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Efficacy and Safety of Adjunctive Armodafinil in Adults With Major Depressive Episodes Associated With Bipolar I Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

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ABSTRACT

Objective: To examine the efficacy and safety of adjunctive armodafinil for major depressive episodes associated with bipolar I disorder.

Method: Adults meeting *DSM-IV-TR* criteria for bipolar I disorder and currently experiencing a major depressive episode while taking at least 4 weeks of conventional maintenance medication were enrolled in a placebo-controlled evaluation of adjunctive armodafinil 150 or 200 mg (conducted January 2010–March 2012). The primary efficacy measure was change from baseline to week 8 on the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C_{30}) total score in the 150-mg armodafinil group versus placebo.

Results: Of 786 patients screened, 433 were randomized (placebo, n = 199; armodafinil 150 mg, n = 201; armodafinil 200 mg, n = 33). The 200-mg armodafinil group was discontinued by protocol amendment due to lower than expected patient enrollment. For the 150-mg armodafinil group versus placebo, there was a significantly greater decrease in least squares mean (standard error of mean [SEM]) IDS-C_{30} total score at week 8 (–21.7 [1.1] vs –17.9 [1.1]; $P = .0097$; Cohen d therapeutic effect size = 0.28). The proportion of IDS-C_{30} responders (≥ 50% decrease from baseline) was significantly higher for the 150-mg armodafinil group versus placebo at final visit (46% [91/197] vs 34% [67/196]; $P = .0147$). The proportion of IDS-C_{30} remitters (total score ≤ 11) was 21% (42/197) for armodafinil 150 mg versus 17% (34/196) for placebo ($P = .3343$) at final visit. Adverse events (AEs) observed in > 5% of either the armodafinil 150 mg or placebo groups and more frequently with 150 mg armodafinil were diarrhea (9% [17/198] vs 7% [13/199]), and nausea (6% [11/198] vs 5% [9/199]), respectively. In the 200-mg armodafinil group, there were 2 serious AEs (n = 1, hepatic failure leading to death; n = 1, acute hepatitis). The death was not considered related to study treatment.

Conclusions: Adjunctive armodafinil 150 mg significantly improved symptoms of major depressive episodes associated with bipolar I disorder versus placebo and was generally well tolerated.

Trial Registration: ClinicalTrials.gov identifier: NCT01072929

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Bipolar disorders are disabling and lifelong mental health disorders associated with early symptom onset, variable disease severity, suicide, and high rates of co-occurring mental illnesses.[1,2] Depressive symptoms, which occur 3 times more frequently than mood elevation symptoms among symptomatic patients with bipolar I disorder,[3] contribute to the majority of the disability.[4–6] Given that the lifetime prevalence of bipolar I and II disorders combined has been estimated at 2.5% for adults in the United States,[7] there is great need for the development of clinical treatments for bipolar depression.

Although numerous agents are approved by the US Food and Drug Administration (FDA) for mania associated with bipolar disorder,[8] only 3 treatments are currently FDA approved specifically for depressive episodes associated with bipolar disorder—quetiapine monotherapy,[9–13] olanzapine plus fluoxetine combination,[14] and lurasidone as monotherapy or as adjunctive therapy with lithium or valproate.[15,16]

Armodafinil (*R*-modafinil) is currently approved in the United States for the treatment of excessive sleepiness associated with shift-work disorder and narcolepsy and as an adjunct to continuous positive airway pressure in patients with obstructive sleep apnea.[17–21] A phase 2 proof-of-concept study found that armodafinil as adjunctive therapy significantly improved symptoms of a major depressive episode associated with bipolar I disorder compared with placebo as measured by the 30-item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C_{30}) total score.[22] The objective of the current phase 3 study was to evaluate the efficacy and safety of armodafinil as adjunctive therapy to maintenance medications for the treatment of major depressive episodes associated with bipolar I disorder in adults.

METHOD

Study Design

This phase 3, 8-week, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose multicenter study evaluated the safety and efficacy of armodafinil 150 mg/d in adults with bipolar I disorder who were currently experiencing a major depressive episode while being treated with maintenance medication. The study (ClinicalTrials.gov identifier: NCT01072929) was conducted at 70 centers in 10 countries from January 2010–March 2012. It was conducted in accordance with International Conference on Harmonization good clinical practice guidelines as currently amended (http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html), and the study protocol was approved by the independent ethics committee or institutional review board at each

Clinical Points

- Treatment options for bipolar depression are currently limited, and there is a need for adjunctive therapies.
- Adjunctive armodafinil significantly improved symptoms of bipolar depression and was generally well tolerated, although the treatment effect size was modest.
- The clinical significance of investigational armodafinil for bipolar depression in the adjunctive treatment setting remains to be determined.

participating center. Written informed consent, including an explanation of treatments and potential side effects, was obtained from each patient prior to screening. Patients were free to withdraw at any time.

