Data Supplement for Durgam et al., An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. Am J Psychiatry (doi: 10.1176/appi.ajp.2015.15020164)

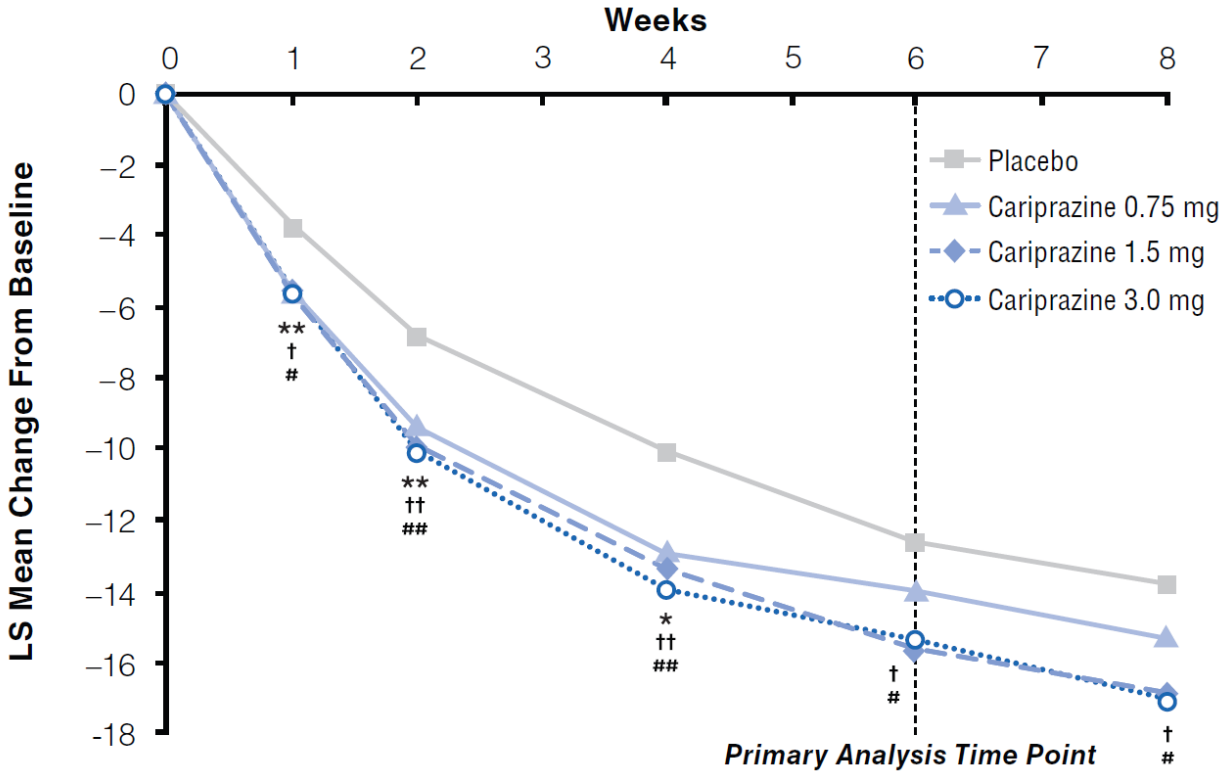
TABLE S1. Blinding, Randomization, and Key Criteria for Study Exclusion

Blinding and Randomization Method
• Investigators and patients were blinded to assigned treatment; unblinding disqualified a patient from further participation
• Patients were sequentially assigned a unique identification number at the screening visit
• An interactive Web-based response system was used to monitor enrollment and investigational product allocation if the patient met randomization criteria
• The study center contacted the response system, which randomized the patient to the appropriate treatment arm (placebo, cariprazine 0.75 mg/d, cariprazine 1.5 mg/d, or cariprazine 3.0 mg/d) and determined the investigational product number to be assigned to the patient based on the randomization
Key Exclusion Criteria
• Young Mania Rating Scale total score>10
• Principal DSM-IV-TR–based axis I diagnosis other than bipolar disorder or any axis I disorder other than bipolar disorder that was the primary focus of treatment within 6 months of study; secondary diagnoses of comorbid generalized anxiety disorder, social anxiety disorder, or specific phobias were acceptable
• Four or more episodes of a mood disturbance (i.e. depression, mania, hypomania, or mixed state) within 12 months before screening
• History of meeting DSM-IV-TR criteria for various disorders including: cognitive disorders, psychotic disorders (e.g. schizophrenia, schizoaffective disorder), mental retardation, axis II disorder (e.g. borderline or antisocial personality disorder) severe enough to interfere with study participation
• Alcohol or substance abuse/dependence within 6 months; positive result on blood alcohol test or urine drug screen for methadone, phencyclidine, amphetamines, or cocaine
• History of intolerance or hypersensitivity to other drugs of the same class as cariprazine or to rescue medications
• Nonresponse to≥2 treatment trials of fluoxetine/olanzapine combination, quetiapine, lithium monotherapy, or mood stabilizer/antidepressant combination during the current depressive episode
• Imminent risk of injuring self or others; suicide risk (i.e. suicide attempt within the past year; significant risk as judged by the Investigator, based on the psychiatric interview, or Columbia-Suicide Severity Rating Scale information; HAM-D item 3 score≥3; MADRS item 10 score≥4)
• Treatment-related criteria including electroconvulsive therapy, treatment with a depot neuroleptic within 1 treatment cycle before study, use of clozapine with 2 years of study, prior participation in any investigational study of cariprazine, central nervous system treatment (i.e. vagus nerve stimulation, transcranial magnetic stimulation, or any experimental treatment) within 6 months, initiation or termination of psychotherapy for depression (within 3 months) or phototherapy (within 2 weeks)
• Requiring concomitant treatment with any of the prohibited medications, supplements, or herbal products, including any psychotropic drug or any drug with psychotropic activity or with a potentially psychotropic component (exceptions: eszopiclone, zolpidem, zolpidem extended-release, zopiclone, chloral hydrate, zaleplon [insomnia]; lorazepam (or oxazepam or diazepam in countries where lorazepam is not readily available); diphenhydramine, benztropine or equivalent, or propranolol for extrapyramidal symptoms
• Any concurrent medical condition that, in the judgment of the Investigator, might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the patient's well-being

(Continued)

• Medical criteria: pregnancy, not≥2 years postmenopausal, surgically sterile, homosexual female, or practicing a reliable method of contraception, clinically significant cardiovascular disease, a risk of seizure, hypo- or hyperthyroidism (unless stabilized on appropriate pharmacotherapy), psychiatric symptoms possibly secondary to any other general medical condition, any condition that would be expected to affect drug absorption, history of cataracts, known human immunodeficiency virus infection, positive hepatitis C antibody (may be allowed under certain conditions), positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M, screening liver enzyme test (aspartate aminotransferase and/or alanine aminotransferase) results>2×upper limit of normal, history of tardive dyskinesia, serotonin syndrome, or neuroleptic malignant syndrome
• Treatment with any investigational drug during the study and within the 6 months (or at least 5 half-lives, whichever is longer) before screening
HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

FIGURE S1. MADRS Total Score Least Squares Mean Change From Baseline to Week 8 for Study Completers (mixed-effects model for repeated measures, completer population)



*p<0.05 CAR 0.75 vs placebo; **p<0.01 CAR 0.75 vs placebo;
†p<0.05 CAR 1.5 vs placebo; ††p<0.01 CAR 1.5 vs placebo;
#p<0.05 CAR 3.0 vs placebo; ##p<0.01 CAR 3.0 vs placebo.
p Values were not adjusted for multiple comparisons.