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Research paper

Long-term safety and tolerability of asenapine: A double-blind, uncontrolled, long-term extension trial in adults with an acute manic or mixed episode associated with bipolar I disorder

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ABSTRACT

Background: Asenapine (ASN) is approved in the United States as monotherapy and adjunctive therapy (to lithium or valproate) in adults with bipolar mania, and as monotherapy in pediatric patients with bipolar mania. This is the first long-term study evaluating safety and tolerability of ASN fixed doses in this population.

Methods: After completing a 3-week, randomized, placebo (PBO)-controlled acute trial, patients could enroll in this 26-week, fixed-dose (5 or 10 mg twice daily), double-blind extension study. Select predefined treatment-emergent adverse events (TEAEs) and metabolic parameters were reported.

Results: Overall, 164 patients were treated; 88 completed the study. The incidence of ≥1 TEAE was greater for PBO/ASN 5 mg (68.3%) versus ASN 5 mg/ASN 5 mg (54.7%) and ASN 10 mg/ASN 10 mg (51.0%) with sedation, headache, somnolence, akathisia, and dizziness occurring as the most prevalent TEAEs. Predefined TEAEs were more common for PBO/ASN 5 mg (33.3%) versus ASN 5 mg/ASN 5 mg (15.1%) and ASN 10 mg/ASN 10 mg (15.7%). Weight gain (≥7% increase from baseline to endpoint) was more frequent for ASN 10 mg/ASN 10 mg (16.3%) versus ASN 5 mg/ASN 5 mg (13.7%) and PBO/ASN 5 mg (8.9%). No clinically significant metabolic changes were observed. The incidence of serious AEs was low and primarily related to underlying bipolar I disorder.

Limitations: This study lacked a comparator group and was not powered for direct comparisons of ASN regimens. Results may not be applicable to the general bipolar population.

Conclusions: ASN was generally safe and well tolerated in adults with an acute manic or mixed episode associated with bipolar I disorder.

1. Introduction

Bipolar disorder is a serious, psychiatric condition that can result in marked functional impairment and a substantial reduction in quality of life (Miller et al., 2014; Shippee et al., 2011; Sierra et al., 2005). Bipolar disorder is also associated with excess mortality, in part due to a significantly increased risk of suicide (da Silva Costa et al., 2015; LeardMann et al., 2013; Ösby et al., 2001). Major mood alterations associated with bipolar I disorder include manic, depressive, or mixed episodes that often fail to completely resolve, resulting in residual mood symptoms and functional difficulties that linger between acute episodes (American Psychiatric Association, 2000).

It is estimated that more than 90% of those who experience a single manic episode will have future episodes (American Psychiatric Association, 2000). These recurrent episodes can result in illness progression, contributing to increased illness severity and burden

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; ASN, asenapine; ATS, All Treated Set; bid, twice daily; BMI, body mass index; CGI-BP-OS, Clinical Global Impression scale for use in Bipolar illness, Overall Severity; CGI-BP-I, Clinical Global Impression-Bipolar Mania-Improvement; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EOT, end of treatment; EPS, extrapyramidal symptoms; FAS, Full Analysis Set; FU, follow-up; LOCF, last observation carried forward; MedDRA, Medical Dictionary for Regulatory Activities; OC, observed case; PBO, placebo; PDLC, predefined limit of change; SAEs, serious adverse events; SD, standard deviation; SOC, system organ class; TEAE, treatment-emergent adverse event; YMRS, Young Mania Rating Scale

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(Post, 1992; Roy-Byrne et al., 1985). In 1990 and 2010, the US Burden of Disease Collaborators ranked bipolar disorder (of which there are several different types, including bipolar I disorder) among the top 18 diseases in terms of years lived with disability (Murray et al., 2013). Bipolar disorder represents a greater economic burden to society than many other psychiatric disorders, entailing large direct medical costs and even larger indirect costs such as lost productivity and the negative impact extending to family/caregivers (Laxman et al., 2008; Peele et al., 2003). Therefore, effective long-term prevention of episodes is essential to maintain quality of life and reduce burden on patients, caregivers, and the healthcare system.

Current treatment options for bipolar I disorder have proven inadequate for many patients. Although most patients symptomatically recover from acute episodes, only a minority functionally recover. In addition, tolerability issues contribute to patients being unable or unwilling to continue treatment (McIntyre, 2011; McIntyre and Konarski, 2005; Perlis et al., 2006; Tohen et al., 2003). Consequently, there is a need for safe and tolerable treatment options that also achieve syndromal, symptomatic, and functional recovery (McIntyre, 2011).

Asenapine (ASN) is a fast-dissolving, rapidly absorbed, sublingual atypical antipsychotic, initially approved by the US Food and Drug Administration in adults with bipolar mania (in 2009 as monotherapy and in 2010 as an adjunct to either lithium or valproate). In March 2015, ASN was approved for the treatment of pediatric patients with bipolar mania. In addition, ASN is approved for both acute and maintenance treatment of adults with schizophrenia. An initial phase 3, randomized, double-blind, multicenter, placebo (PBO)-controlled, 3-week trial explored the dose–response relationship of ASN 5 and 10 mg twice daily (bid) fixed doses to determine the minimum effective dose in acute mania, with both doses demonstrating efficacy in terms of reducing both manic and depressive symptoms (Landbloom et al., 2016). The objective of the current study was to evaluate the long-term safety/tolerability of ASN 5 and 10 mg bid in adults with an acute manic or mixed episode associated with bipolar I disorder.