Selection of Subjects

To participate in this study, patients 18–65 years old underwent a 1- to 6-week screening period during which they were required to have a major depressive episode associated with bipolar I disorder according to the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-CT).[23] Investigators established via medical record documentation, or by history provided by the patient and at least 1 other reliable informant, that the patient had at least 1 previous manic or mixed episode resulting in functional impairment that was treated with maintenance therapy (mood-stabilizing or antipsychotic medication) and no more than 6 mood episodes in the year prior to study entry. The current major depressive episode must have started no less than 2 weeks and no more than 12 months prior to the screening visit. The date of onset of the patient's current major depressive episode must have started at least 8 weeks after resolution of any previous mood episode. Maintenance medications, which must have been maintained at stable dosages for at least 4 weeks prior to the onset of the depressive episode and during screening, included lithium, valproic acid, aripiprazole, olanzapine, lamotrigine, risperidone, or ziprasidone (ziprasidone only if taken in combination with lithium or valproic acid). For patients taking 2 maintenance medications, at least 1 of the 2 drugs must have been lithium or valproic acid. Dose adjustments could be made to maintain therapeutic levels of lithium or valproic acid. In addition, patients were required to have a total score of ≥ 13 on the 16-item Quick Inventory of Depressive Symptomatology–Clinician-Rated (QIDS-C_{16}) scale[24] and a total Young Mania Rating Scale (YMRS)[25] score of ≤ 10; a YMRS score of 0 or 1 on items 1 (elevated mood), 2 (increased motor activity-energy), and 3 (sexual interest) at screening and the baseline visit; and a Hamilton Anxiety Rating Scale (HARS)[26] total score of ≤ 16. Any patient with a total YMRS score of ≥ 15 or who met the *DSM-IV* criteria for a manic or mixed episode was withdrawn from the study.

Patients were excluded if they had any Axis I disorder, apart from bipolar I disorder, that was the primary focus of treatment within 6 months prior to screening, or any Axis II disorder that could interfere with the conduct of the study (determined at the discretion of the clinical investigator). Patients with psychotic symptoms or psychosis within 4 weeks prior to screening were also excluded. Additional exclusion criteria included current active suicidal ideation, risk for self-harm, or history of significant suicidal ideation or suicide attempt that caused present concern; history of alcohol or substance abuse or dependence (exclusive of nicotine) within 3 months of screening; previous treatment with modafinil or armodafinil; and history of any cutaneous drug reaction, any clinically significant hypersensitivity reaction, or multiple clinically relevant allergies.

Interventions

Eligible patients were randomly assigned to receive treatment with armodafinil 150 or 200 mg/d or matching placebo in a 1:1:1 ratio and in a 1:1 ratio after the 200-mg group was discontinued early by protocol amendment. Randomization was stratified on the basis of maintenance medication (categorized as lithium, anticonvulsants, or antipsychotics) and region of the world. Patients taking > 1 maintenance medication were classified according to the medication class that was considered therapeutic, or if both were considered therapeutic, the class they had been taking for the longest period of time. On day 1, patients received armodafinil or matching placebo at 50 mg/d, which was titrated by 50-mg increments on days 2, 4, and 6 (4 tablets/d administered orally in the morning) up to either 150 or 200 mg/d.

Efficacy Assessments

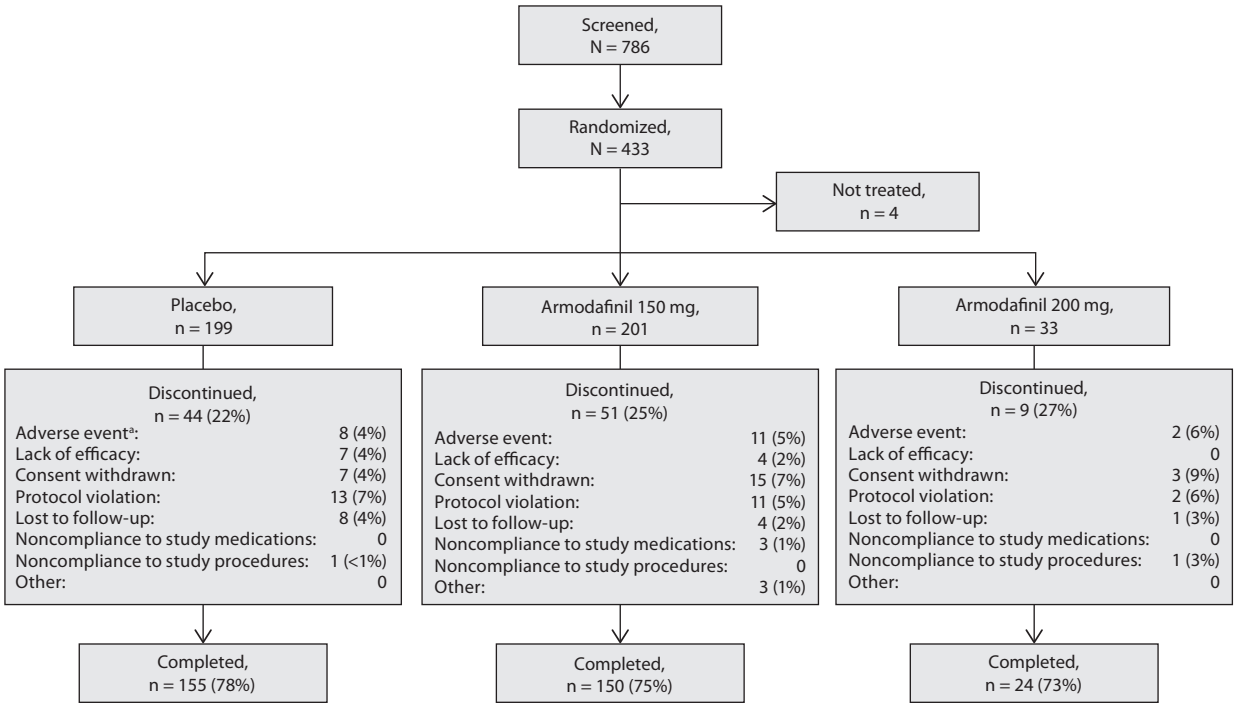
The primary efficacy assessment was change from baseline to week 8 in IDS-C_{30} total score, which assesses the severity of depressive symptoms based on *DSM-IV* criteria for major depressive episodes.[27] The IDS-C_{30} total score was analyzed using a mixed-model repeated-measures (MMRM) analysis.

