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Research paper

Long-term safety and efficacy of armodafinil in bipolar depression: A 6-month open-label extension study

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ABSTRACT

Background: Safe/well-tolerated treatments for bipolar I depression remain limited. We assessed safety/tolerability of adjunctive open-label armodafinil, a wakefulness-promoting agent evaluated in 3 acute, controlled efficacy studies with variable efficacy results.

Methods: Completers of three 8-week, double-blind, placebo-controlled adjunctive armodafinil studies (150–200 mg/day added to ongoing stable maintenance doses of 1 or 2 protocol-defined mood stabilizers) in bipolar I depression could enter this 6-month, open-label extension study. Objectives included evaluation of safety/tolerability (primary) and efficacy (secondary).

Results: 867 patients enrolled; 863 received ≥1 dose of armodafinil and 506 (58%) completed the 6-month study. Headache, insomnia, and anxiety were the most common adverse events (AEs) reported, whereas akathisia, nausea, sedation/somnolence, and weight increase were uncommon. Mean measures assessing emergence of mania, anxiety, insomnia, or suicidality showed no worsening. Discontinuations due to AEs occurred in 57 (7%) patients. Serious AEs occurred in 27 (3%) patients and were considered treatment-related in 8 (1%) patients. Depressive symptoms improved over the 6 months, as did patient functioning.

Limitations: Lack of placebo control.

Conclusions: Adjunctive armodafinil was generally safe and well tolerated over 6 months of open-label treatment at 150–200 mg/day when taken with protocol-defined mood stabilizers for bipolar I depression. This 6-month open-label study suggested that armodafinil augmentation of bipolar maintenance therapies may have a favorable risk profile and may improve depressive symptoms in some patients with bipolar I depression.

1. Introduction

Bipolar I disorder has an estimated lifetime prevalence of 1% in the United States (Merikangas et al., 2007). Recurrent mood symptoms that characterize the disorder can lead to severe disability (Calabrese et al., 2004; Post et al., 2003; World Health Organization, 2008), and it is estimated that there are 22.2 million patients with bipolar disorder worldwide who endure moderate to severe functional impairment (World Health Organization, 2008). Although the manic phase of the illness has received more attention in terms of pharmaceutical development, patients experience depressive symptoms 3 times more frequently than manic symptoms (Judd et al., 2002; Kupka et al., 2007; Post et al., 2003). In addition, compared with manic episodes, the depressed phase of bipolar I disorder is associated with more frequent and severe disability, including functional and occupational deficits, and higher risk of suicide (Baldessarini et al., 2012; Bauer et al., 2001; Calabrese et al., 2004; Merikangas et al., 2007, 2011).

Management of bipolar I depression is challenging, and currently there are only 3 treatments that have been approved by the US Food and Drug Administration (FDA) for acute depressive episodes occurring in the context of bipolar I disorder (Frye et al., 2014; Ketter et al., 2014). Unfortunately, a recent meta-analysis found that standard antidepressants that are effective in the relief of unipolar depression did not provide any significant advantage over placebo for acute bipolar I depression (Sidor and Macqueen, 2011). Thus, there remains a large unmet need for new treatment options in acute bipolar I depression (Frye et al., 2014).

Armodafinil (*R*-modafinil) is an indirect dopamine agonist that binds in vitro to the dopamine transporter, inhibiting dopamine reuptake. Armodafinil promotes wakefulness, similar to

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amphetamine and methylphenidate, but has a different pharmacologic profile. Because of its efficacy in wakefulness promotion, armodafinil is currently approved by the FDA for the treatment of excessive sleepiness associated with the conditions of shift work disorder (Czeisler et al., 2009), narcolepsy (Harsh et al., 2006), and obstructive sleep apnea (Hirshkowitz et al., 2007; Roth et al., 2006). A placebo-controlled phase 2 investigation of armodafinil (150 mg/day for 8 weeks) administered adjunctively to lithium, valproic acid, and/or olanzapine in bipolar I depression showed significant improvement in depressive symptoms, relative to placebo, as assessed by the 30-Item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C_{30}) (Calabrese et al., 2010). Based on these results, a phase 3 clinical development program was initiated to further assess the potential efficacy and safety of armodafinil in bipolar I depression. This included 3 similarly designed acute-phase studies of adjunctive armodafinil vs. placebo and a long-term open-label extension study.

In the first of these phase 3 studies, adjunctive armodafinil significantly improved depressive symptomatology over adjunctive placebo, supporting the prior phase 2 results (Calabrese et al., 2014). Two subsequent phase 3 studies found a generally favorable tolerability profile of adjunctive armodafinil in bipolar I depression, but positive efficacy findings from earlier studies were not replicated (Frye et al., 2015; Ketter et al., 2015). Thus, insufficient efficacy results prompted a decision by the sponsor to terminate the clinical development of armodafinil for this indication.

