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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

Terence A. Ketter[a,*], Suresh Durgam[b], Ronald Landbloom[c], Mary Mackle[c], Xiao Wu[b], Maju Mathews[d]

[a] Stanford University School of Medicine, Stanford, CA, USA
[b] Allergan, Jersey City, NJ, USA
[c] Merck, Whitehouse Station, NJ, USA
[d] Forest Research Institute, an Allergan affiliate, Jersey City, NJ, USA

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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

* Correspondence to: Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, MC5723, Stanford, CA 94305, USA.
E-mail address: tketter@stanford.edu (T.A. Ketter).

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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

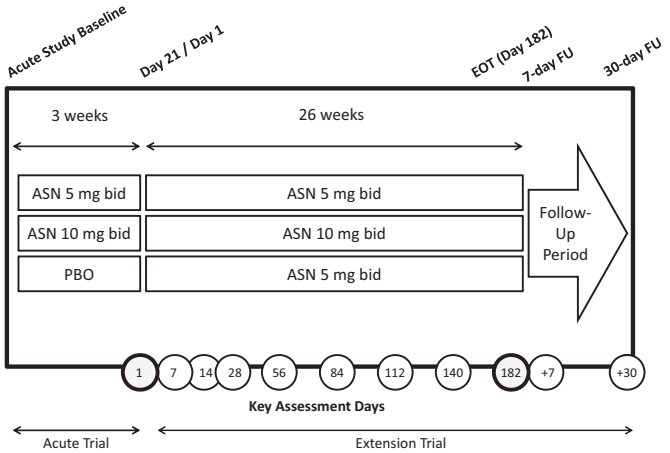

Fig. 1. Study design. Day 21 refers to day 21 of the acute mania trial; Day 1 refers to day 1 of the extension trial. ASN, asenapine; bid, twice daily; EOT, end of treatment; FU, follow-up; PBO, placebo.

become pregnant during the long-term extension trial; meeting DSM-IV-TR criteria for substance abuse or dependence (excluding nicotine) within the time period from 6 months prior to the acute trial and extension study baseline; a diagnosis of a psychotic disorder or a behavioral disturbance thought to be substance induced or due to substance abuse; imminent risk of self-harm or harm to others; a history of imprisonment, parole, or assaultive behavior within the prior 2 years; current involuntary inpatient commitment; and symptoms suggesting allergy or sensitivity to ASN in the acute trial. Current use of antipsychotics (other than trial medication), St John's Wort and other herbal supplements for the treatment of psychiatric symptoms, antiemetics containing a dopamine antagonist, illicit drugs, stimulants, medium- and long-acting benzodiazepines, psychotherapy, and electroconvulsive therapy also were grounds for exclusion.

2.3. Procedures

An interactive voice response system was used to assign unique patient identification numbers for the current study, maintain the blinding from the acute trial, and track patient enrollment and retention. In addition, the packaging and labeling of the trial medication maintained the double-blind design of the trial. Trial medication included two different doses of active fast-dissolving ASN tablets, which were made to look identical in appearance. Neither the patient nor the investigational staff were aware of which treatment the patient received. Patients taking double-blind ASN 5 or 10 mg bid at the end of the prior acute mania trial were assigned to continue in the same regimen in the 26-week extension trial. Patients randomly assigned to PBO in the prior acute mania trial were allocated to double-blind ASN 5 mg bid in the 26-week extension trial.

Patients were contacted on day 2 of the extension trial to ensure they understood the instructions for dosing and how to assess AEs. Patients had clinical research visits at baseline and weeks 1, 2, 4, 8, 12, 16, 20, and 26, with additional visits scheduled to assess safety, tolerability, and illness severity as required. Patients were contacted weekly via telephone between visits. Upon completion or discontinuation of the trial, patients had a follow-up visit 7 days after their final dose of ASN; 30 days after trial completion/discontinuation, each patient was telephoned to establish whether any serious adverse events (SAEs) or pregnancies had occurred and to update the status of unresolved AEs/SAEs.