Protocol-specified secondary efficacy assessments included IDS-C_{30} score at weeks 1, 2, 4, 6, 7, and 8 or at final visit (last observation carried forward [LOCF]); proportion of responders (≥ 50% reduction in IDS-C_{30} total score); proportion of remitters (total IDS-C_{30} score ≤ 11); change from baseline in QIDS-C_{16} score; change from baseline in Clinical Global Impressions-Severity of Illness scale (CGI-S)[24] score; and proportion of CGI-S responders (≥ 2-category improvement in severity from baseline), all at weeks 1, 2, 4, 6, 7, and 8 or at final visit. In addition, the Global Assessment of Functioning (GAF)[28] scale was assessed at weeks 4 and 8 or at final visit.

Safety Assessments

Safety assessments included adverse events (AEs), clinical laboratory tests, vital signs, electrocardiogram (ECG), and physical examination that included skin examination and body weight measurement. Skin rash, hypersensitivity reactions, emergent suicidal ideation or suicide attempt, and psychosis were prospectively considered AEs of special interest. All AEs were recorded at all patient visits along with vital signs and concomitant medication usage. The ECG was performed at screening, baseline, and final visits. Additional safety assessments included YMRS, Columbia-Suicide Severity Rating Scale-Since Last Visit (C-SSRS-SLV),[29] the HARS,

Figure 1. Patient Disposition



[a]One placebo patient discontinued after randomization but before receiving treatment.

and Insomnia Severity Index (ISI),[30] administered at weeks 1, 2, 4, 6, 7, and 8, or last postbaseline observation.

Statistical Analysis

Patients with ≥ 1 postbaseline IDS-C_{30} assessment were analyzed for efficacy, and patients receiving ≥ 1 dose of study drug were analyzed for safety. The primary outcome measure, IDS-C_{30} total score, was analyzed using MMRM, with change from baseline to each scheduled visit in IDS-C_{30} total score as the dependent variable; visit, treatment group, treatment-by-visit, concurrent maintenance therapy, and region of the world (4 regions in order to include countries with similar clinical practices) as fixed factors; and patient as a random factor. An unstructured covariance matrix was used for the within-patient correlation. The primary statistical comparison was between the 150-mg/d armodafinil group and the placebo group at week 8. All secondary continuous efficacy variables were analyzed using analysis of variance (ANOVA), with treatment group, region of the world, and concurrent maintenance therapy as factors. Data for the final visit were derived using LOCF. All categorical secondary efficacy variables were analyzed using a Cochran-Mantel-Haenszel test, stratified by concurrent maintenance therapy and region of the world (as previously described).

RESULTS

Disposition and Demographics

Of the 786 patients screened, 433 were randomized (Figure 1). The safety analysis data set included 429 patients (placebo, n = 199; armodafinil 150 mg, n = 201; armodafinil 200 mg, n = 32) who received at least 1 dose of study medication, and, of these, 424 had ≥ 1 postbaseline assessment and were analyzed for efficacy in the full analysis data set (placebo, n = 196; armodafinil 150 mg, n = 197; armodafinil 200 mg, n = 31). Four percent (8/199) of the placebo group, 5% (11/201) of the 150-mg armodafinil group, and 6% (2/33) of the 200-mg armodafinil group withdrew due to adverse events.

Demographic characteristics were generally similar between the 3 groups (Table 1). The mean ± SD time since the current major depressive episode started was comparable between the placebo (14 ± 11 weeks) and the 150-mg armodafinil groups (13 ± 9 weeks). A post hoc analysis was conducted to more accurately describe the concomitant maintenance therapies that patients were taking at randomization (Supplementary eTable 1). The percentages of patients taking 1 maintenance medication (placebo, 85% [169/199]; armodafinil 150 mg, 87% [174/201]; armodafinil 200 mg, 91% [30/33]) or 2 maintenance medications (placebo, 14% [28/199]; armodafinil 150 mg, 13% [27/201]; armodafinil 200 mg, 9% [3/33]) were generally comparable in each group. In addition, 2 patients in the placebo group were taking 3 maintenance medications, of which aripiprazole was stopped prior to randomization. The most frequently taken medication used as a single agent was valproic acid. The total number of different maintenance medication combinations that the randomized patients were taking was 44 (19 for placebo, 17 for armodafinil 150 mg, and 8 for armodafinil 200 mg).

