed. The mean body weight increase was greater in all active-treatment groups than in the placebo group. For cariprazine, the mean increase in body weight was lower in the lower-dose groups than in the 9–12 mg group. Weight increase for cariprazine in the approved dose range was similar to aripiprazole, and in the 9–12 mg/day group, it was similar to risperidone. In the approved dose range, weight gain of 7% or more occurred in $\sim 8\%$ of cariprazine patients, which was less than that in the cariprazine 9–12 mg (17.2%) and risperidone (16.7%) groups, and similar to the aripiprazole (6.0%) group. Collectively, these values suggest that cariprazine in the approved dose range is on the lower end of the atypical antipsychotic weight gain hierarchy.

Despite improved safety profiles for atypical antipsychotics versus first-generation agents, EPS and akathisia are consistently noted in the literature (Caroff *et al.*, 2002; Kane *et al.*, 2009; Kumar and Sachdev, 2009; Kane *et al.*, 2010; Poyurovsky, 2010). Analyses from the CATIE study found no significant differences in the incidence of EPS for some second-generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone) relative to each other or to perphenazine, a mid-potency first-generation agent (Miller *et al.*, 2008). In the current analyses, akathisia was among the most frequent TEAEs for cariprazine and both active-comparator groups. A dose–response relationship was observed for cariprazine,

with a lower risk for akathisia and EPS (grouped terms) in the approved dose range. The incidence of akathisia TEAEs in the lowest cariprazine-dose group (9.1%) was slightly higher than aripiprazole (7.2%) and risperidone (8.6%), and EPS across the cariprazine-dose groups (14.8–20.2%) was lower than risperidone (27.1%). At doses up to 6 mg/day, the rates of akathisia with cariprazine were similar to some antipsychotic agents marketed in the USA (e.g. lurasidone = 6–22%, asenapine = 4–11%) (Latuda, 2013; Saphris, 2014) and EPS was lower than others (risperidone and olanzapine = 20–30%) (Zyprexa, 2011; Risperdal, 2014).

In clinical practice, akathisia is a routinely managed treatment-induced symptom (Lehman *et al.*, 2004). For cariprazine, most EPS-related TEAEs were considered mild or moderate and resulted in relatively few discontinuations. Medication use to manage EPS generally correlated with symptom severity. In short-term aripiprazole schizophrenia trials, the rates of akathisia that were considered severe ($< 10\%$) or led to study discontinuation (0.3%) (Kane *et al.*, 2010) were consistent with this cariprazine analysis. Collectively, these results suggest that akathisia and EPS were manageable for most cariprazine-treated patients.

Another noteworthy safety consideration for cariprazine-treated patients was the absence of increase in the prolactin level, which is important since hyperprolactinemia increases the risk of sexual function side effects (Henderson and Doraiswamy, 2008). In addition, although some atypical antipsychotics produce undesirable sedation and somnolence (Kane and Sharif, 2008), these effects for overall cariprazine were similar to placebo, less than risperidone, and slightly greater than (sedation) or equal to (somnolence) aripiprazole. The rates of sedation were lower in the cariprazine approved dose range than in the 9–12 mg/day group. A modest dose-related increase in the mean CPK level, which did not result in altered renal function, was observed in cariprazine-treated patients; large SDs suggest considerable fluctuations in CPK level over time, although cariprazine may cause transient increases that normalize with continued treatment. Cariprazine was not associated with an increased risk of suicidality, an essential finding considering that individuals with schizophrenia compared with the general population have a 12-fold higher risk of dying from suicide (Saha *et al.*, 2007). Ophthalmologic testing indicated no evidence of retinal toxicity or clinically significant lenticular changes.

These analyses were subject to the limitations inherent in post-hoc analyses. Safety parameters were analyzed by descriptive statistics; no inferential statistical analyses were carried out. A tolerability bias in favor of patients in the higher modal daily dose groups may exist as patients with tolerability issues at lower doses may have been more likely to discontinue the study and less likely to increase their

dosage. Short treatment duration and the inclusion of active comparators in only two studies are additional limitations.

Conclusion

In this pooled analysis of four short-term clinical trials, cariprazine at doses of 1.5–12 mg/day was generally safe and well tolerated. Patients in the modal dose group above 6 mg/day showed a higher likelihood for AEs, EPS, akathisia, weight increases, and blood pressure changes, as well as higher rates of CPK and transaminase elevations. This observation, together with the beneficial effects observed on efficacy, resulted in the FDA approving a recommended dose range for schizophrenia of 1.5–6 mg/day. Within the FDA-approved dose range, cariprazine was a generally safe and well-tolerated treatment option for patients with schizophrenia.

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Conflicts of interest

Willie Earley, Suresh Durgam, and Kaifeng Lu are employees of Allergan. István Laszlovszky is an employee of Gedeon Richter Plc. Marc Debelle is a former employee of Gedeon Richter Plc. John M. Kane serves or has served as a consultant for Alkermes Plc.; Bristol-Myers Squibb Company; Eli Lilly and Company; Forest Laboratories Inc.; FORUM Pharmaceuticals; Genentech Inc., a Member of the Roche Group; H. Lundbeck A/S; Hoffmann-La Roche Inc.; Intra-Cellular Therapies Inc.; Janssen Pharmaceuticals Inc.; Johnson & Johnson Services Inc.; Otsuka Pharmaceutical Co. Ltd; Pierre Fabre; Reviva Pharmaceuticals Inc.; and Teva. He also serves or has served on speaker bureaus for Bristol-Myers Squibb Company; Genentech Inc., a member of the Roche Group; Janssen Pharmaceuticals Inc.; and Otsuka Pharmaceutical Co. Ltd. He owns or has owned shares in LB Pharmaceuticals; MedAvante Inc.; and Vanguard Research Group.

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