2.4. Safety outcomes

AEs (coded using the most recent Medical Dictionary for Regulatory Activities [MedDRA] at time of database lock, MedDRA version 17.1) were reported from extension-trial baseline through last date of trial medication intake +7 days. SAEs were reported from baseline through last date of trial medication +30 days. AEs were designated as treatment-emergent adverse events (TEAEs) for new or worsening reported events after the extension-trial baseline. Select prespecified TEAEs of interest based on ASN drug class were monitored throughout the study and included: the combination of somnolence, sedation, and hypersomnia; dizziness; insomnia; oral hypoesthesia combined with dysgeusia; akathisia; extrapyramidal symptoms (EPS); and a predefined limit of change (PDLC) of body weight at endpoint (i.e., ≥7% increase from baseline). Other TEAEs occurring in ≥5% of patients were reported and additional safety assessments included laboratory tests, vital signs, SAEs, AEs, weight/abdominal girth, physical examination, electrocardiograms, Abnormal Involuntary Movement Scale, EPS (using Barnes Akathisia Scale and Simpson Angus Rating Scale), and Columbia Suicide Severity Rating Scale.

2.5. Efficacy outcomes

No efficacy hypothesis was tested, and there were no primary efficacy parameters as this study lacked a PBO control group. However, the following exploratory efficacy endpoints, based on the primary and secondary endpoints in the prior acute trial, were assessed during the study: change from acute trial baseline in Young Mania Rating Scale (YMRS) total score, the rate of YMRS response (≥50% reduction from acute trial baseline), the rate of YMRS remission (final total score ≤12), change from acute trial baseline in CGI-BP-OS score, and the rate of Clinical Global Impression-Bipolar Mania-Improvement (CGI-BP-I) of Overall Bipolar Illness response. CGI-BP-I was compared with the impression of severity of illness at acute trial baseline, which served as the pretreatment reference level against which changes that occurred while taking trial medication were measured. A patient was considered a CGI-BP-I responder if, when compared with acute trial baseline, the change was measured as minimally improved, much improved, or very much improved.

2.6. Sample size

Sample size was determined by the number of patients who completed the acute trial and who continued into the current trial. All eligible patients completing the acute trial and who may benefit from treatment with ASN were able to participate in this trial. Based on the projection that 70% of the 366 patients randomized in the acute trial would complete the study and that 90% of those patients would enroll in the long-term extension trial, 230 patients were predicted to enroll in the extension study.

2.7. Data presentation

For presentation purposes, both the acute and extension trial treatments were included in treatment group labels: PBO/ASN 5 mg indicates those patients allocated to PBO in the acute trial who were subsequently allocated to ASN 5 mg bid in the extension trial; ASN 5 mg/ASN 5 mg indicates those patients taking ASN 5 mg bid at the end of the acute trial who continued to take ASN 5 mg bid in the extension trial; ASN 10 mg/ASN 10 mg indicates those patients taking ASN 10 mg bid at the end of the acute trial who continued to take ASN 10 mg bid in the extension trial. In addition to these three treatment groups, all patients treated with ASN 5 mg bid in the extension trial were combined for evaluation as an additional treatment arm (ASN 5 mg overall).

2.8. Statistical analysis

For the evaluation of safety/tolerability and efficacy endpoint continuous variables, analysis of covariance was used. Point estimates and 95% confidence intervals (CIs) were obtained by treatment group and visit, with the baseline value and investigative site (or pooled site) as covariates. No *P* values were presented. For safety/tolerability and efficacy endpoint categorical variables, adjusted proportions of patients who experienced each endpoint were calculated. Analyses were performed by treatment group and visit, with adjustment for investigative site (or pooled site). Variance and confidence intervals for each treatment group were calculated. Demographic variables were summarized by treatment group and overall for the All Treated Set (ATS) and Full Analysis Set (FAS) populations. Previous and/or current psychiatric diagnosis and bipolar I disorder psychiatric history were summarized by treatment group and overall for the ATS population.

There were no prespecified key safety/tolerability endpoints or hypothesis testing of safety/tolerability data, and all safety/tolerability analyses used the ATS population, which by definition included all patients who received ≥1 dose of the extension trial medication. Analysis was performed under the treatment group that the patients actually received; the single patient for whom blinding was broken in the acute trial was not excluded from the ATS population. Changes from extension trial baseline analyses were relative to the first day of

the extension trial/last day (day 21) of the acute mania trial unless otherwise noted (i.e., ≥7% weight increase). Summary statistics reflected the extension trial period only. The analysis of safety data followed a tiered approach with the tiers differing with respect to the analyses that were performed.