Efficacy

In patients receiving armodafinil 150 mg/d, there was greater improvement in symptoms of depressive episodes associated with bipolar I disorder compared with placebo,

indicated by a significantly greater decrease in the primary outcome measure, least squares (LS) mean (standard error of mean [SEM]) IDS-C_{30} total score at week 8 (–21.7 [1.1] vs –17.9 [1.1]; 95% CI, –6.58 to –0.92; $P = .0097$ [MMRM]). The Cohen *d* therapeutic effect size, determined by post hoc analysis, was 0.28 for armodafinil 150 mg. Mean IDS-C_{30} scores by visit (ANOVA) are presented in Figure 2. Significant improvements in the 150-mg armodafinil group were observed compared with placebo at weeks 7 (LS mean [SEM] changes, –19.5 [1.4] vs –16.5 [1.3]; $P = .0402$) and 8 (–21.2 [1.4] vs –17.5 [1.3]; $P = .0092$).

The proportion of IDS-C_{30} responders was significantly greater in the 150-mg armodafinil group compared with placebo, respectively, at week 8 (55% [83/150] vs 39% [61/155], $P = .0084$) and final visit (46% [91/197] vs 34% [67/196], $P = .0147$). Numerically greater percentages of patients receiving armodafinil 150 mg/d achieved remission compared with placebo according to the IDS-C_{30} at week 8 (28% [42/150] vs 22% [34/155], $P = .2766$) and final visit (21% [42/197] vs 17% [34/196], $P = .3343$), but the differences were not statistically significant.

Patients treated with armodafinil 150 mg showed significantly better response as measured by LS mean (SEM) QIDS-C_{16} total scores at week 8 (–8.8 [0.5] vs –6.9 [0.5], $P = .0011$) and final visit (–7.2 [0.5] vs –5.8 [0.5], $P = .0096$) compared with placebo. The percentage of CGI-S responders was not significantly different between armodafinil 150 mg and placebo over time. At final visit, 46% (91/197) of patients in the 150-mg armodafinil group and 39% (77/196) of patients in the placebo group were responders according to the CGI-S ($P = .1636$). The LS mean (SEM) change in GAF score was significantly greater for the 150-mg armodafinil group compared with placebo at week 8 (14.1 [1.5] vs 9.9 [1.4]; $P = .0067$) but not at final visit (11.6 [1.2] vs 9.0 [1.2]; $P = .0556$).

The 200-mg armodafinil group was too small for statistical comparisons to be made. Patients receiving armodafinil 200 mg demonstrated improvement in IDS-C_{30} scores at week 8 (mean [SD] change, –17.0 [14.6]). The proportion of IDS-C_{30} responders was 42% (10/24) at week 8 and 39% (12/31) at final visit, and the proportion of IDS-C_{30} remitters was 17% (4/24) and 13% (4/31) for week 8 and final visit, respectively. Mean changes in QIDS-16 and CGI-S at final visit in the 200-mg group were numerically similar to placebo. Mean (SD) change in GAF score was 12.2 (14.11) at final visit.

Table 1. Patient Demographics, Bipolar Illness History, and Efficacy and Safety Measures at Baseline (randomized patients)

Variable	Placebo (n = 199)	Armodafinil 150 mg (n = 201)	Armodafinil 200 mg (n = 33)
Patient demographics			
Age, mean (SD), y	43 (10)	44 (11)	45 (12)
BMI, mean (SD)	30 (7)	30 (7)	31 (7)
Male, n (%)	70 (35)	68 (34)	7 (21)
Race, n (%)			
White	163 (82)	179 (89)	27 (82)
Black	29 (15)	17 (8)	4 (12)
Other	7 (4)	5 (2)	2 (6)
Bipolar illness history			
Years since first manic or mixed episode, mean (SD)	12 (10)	13 (11)	17 (12)
Years since first depressive episode, mean (SD)	14 (10)	15 (12)	20 (12)
Weeks since start of current depressive episode, mean (SD)	14 (11)	13 (9)	15 (10)
Patients ever hospitalized for bipolar depression, n (%)	142 (71)	129 (64)	15 (45)
Efficacy assessments			
IDS-C_{30} total score, mean (SD)	43.7 (6.9)	43.1 (7.1)	42.4 (6.4)
GAF total score, mean (SD)	51.9 (6.9)	51.9 (6.7)	51.6 (6.2)
CGI-S total score, mean (SD)	4.6 (0.5)	4.7 (0.6)	4.5 (0.6)
Safety assessments			
YMRS total score, mean (SD)	3.8 (2.5)	3.6 (2.1)	4.4 (1.9)
HARS total score, mean (SD)	12.6 (2.7)	12.8 (3.3)	12.6 (2.6)
C-SSRS-SLV, n (%)			
Patients with history of suicide attempt	34 (17)	32 (16)	6 (18)
Patients with history of nonspecific active suicidal thoughts	32 (16)	31 (15)	8 (24)