Here we report results from an open-label, long-term extension trial. The primary hypothesis was that open-label adjunctive armodafinil 150–200 mg/day for 6 months in recently depressed bipolar I disorder patients was safe and well tolerated; the secondary hypothesis was that open-label adjunctive armodafinil 150–200 mg/day for 6 months in recently depressed bipolar I disorder patients was efficacious for depressive symptoms and global functioning.

2. Methods

2.1. Study design

This phase 3, multicenter, 6-month, open-label extension study (NCT01121536) evaluated armodafinil at dosages of 150 and 200 mg/day, given adjunctively to ongoing bipolar maintenance therapies. For those who participated, the final visit of the previous double-blind acute study served as the enrollment visit for the open-label extension study. At enrollment, armodafinil was initiated at a dose of 50 mg/day and was increased to 100 mg/day on day 2 and to 150 mg/day on day 4. Thereafter, armodafinil could be increased to 200 mg/day on day 6 or later at the discretion of the investigator based on efficacy and/or safety and tolerability.

The study protocol was approved by independent ethics committees or institutional review boards associated with each study center, and the study was conducted according to Good Clinical Practice guidelines as approved by the International Council for Harmonisation. All patients provided written informed consent prior to any study procedures or assessments. An external data and safety monitoring board reviewed safety on a regular basis.

2.2. Participants

Patients who had completed 8 weeks of treatment in 1 of the previous acute phase 3 double-blind studies evaluating adjunctive armodafinil vs adjunctive placebo in bipolar I depression (Studies 3071 [NCT01072929], 3072 [NCT01072630], or 3073 [NCT01305408]) (Calabrese et al., 2014; Frye et al., 2015; Ketter et al., 2015) were eligible for this open-label study. Enrollment in the double-blind studies required patients to be between the ages of 18 and 65 years and in good physical health. The diagnosis of bipolar I disorder with a current major depressive episode was made on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria. Patients with other Axis I or II disorders, psychotic symptoms, or suicidal ideation were ineligible. For patients to be included in the extension study, the clinical investigator must have determined that they were in need of continued treatment for depression. Patients also were required to have a Young Mania Rating Scale (YMRS) total score ≤ 14. In addition, patients were required to be willing to continue 1 or 2 of the following protocol-allowed mood stabilizers: lithium, valproic acid, olanzapine, quetiapine, aripiprazole, lamotrigine, risperidone, or ziprasidone (ziprasidone only if taken in combination with lithium, valproic acid, or lamotrigine). If 2 protocol-allowed mood stabilizers were taken at baseline, 1 had to be lithium, valproate, or lamotrigine. The use of any antipsychotic or anticonvulsant other than those listed above was prohibited; no antidepressant agents were allowed. Adjunctive benzodiazepines (up to 2 mg of lorazepam-equivalents per day) or hypnotics (zolpidem 5–10 mg or zaleplon 5–10 mg at bedtime) were allowed provided their use did not occur within 12 h of any study assessment and did not exceed 3 times per week.

2.3. Assessments

The final visit of the previous double-blind acute study served as the baseline visit for this open-label extension study. Study center visits during open-label treatment were conducted at week 1 and months 1, 2, 4, and 6 (or early termination if prior to month 6). In addition, telephone contacts were made at weeks 2 and 3 and at months 3 and 5 to evaluate study drug tolerability through assessment of adverse events (AEs) and to collect data on concomitant medication use. Protocol-defined treatment-emergent AEs of clinical interest, including skin rash, hypersensitivity reaction, suicidal ideation or suicide attempt, and psychosis were monitored for expedited reporting. Safety assessments collected during the 5 study center visits included vital sign measurements, the YMRS, the Columbia-Suicide Severity Rating Scale-Since Last Visit (C-SSRS-SLV), and the Insomnia Severity Index (ISI). At month 6 or the last post-baseline visit, clinical laboratory test results, electrocardiography (ECG), physical examination, and Hamilton Anxiety Rating Scale (HAM-A) score were monitored.

The efficacy of adjunctive armodafinil was assessed at week 1, and months 1, 2, 4, and 6 (or last post-baseline visit) using the total score from the IDS-C_{30} and the Clinician Global Impression of Severity (CGI-S) for depression. The 16-Item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) derived from the IDS-C_{30} was obtained at week 1 and months 1, 2, 4, and 6 (or last post-baseline visit). The Global Assessment of Functioning (GAF) scale score was assessed at month 6 (or last post-baseline visit).

2.4. Statistical analysis

Sample size was not based upon a statistical power analysis; approximately 800–900 patients were planned for enrollment to obtain at least 200 patients who received adjunctive armodafinil for 6 months. The safety analysis set included all patients who took ≥ 1 dose of study drug. The full analysis set included all patients in the safety analysis set who had ≥ 1 post-baseline efficacy assessment. Descriptive statistics were used to describe patient disposition, demographic and baseline characteristics, study drug exposure, incidence of AEs, and all other safety