Tier 1 safety/tolerability endpoints were safety/tolerability parameters or TEAEs of special interest that were identified *a priori*/predefined by drug class. Tier 1 endpoints included the combination of somnolence, sedation, and hypersomnia; dizziness; insomnia; oral hypoesthesia combined with dysgeusia; akathisia; EPS; and a PDLC of body weight (i.e., ≥7% increase from baseline). TEAEs and PDLCs that were not prespecified as Tier 1 endpoints were classified as Tier 2 or Tier 3. Tier 2 TEAEs included change from baseline to study endpoint in fasting glucose, fasting triglycerides, fasting cholesterol, prolactin, fasting insulin, glycosylated hemoglobin, and specific TEAEs with incidence of ≥4 patients in any treatment group. Tier 3 TEAEs included all other AEs and PDLCs. Tier 1 and Tier 2 parameters were assessed via point estimates with 95% CIs; only point estimates by treatment group were provided for Tier 3 parameters. Descriptive (rather than inferential) statistics were performed for all tiers. Postbaseline values for changes in vital signs and body weight were flagged as potentially clinically relevant if PDLCs were met. PDLCs were defined as: pulse, sitting=change of ≥15 bpm from acute trial baseline (≥120 bpm or ≤50 bpm); systolic blood pressure, sitting=-change of ≥20 mmHg from acute trial baseline (≥180 mmHg or ≤90 mmHg); diastolic blood pressure, sitting=change of ≥15 mmHg from acute trial baseline (≥105 mmHg or ≤50 mmHg); and body weight=change of ≥7% from acute trial baseline.

Exploratory statistical analyses of efficacy endpoints were summarized by treatment group, and baseline analyses were relative to the acute trial baseline. Summary statistics reflected data from the extension trial treatment period only; the baseline visit from the acute trial was also included. All efficacy analyses used the FAS, defined as all randomized patients from the acute trial who received ≥1 dose of the extension trial medication and had ≥1 postbaseline YMRS total score measurement. Analysis was performed by the treatment group patients were randomized to in the acute trial, and patients for whom blinding was broken were not excluded from the FAS population. Descriptive statistics were summarized by treatment group. For each postbaseline visit in which the applicable measures were assessed, the change from both baselines was calculated by both observed case (OC) and last observation carried forward (LOCF) methods.

3. Results

3.1. Patients

Of the 264 patients (placebo, n=93; ASN 5 mg, n=87; ASN 10 mg, n=84) who completed the acute trial, 165 patients continued into this extension study; 164 were treated and included in the ATS and 161 were included in the FAS (Fig. 2). Of the 165 enrolled patients, 88 (53.3%) completed the full treatment phase of the study, with similar numbers completing across treatment groups. A total of 55 ASN-treated patients (53%; 29 ASN 5 mg and 26 ASN 10 mg) and 33 PBO-treated patients (55%) completed treatment in the extension trial. Non-compliance with the study protocol was the most common single reason for discontinuation across all treatment groups (20.0%), followed by AEs (10.3%) and those lost to follow-up (6.7%). Among those patients who discontinued owing to AEs, psychiatric disorders were the most common cause.