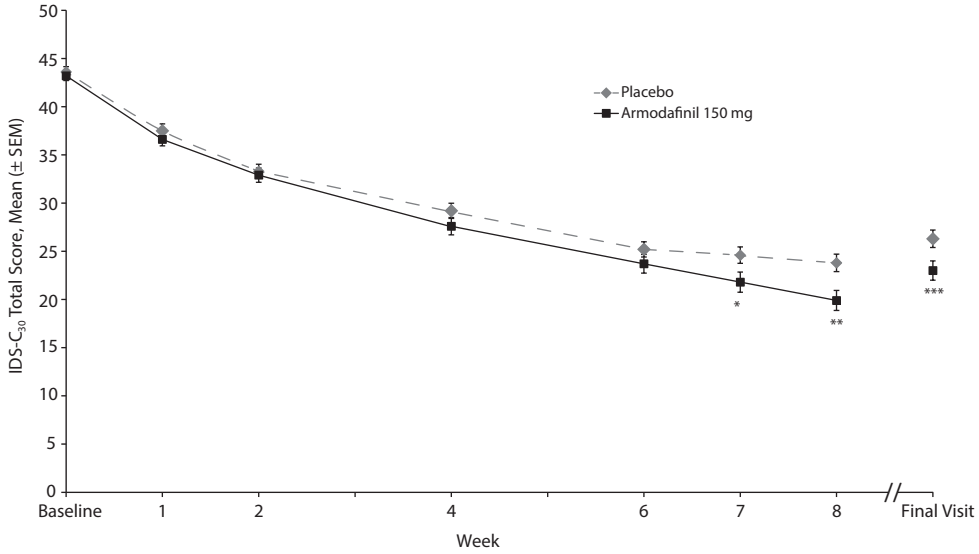
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, C-SSRS-SLV = Columbia-Suicide Severity Rating Scale-Since Last Visit, GAF = Global Assessment of Functioning, HARS = Hamilton Anxiety Rating Scale, IDS-C_{30} = 30-item Inventory of Depressive Symptomatology-Clinician Rated, YMRS = Young Mania Rating Scale.

Safety

Adverse events observed in > 5% of either the 150-mg armodafinil or placebo groups and more frequently in the 150-mg armodafinil group were diarrhea (9% [17/198] vs 7% [13/199]), and nausea (6% [11/198] vs 5% [9/199]), respectively. Adverse events observed in at least 5% of patients in any treatment group are shown in Table 2. Anxiety was the AE with the greatest percent difference between the 150-mg armodafinil group and placebo (4% [7/198] vs 0%, respectively). Adverse events designated as being of special interest (skin rash, hypersensitivity reactions, emergent suicidal ideation or suicide attempt, and psychosis) were reported in 4% (7/198) of patients in the 150-mg armodafinil group and 2% (4/199) of patients in the placebo group; 6 patients had suicidal ideation or suicide attempt (4 patients in the 150-mg armodafinil group, 1 of whom withdrew from the study as a result, and 2 patients in the placebo group), and 2 patients had psychotic disorder (both in the 150-mg armodafinil group). One additional patient in the placebo group was reported by the investigator to have depression as an AE of special interest. Adverse events of special interest related to skin rash were experienced by 1 patient each (drug eruption and pruritic rash in the 150-mg armodafinil group and contact dermatitis in the placebo group).

Serious adverse events occurred in 2% (3/198) of 150-mg armodafinil patients (n = 1 irritability, n = 2 psychotic disorder, n = 2 suicidal ideation, n = 1 aggression, n = 1 depressive symptom) and 3% (5/199) of placebo patients (n = 1 chest pain, n = 2 intentional overdose, n = 3 depression, n = 1 suicide attempt). In the safety analysis set, 6% (11/198) of the

Figure 2. Mean IDS-C_{30} Total Scores Over Time (full analysis set, LOCF)[a]



[a]Analysis of variance, with treatment, concurrent maintenance therapy, and region of the world as factors. *P* values are for week 7, week 8, and final visit change for 150-mg armodafinil versus placebo, respectively.
*$P = .0402$.
**$P = .0092$.
***$P = .0364$.
Abbreviations: IDS-C_{30} = 30-item Inventory of Depressive Symptomatology-Clinician Rated, LOCF = last observation carried forward, SEM = standard error of mean.

Table 2. Adverse Events Occurring in ≥ 5% of Patients in Any Treatment Group (safety analysis set)[a]

Adverse Event, n (%)	Placebo (n = 199)	Armodafinil 150 mg (n = 198)	Armodafinil 200 mg (n = 32)
At least 1 adverse event	91 (46)	95 (48)	23 (72)
Headache	20 (10)	19 (10)	7 (22)
Diarrhea	13 (7)	17 (9)	2 (6)
Nausea	9 (5)	11 (6)	3 (9)
Dry mouth	4 (2)	9 (5)	1 (3)
Insomnia	8 (4)	8 (4)	4 (13)
Feeling jittery	1 (< 1)	1 (< 1)	2 (6)
Migraine	1 (< 1)	0 (0)	2 (6)

[a]Adverse events are presented in order of decreasing frequency for the 150-mg armodafinil group.