2. Methods

Details of the phase 3b, international, double-blind, fixed-dose, parallel-group, 3-week PBO-controlled trial of ASN 5 and 10 mg bid in adults with an acute bipolar I disorder manic or mixed episode (NCT00764478) have been previously published (Landbloom et al., 2016). After completing the acute trial, patients could enroll in the present study, a 26-week, double-blind, fixed-dose, multicenter, long-term, phase 3b extension trial (NCT01395992) to evaluate the long-term safety of ASN 5 mg and 10 mg bid in individuals with a diagnosis of bipolar I disorder and acute manic exacerbation at the time of enrollment in the acute trial (Fig. 1). The current trial consisted of a baseline visit (day 21/end of treatment for the prior 3-week acute trial), an extension treatment period of 26 weeks, and a follow-up period. The first day of this extension trial overlapped with day 21/end of treatment for the prior acute mania trial.

The trial was conducted from May 9, 2012, to December 3, 2014, at 38 centers in the United States, Bulgaria, Russia, Croatia, and Ukraine. Diagnosis of bipolar I disorder with a current manic or mixed episode was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR] (American Psychiatric Association, 2000), at entry into the prior acute mania trial. Independent ethics committees associated with each study site reviewed and approved the protocol and applicable amendments. The trial was conducted in conformance with good clinical practice guidelines and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Written informed consent for the extension trial was provided by patients before performing any study-specific assessments unique to the extension trial (separate informed consent was signed for any baseline procedures that were performed as part of the end-of-trial visit for the acute mania trial). Patients could withdraw consent at any time for any reason and, if deemed necessary, the investigator or subinvestigator could discontinue patients. Discontinuation was permanent and patients who discontinued the study were not replaced. Concomitant medications were coded using the most recent version of the World Health Organization drug dictionary (March 2014) at the time of database lock.

2.1. Inclusion criteria

Patients aged ≥18 years who completed the prior acute mania trial and were considered likely to benefit from continued treatment (whether or not they had shown improvement during the acute trial) were eligible for enrollment in the extension trial. A key inclusion criterion from the prior acute trial was a diagnosis at entry of bipolar I disorder with a current manic or mixed episode according to the DSM-IV-TR. For enrollment in the extension trial, patients were required to demonstrate an acceptable degree of adherence with trial medication, visits, and other requirements in the acute trial, and have a person considered reliable who agreed to act as a contact person for the patient during the trial. In addition, patients must have agreed not to begin formal, structured psychotherapy targeting the symptoms of bipolar I disorder during treatment in the trial.

2.2. Exclusion criteria

Patients with an uncontrolled, unstable, clinically significant medical condition that may interfere with interpretation of safety/tolerability and efficacy evaluations were excluded from the trial, as were those with any newly diagnosed or discovered medical condition that would have excluded the patient from participation in the acute trial. Also excluded were those with any newly diagnosed psychiatric condition that would have excluded the patient from participation in the acute trial, such as a primary Axis I disorder other than bipolar I disorder. Patients with any other clinically significant situation that would interfere with the trial evaluations or optimal trial participation, or any occurrence(s) of an adverse event (AE) or other clinically significant findings in the acute mania trial that would prohibit continuation in the long-term extension trial also were excluded. Additional criteria that warranted exclusion included having any of the following at baseline of the extension study: a Clinical Global Impression scale for Bipolar Disorder, Overall Severity (CGI-BP-OS) score ≥6 (severely ill); a positive serum pregnancy test or intention to

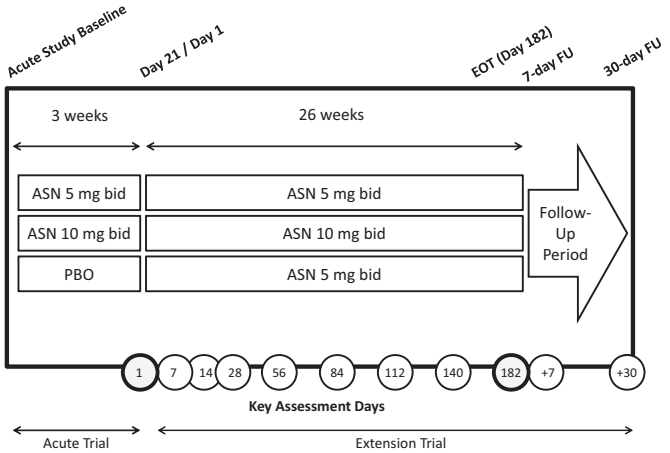

Fig. 1. Study design. Day 21 refers to day 21 of the acute mania trial; Day 1 refers to day 1 of the extension trial. ASN, asenapine; bid, twice daily; EOT, end of treatment; FU, follow-up; PBO, placebo.