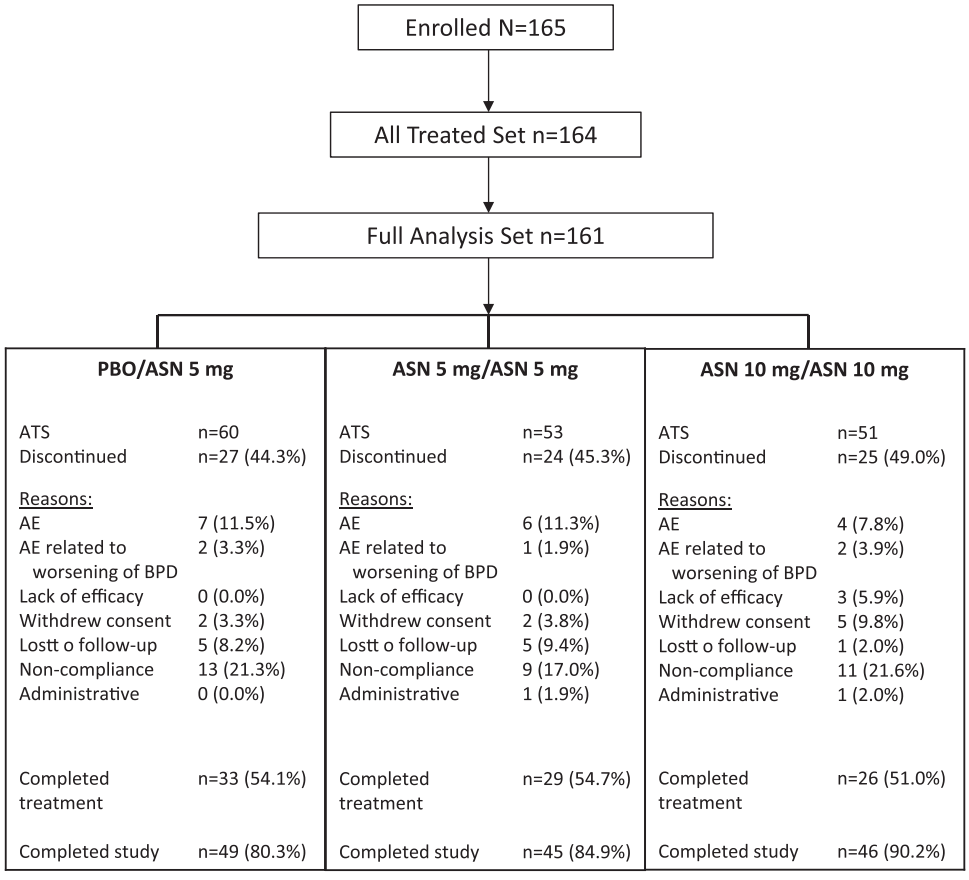

Fig. 2. Patient disposition. The All Treated Set (ATS) population includes randomized patients from the acute trial who received ≥1 dose of the extension trial medication. The Full Analysis Set (FAS) population is defined as all randomized patients from the acute trial who received ≥1 dose of extension trial medication and had ≥1 postbaseline Young Mania Rating Scale total score measurement. AE, adverse event; ASN, asenapine; ATS, All Treated Set; BPD, bipolar I disorder; PBO, placebo.

Baseline characteristics were well matched between treatment groups (Table 1). The mean age of all patients who received ≥1 dose of study medication was 44.4 ± 10.4 years, and there were more female than male patients (54.3% vs 45.7%). Overall, upon entry to the prior acute mania trial, 93 (56.7%) and 71 (43.3%) patients met the DSM-IV-TR criteria for manic and mixed episodes of bipolar I disorder, respectively, and the mean duration of bipolar I disorder was 13.9 ± 8.6 years. Between 75% and 82% of patients in each treatment group received concomitant medications during the extension study. Supplemental Table 1 lists the most common concomitant medications by ATC class and preferred term and the number of patients receiving each.

3.2. Safety/tolerability

No deaths were reported during the trial. Eight patients experienced severe TEAEs: 3 (5.0%) in the PBO/ASN 5 mg group, 2 (3.8%) in the ASN 5 mg/ASN 5 mg group, and 3 (5.9%) in the ASN 10 mg/ASN 10 mg group. Five patients experienced ≥1 SAE: 3 (5.0%) in the PBO/ASN 5 mg group, 0 (0.0%) in the ASN 5 mg/ASN 5 mg group, and 2 (3.9%) in the ASN 10 mg/ASN 10 mg group. Most SAEs (3/5) belonged to the psychiatric disorders class and were related to the patient's underlying bipolar I disorder. One patient (in the ASN 10 mg/ASN 10 mg group) experienced a cardiac SAE. On study day 21, this patient, a 42-year-old white male, had chest pain and was hospitalized; this patient recovered and was released from the hospital on study day 27. ASN was discontinued due to lack of efficacy and the last dose was administered on study day 57. Another patient (in the PBO/ASN 5 mg group) experienced a hepatobiliary SAE. On study day 22, this patient, a 50-year-old white female, was hospitalized for a gall bladder attack; this event resolved and the patient was discharged from the hospital on study day 23. ASN was not discontinued and the patient completed the study per protocol. The proportion of patients who discontinued treatment due to AEs was similar in the PBO/ASN 5 mg (11.7%), ASN 5 mg/ASN 5 mg (11.3%), and ASN 5 mg overall (11.5%), groups, and slightly lower for the ASN 10 mg/ASN 10 mg group (7.8%). Psychiatric and nervous system disorders leading to treatment discontinuation were reported in all three individual treatment groups (5.0% PBO/ASN 5 mg, 5.7% ASN 5 mg/ASN 5 mg and 7.8% ASN 10 mg/ASN 10 mg).