150-mg armodafinil group and 4% (7/199) in the placebo group withdrew from the study due to adverse events. The 3 most frequent AEs leading to withdrawal were mania (armodafinil 150 mg, 1% [2/198]; placebo, 1% [2/199]), nausea (armodafinil 150 mg, < 1% [1/198]; placebo, 1% [2/199]), and depression (placebo, 2% [3/199]). All other adverse events leading to withdrawal occurred in only 1 patient each.

For the 200-mg armodafinil group, the 3 most common AEs were headache (22% [7/32]), insomnia (13% [4/32]), and nausea (9% [3/32]). No patients in the 200-mg group reported AEs of special interest. Serious adverse events occurred in 6% (2/32) of 200-mg armodafinil patients (n = 1 acute hepatitis, n = 1 acute liver failure leading to death). The death was considered unrelated to study drug by the investigator. In the safety analysis set, 6% (2/32) of patients in the 200-mg armodafinil group withdrew from the study due to AEs.

There were no clinically meaningful trends in mean changes from baseline for any vital sign variables, laboratory values, or for body weight in any treatment group (Table 3). Mean increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGT) from baseline to final visit were observed in the armodafinil-treated groups and were greater in the 200-mg armodafinil group. Alkaline phosphatase decreased from baseline to final visit in the placebo and armodafinil 150-mg groups and increased slightly in the 200-mg armodafinil group. All mean chemistry values remained within reference ranges at final visit. Post hoc analyses indicated that 5% (9/183) of placebo, 2% (3/186) of armodafinil 150-mg, and 4% (1/28) of armodafinil 200-mg patients had ≥ 7% weight gain at final visit; < 1% (1/183) of placebo, 4% (8/186) of armodafinil 150-mg, and no armodafinil 200-mg patients had ≥ 7% weight loss from baseline.

The YMRS, HARS, and ISI scores decreased from baseline to final visit in all treatment groups and there was no observable difference between the armodafinil 150-mg and placebo groups (Table 3). There were 2 patients in the placebo group and 3 patients in the armodafinil 150-mg group with mania reported as an AE and 1 placebo patient with hypomania. There were few changes from baseline to end point in suicidal ideation or suicidal behavior as assessed by the C-SSRS-SLV, and assessments were similar in all treatment groups.

DISCUSSION

This phase 3 study demonstrated that, compared with adjunctive placebo, armodafinil 150 mg/d significantly

Table 3. Tolerability Assessments at Final Visit (safety analysis set)

Measure	Placebo (n = 199)	Armodafinil 150 mg (n = 198)	Armodafinil 200 mg (n = 32)
YMRS score, mean (SD)			
At final visit	2.6 (3.2)	2.4 (2.9)	3.3 (2.1)
Change from baseline	−1.1 (3.4)	−1.1 (3.1)	−1.0 (2.4)
HARS score, mean (SD)			
At final visit	8.4 (4.8)	8.6 (5.6)	9.4 (4.4)
Change from baseline	−4.2 (4.7)	−4.2 (5.9)	−3.3 (4.3)
ISI score, mean (SD)			
At final visit	9.7 (6.8)	9.1 (6.9)	10.4 (7.2)
Change from baseline	−6.4 (6.9)	−6.5 (7.2)	−5.6 (6.3)
Sitting blood pressure, mean (SD)			
Change in systolic blood pressure, mm Hg	−0.1 (9.9)	−0.9 (8.9)	−2.6 (11.6)
Change in diastolic blood pressure, mm Hg	0.2 (8.6)	0.0 (8.3)	−1.4 (7.7)
Electrocardiogram			
Mean (SD) Change in heart rate, mean (SD), bpm	−0.2 (11.2)	−0.8 (10.9)	0.3 (9.7)
QT interval, mean (SEM), msec	0.8 (23.1)	1.2 (24.0)	0.2 (25.5)
Chemistry, mean (SD)			
Change in AST, U/L	−0.1 (8.5)	1.7 (13.9)	10.5 (50.0)
Change in ALT, U/L	0.8 (11.1)	1.8 (16.4)	21.0 (82.9)
Change in GGT, U/L	−0.9 (18.2)	5.2 (26.5)	16.9 (54.7)
Alkaline phosphatase, U/L	−1.6 (11.5)	−1.3 (13.3)	5.4 (21.9)
Change in body weight, mean (SD), kg	0.2 (3.8)	−0.4 (2.7)	−0.1 (2.9)

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase, HARS = Hamilton Anxiety Rating Scale, ISI = Insomnia Severity Index, SEM = standard error of mean, YMRS = Young Mania Rating Scale.

improved symptoms of major depressive episodes associated with bipolar I disorder when given adjunctive to maintenance medication, although the effect size was modest. Statistically significant improvement in mean IDS-C_{30} score was observed in the 150-mg armodafinil group by week 7. There were 33 patients randomized to the 200-mg treatment group before discontinuation of this group early in the course of the study. This dose, which was not included in the phase 2 proof-of-concept study, was added to assess possible incremental benefit. However, due to lower than expected patient enrollment, the protocol was amended to remove the 200-mg group.

Adverse events were consistent with the known profile of armodafinil, and safety data indicate that adjunctive armodafinil 150 mg was generally well tolerated. The YMRS, C-SSRS-SLV, HARS, and ISI scores indicated that there was no worsening in symptoms of hypomania or mania, suicidal ideation/suicidal behavior, symptoms of anxiety, or insomnia, respectively. Discontinuation rates due to AEs were similar between the 150-mg armodafinil and placebo groups, suggesting armodafinil was well tolerated. In addition, no clinically meaningful trends were observed in mean changes from baseline for any vital sign variables, laboratory values, or body weight in the 150-mg armodafinil and placebo groups. A post hoc analysis did not find any clinically meaningful differences in the percentages of patients with ≥ 7% weight gain in the 150-mg armodafinil (2% [3/186]) group compared with placebo (5% [9/183]); however, long-term studies are required to better evaluate the effect of adjunctive armodafinil on changes in body weight in this patient population.

There were 2 serious hepatic AEs reported in the 200-mg group, of which 1 (acute hepatitis) was considered possibly related to study drug. In regard to potential hepatotoxicity, armodafinil and modafinil have been associated with modest elevations in GGT and alkaline phosphatase levels[19,20,31,32]; however, reports of clinically apparent liver toxicity are lacking in the literature. These compounds have been associated with rare instances of serious rash, including Stevens-Johnson syndrome, and multiorgan hypersensitivity reactions, which may be accompanied by evidence of hepatic involvement or injury.[32,33] In this study, mean elevations in other liver enzymes were noted among patients taking armodafinil; however, these patients were also taking various other concomitant medications that could affect these values, and the mean changes were not considered clinically significant.

This multicenter, randomized, double-blind, placebo-controlled study to examine treatment for major depressive episodes associated with bipolar I disorder used an adjunctive trial design that enrolled patients receiving diverse 1- and 2-drug maintenance therapies. Participants were also required to prospectively cycle into a depressive event to demonstrate that armodafinil was functioning as adjunctive therapy and to reduce the ambiguity of other potential reasons for treatment effect. These aspects of the study design differ from previous, mostly monotherapy, trials for major depressive episodes associated with bipolar I disorder.

Another important aspect of this trial design was the use of the IDS-C_{30} to assess depressive symptoms. Unlike other depression scales, the IDS-C_{30} assesses all 9 *DSM-IV* criterion domains of major depressive disorders (including melancholic and atypical features).[34] These additional domains were considered of possible relevance to the effects of armodafinil. Furthermore, this scale has been utilized in several studies of bipolar depression, including earlier successful studies with modafinil and armodafinil.[22,35,36] The psychometric properties of the IDS have been shown to be reliable and to correlate highly with the Hamilton Depression Rating Scale[27] and the Montgomery-Asberg Depression Rating Scale.[34]

There are limitations associated with this study design that should be considered in context of the results. This adjunctive trial design included a more heterogeneous population as a result of the wide variety of maintenance medications. Some of the included maintenance medications have themselves demonstrated short- and long-term efficacy in the treatment of bipolar depression, which may have confounded the results.[8] In particular, the effect size in the current study was smaller than that reported in previous studies of adjunctive treatment with modafinil and armodafinil, which utilized greater restrictions on allowed maintenance medications.[22,36] The different effect sizes between armodafinil and modafinil

may be related to differences in study designs rather than differences in the 2 molecular compounds. Also, the onset of efficacy in the current study was somewhat different from the previous armodafinil and modafinil studies, which noted a significant treatment difference as early as week 2, although this was not always maintained at each study visit.[22,36] Again, this could be related to study design and assay sensitivity. On the other hand, a delayed onset of treatment effect may also suggest a different mechanism of action from that of armodafinil's wakefulness-promoting effects. Also, the absence of enrollment of participants taking quetiapine was a potential limitation in terms of generalizability, but a potential strength with respect to assay sensitivity. Finally, with the exception of the Insomnia Severity Index, all other outcome measures were investigator/clinician based.

In addition to the trial design, the study results should also be put into context with the molecular characteristics of armodafinil. Although armodafinil and modafinil have similar terminal half-lives (16.5 hours and 14.4 hours, respectively), the systemic exposure to armodafinil is greater, and the 2 compounds are not bioequivalent.[37] The exact mechanism of action of armodafinil and modafinil is not yet known, although enhancement of dopaminergic activity may be 1 mechanism by which these compounds impact depression associated with bipolar I disorder.[38] Armodafinil has been shown to significantly increase dopamine levels in the human brain,[39] and both armodafinil and modafinil, in vitro, bind to the dopamine transporter and inhibit dopamine reuptake.[40] Studies have shown an influence on additional neurotransmitters, including noradrenergic, glutamatergic, GABAergic, and serotoninergic pathways[41,42]; however, these compounds do not demonstrate any measurable binding with serotonin or norepinephrine transporters.[40,43]

Since completion of the present analysis, results from 2 additional phase 3 studies[44,45] of armodafinil as adjunctive treatment for major depressive episodes associated with bipolar I disorder have been reported. These studies, which utilized similar study designs, noted numerical but not statistically significant improvement in IDS-C_{30} scores for the primary end point compared with adjunctive placebo. Armodafinil was well tolerated in both study populations. Therefore, further examination of the clinical relevance of the present study's findings with consideration of adjunctive study designs for capturing the true treatment effect may be warranted.