Overall, the incidence of TEAEs was greater in the PBO/ASN 5 mg group (68.3% with ≥1 TEAE) compared with the ASN 5 mg/ASN 5 mg (54.7%) and ASN 10 mg/ASN 10 mg (51.0%) groups. The most prevalent TEAEs were those classified as Nervous System disorders, with 39 patients experiencing TEAEs within this class: 31.7% (19/60) patients in the PBO/ASN 5 mg group, 22.6% (12/53) patients in the ASN 5 mg/ASN 5 mg group, and 15.7% (8/51) patients in the ASN 10 mg/ASN 10 mg group. In general, Tier 1 TEAEs were more common in the PBO/ASN 5 mg treatment group (Table 2). The Tier 1 event of dizziness was reported only in the PBO/ASN 5 mg treatment group (5.0%, 3/60). A dose-dependent effect among Tier 1 TEAEs was not evident. Tier 1 SAEs/AEs leading to treatment discontinuation included somnolence (in 1 patient [1.9%] in the ASN 5 mg/ASN 5 mg group and 1 patient [2.0%] in the ASN 10 mg/ASN 10 mg group) and sedation (in 1 patient [1.7%] in the PBO/ASN 5 mg group).

Weight gain (≥7% increase from acute trial baseline to endpoint) was more frequent in the ASN 10 mg/ASN 10 mg group compared with the other treatment groups (Table 2). Weight gain was reported as a TEAE for 2 patients (one in the PBO/ASN 5 mg group and one in the ASN 5 mg/ASN 5 mg group).

Tier 2 TEAEs were most commonly reported in the PBO/ASN 5 mg treatment group, with 40.0% of patients reporting ≥1 Tier 2 TEAE compared with 32.1% in the ASN 5 mg/ASN 5 mg group and 27.5% in the ASN 10 mg/ASN 10 mg group (Table 2). The most common Tier 2

Table 1
Demographic and clinical characteristics (ATS).

Characteristics	PBO/ASN 5 mg n=60	ASN 5 mg/ ASN 5 mg n=53	ASN 5 mg overall n=113	ASN 10 mg/ ASN 10 mg n=51	Total N=164
Sex, n (%)					
Male	28 (46.7)	25 (47.2)	53 (46.9)	22 (43.1)	75 (45.7)
Female	32 (53.3)	28 (52.8)	60 (53.1)	29 (56.9)	89 (54.3)
Race, n (%)					
White	24 (40.0)	26 (49.1)	50 (44.2)	28 (54.9)	78 (47.6)
Black	29 (48.3)	24 (45.3)	53 (46.9)	23 (45.1)	76 (46.3)
Other	7 (11.7)	3 (5.7)	10 (8.8)	0 (0.0)	10 (6.1)
Age category, n (%)					
18 to 64 years	58 (96.7)	53 (100.0)	111 (98.2)	50 (98.0)	161 (98.2)
≥65 years	2 (3.3)	0 (0.0)	2 (1.8)	1 (2.0)	3 (1.8)
Age (y), mean (SD)	43.9 (10.9)	44.8 (9.6)	44.4 (10.3)	44.6 (10.7)	44.4 (10.4)
Weight (kg), mean (SD)	86.2 (17.4)	84.4 (18.8)	85.4 (18.0)	83.5 (15.8)	84.8 (17.3)
BMI ($kg/m^{2)}$, mean (SD)	29.8 (5.3)	29.4 (5.9)	29.6 (5.5)	29.3 (5.2)	29.5 (5.4)
Principal diagnosis, n (%)[a]					
Manic[b]	35 (58.3)	28 (52.8)	63 (55.8)	30 (58.8)	93 (56.7)
Mixed[c]	25 (41.7)	25 (47.2)	50 (44.2)	21 (41.2)	71 (43.3)
Duration of bipolar disorder (y), mean (SD)	13.7 (7.8)	13.8 (9.5)	13.7 (8.6)	14.4 (8.6)	13.9 (8.6)
Duration of current episode, n (%)					
< 1 week	3 (5.0)	4 (7.5)	7 (6.2)	2 (3.9)	9 (5.5)
1 to < 2 weeks	16 (26.7)	17 (32.1)	33 (29.2)	17 (33.3)	50 (30.5)
2 to < 3 weeks	25 (41.7)	15 (28.3)	40 (35.4)	18 (35.3)	58 (35.4)
3 to ≤4 weeks	16 (26.7)	16 (30.2)	32 (28.3)	14 (27.5)	46 (28.0)
> 4 weeks	0 (0.0)	1 (1.9)	1 (0.9)	0 (0.0)	1 (0.6)