In conclusion, compared with placebo, armodafinil 150 mg significantly improved symptoms of a major depressive episode associated with bipolar I disorder when given as adjunctive treatment to maintenance medication as measured by IDS-C_{30} change from baseline to week 8, although the treatment effect was modest. Treatment with armodafinil was generally well tolerated. Further analysis is needed to better clarify the role of armodafinil in adjunctive treatment for bipolar depression.

Drug names: aripiprazole (Abilify), armodafinil (Nuvigil and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lurasidone (Latuda), modafinil (Provigil and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), valproic acid (Depakene and others), ziprasidone (Geodon and others).

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Previous presentations: Data from this study were presented at the US Psychiatric and Mental Health Congress; November 8–11, 2012; San Diego, California ▪ the American College of Neuropsychopharmacology 51st Annual Meeting; December 2–6, 2012; Hollywood, Florida (Calabrese JR, et al. *Neuropsychopharmacology* 2012;38[suppl]:S332–S333) ▪ the International Society for Pharmacoeconomics and Outcomes Research 18th Annual Meeting; May 18–22, 2013 New Orleans, Louisiana ▪ the 53rd Annual Meeting of the New Clinical Drug Evaluation Unit; May 28–31, 2013; Hollywood, Florida ▪ and the 10th International Conference on Bipolar Disorders; June 13–16, 2013; Miami Beach, Florida (Ketter TA, et al. *Bipolar Disord.* 2013;15[suppl 1]:88).

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Additional information: A list of the Armodafinil Treatment Trial Study Network investigators is provided in the supplementary material.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Efficacy and Safety of Adjunctive Armodafinil in Adults With Major Depressive Episodes Associated With Bipolar I Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

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DOI Number: 10.4088/JCP.13m08951

List of Supplementary Material for the article

1. eTable 1 — Maintenance Medications Started Prior to Treatment (Randomized Patients)
2. eInvestigators List — Armodafinil Treatment Trial Study Network

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Supplementary eTable 1. Maintenance Medications Started Prior to Treatment (Randomized Patients)

	Number (%) of Patients		
Maintenance Therapy, n (%)[a]	**Placebo (n=199)**	**Armodafinil 150 mg (n=201)**	**Armodafinil 200 mg (n=33)**
Patients with 1 maintenance medication	**169 (85)**	**174 (87)**	**30 (91)**
Valproic acid	47 (24)	59 (29)	5 (15)
Lithium	31 (16)	35 (17)	11 (33)
Lamotrigine	32 (16)	33 (16)	3 (9)
Olanzapine	20 (10)	13 (6)	7 (21)
Aripiprazole	19 (10)	17 (8)	3 (9)
Risperidone	19 (10)	16 (8)	1 (3)
Ziprasidone	1 (<1)	1 (<1)	0 (0)
Patients with 2 maintenance medications	**28 (14)**	**27 (13)**	**3 (9)**
Valproic acid + aripiprazole	5 (3)	4 (2)	0 (0)
Lithium + lamotrigine	7 (4)	2 (<1)	0 (0)
Lithium + risperidone	4 (2)	3 (1)	2 (6)
Lithium + olanzapine	3 (2)	3 (1)	0 (0)
Lithium + valproic acid	2 (1)	4 (2)	0 (0)
Valproic acid + olanzapine	1 (<1)	4 (2)	1 (3)
Valproic acid + risperidone	2 (1)	2 (<1)	0 (0)
Lithium + aripiprazole	1 (<1)	2 (<1)	0 (0)
Risperidone + lamotrigine	1 (<1)	2 (<1)	0 (0)
Aripiprazole + lamotrigine	2 (1)	0 (0)	0 (0)
Valproic acid + ziprasidone	0 (0)	1 (<1)	0 (0)

	Number (%) of Patients		
Maintenance Therapy, n (%)[a]	**Placebo (n=199)**	**Armodafinil 150 mg (n=201)**	**Armodafinil 200 mg (n=33)**
Patients with 3 maintenance medications[b]	**2 (1)**	**0 (0)**	**0 (0)**
Valproic acid + aripiprazole + risperidone	1 (<1)	0 (0)	0 (0)
Valproic acid + olanzapine + aripiprazole	1 (<1)	0 (0)	0 (0)

[a]Of the 495 courses of maintenance medications patients started prior to treatment, 1 started 4 weeks or less before randomization, 28 were started more than 4 and no more than 8 weeks before randomization, 271 were started more than 8 weeks before randomization, and for 195, the start date was missing or partial.

[b]Two subjects took 3 maintenance medications but stopped using aripiprazole prior to randomization.

Supplementary eInvestigators List. Armodafinil Treatment Trial Study Network

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