ASN, asenapine; ATS; All Treated Set; BMI, body mass index; PBO, placebo; SD, standard deviation.
[a] This information was captured during the acute trial screening period.
[b] *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) category 296.4x.
[c] DSM-IV-TR category 296.6x.

Table 2
Summary of key adverse experiences (ATS).

	PBO/ASN 5 mg n=60	ASN 5 mg/ ASN 5 mg n=53	ASN 5 mg overall n=113	ASN 10 mg/ ASN 10 mg n=51
Patients With Tier 1 TEAEs, n (%)[a]				
≥1 Tier 1 TEAE	20 (33.3)	8 (15.1)	28 (24.8)	8 (15.7)
Tier 1 TEAEs				
Somnolence, sedation, hypersomnia combined	11 (18.3)	6 (11.3)	17 (15.0)	3 (5.9)
EPS	7 (11.7)	1 (1.9)	8 (7.1)	3 (5.9)
Akathisia	5 (8.3)	1 (1.9)	6 (5.3)	1 (2.0)
Oral hypoesthesia combined with dysgeusia	6 (10.0)	1 (1.9)	7 (6.2)	0 (0.0)
Insomnia	4 (6.7)	0 (0.0)	4 (3.5)	3 (5.9)
Dizziness	3 (5.0)	0 (0.0)	3 (2.7)	0 (0.0)
≥7% weight increase[b]	5 (8.9)	7 (13.7)	12 (11.2)	8 (16.3)
Patients With Tier 2 TEAEs, n (%)[c]				
≥1 Tier 2 TEAE	24 (40.0)	17 (32.1)	41 (36.3)	14 (27.5)
Patients With Tier 3 TEAEs, n (%)[d]				
≥1 Tier 3 TEAE	28 (46.7)	23 (43.4)	51 (45.1)	19 (37.3)
Patients With TEAEs, n (%)				
≥1 TEAE	41 (68.3)	29 (54.7)	70 (61.9)	26 (51.0)
Patients With TEAEs (Incidence ≥ 5%, Occurring in ≥1 Treatment Group), n (%)				
Nervous system disorders				
Sedation	6 (10.0)	3 (5.7)	9 (8.0)	2 (3.9)
Headache	4 (6.7)	2 (3.8)	6 (5.3)	3 (5.9)
Somnolence	5 (8.3)	3 (5.7)	8 (7.1)	1 (2.0)
Akathisia	5 (8.3)	1 (1.9)	6 (5.3)	1 (2.0)
Dizziness	3 (5.0)	0 (0.0)	3 (2.7)	0 (0.0)
Gastrointestinal disorders				
Oral hypoesthesia	5 (8.3)	0 (0.0)	5 (4.4)	0 (0.0)
Diarrhea	0 (0.0)	1 (1.9)	1 (0.9)	3 (5.9)
Toothache	0 (0.0)	3 (5.7)	3 (2.7)	0 (0.0)
Psychiatric disorders				
Depression	0 (0.0)	4 (7.5)	4 (3.5)	3 (5.9)
Insomnia	4 (6.7)	0 (0.0)	4 (3.5)	3 (5.9)
Infections and infestations				
Upper respiratory tract infection	7 (11.7)	2 (3.8)	9 (8.0)	2 (3.9)
Injury, poisoning and procedural complications				
Accidental overdose	4 (6.7)	2 (3.8)	6 (5.3)	2 (3.9)
Vascular disorders				
Hypertension	1 (1.7)	3 (5.7)	4 (3.5)	1 (2.0)

ASN, asenapine; ATS, All Treated Set; EPS, extrapyramidal symptoms; PBO, placebo; TEAE, treatment-emergent adverse event.

[a] Tier 1 TEAE, safety parameters, or AEs of special interest that were identified *a priori*/predefined by drug class.

[b] The denominator for percentages is the number of subjects with data at both Baseline and Study Endpoint: PBO/ASN 5 mg, n=56; ASN 5 mg/ASN 5 mg, n=51; ASN 5 mg overall, n=107; ASN 10 mg/ASN 10 mg n=49.

[c] Tier 2 TEAE, change from baseline to study endpoint in fasting glucose, fasting triglycerides, fasting cholesterol, prolactin, fasting insulin, and glycosylated hemoglobin, and specific TEAEs with incidence of ≥4 patients in any treatment group.

[d] Tier 3 TEAE, all other AEs, and predefined limits of change.

TEAEs overall were: sedation, upper respiratory tract infection, headache, and somnolence. The TEAE of oral hypoesthesia was reported only in patients in the PBO/ASN 5 mg group (5 patients, 8.3%). At least 1 Tier 3 TEAE was reported by 46.7% of patients in the PBO/ASN 5 mg group, 43.4% of patients in the ASN 5 mg/ASN 5 mg group, and 37.3% of patients in the ASN 10 mg/ASN 10 mg group (Table 2).

A summary of mean metabolic, lipid, and endocrine parameters at acute study baseline, extension baseline, and endpoint is presented in Table 3. From extension trial baseline to endpoint, increases were observed in mean levels of prolactin across all treatment groups with the largest increase in the ASN 10 mg/ASN 10 mg group. Prolactin levels >4 times the upper limit of normal (PDLC for prolactin) were observed in 3 patients (one in the PBO/ASN 5 mg group and two in the ASN 10 mg/ASN 10 mg group). No TEAEs related to prolactin abnormalities were reported. A mean increase in insulin was observed in the ASN 10 mg/ASN 10 mg group, but not the ASN 5 mg/ASN 5 mg group. Mean increases also were observed across all groups for glucose and in the ASN 5 mg/ASN 5 mg and ASN 10 mg/ASN 10 mg groups for fasting triglycerides.

3.3. Efficacy

Mean changes in efficacy parameters at acute trial baseline, extension baseline, and endpoint are summarized in Table 4. Change in YMRS total score from the acute trial baseline in this uncontrolled extension trial indicated that improvement in mania in the controlled acute trial was maintained through the course of the uncontrolled extension study and was similar across treatment groups. The least-squares (LS) mean change in OC YMRS total score from the acute trial baseline to day 182 (extension-study endpoint) was −22.3 in the PBO/ASN 5 mg group, −22.9 in the ASN 5 mg/ASN 5 mg group, and −22.0 in the ASN 10 mg/ASN 10 mg group.

Increases in OC YMRS responder rates from extension trial baseline were +43.6% in the PBO/ASN 5 mg group, +38.0% in the ASN 5 mg/ASN 5 mg group, and +26.0% in the ASN 10 mg/ASN 10 mg group. Increases in OC YMRS remitter rates from extension trial baseline were +43.3% in the PBO/ASN 5 mg group and +41.8% in the ASN 5 mg/ASN 5 mg group, but were somewhat lower at +18.0% in the ASN 10 mg/ASN 10 mg group.

Change in CGI-BP-OS score from acute trial baseline in this uncontrolled extension trial indicated that improvement in overall severity of bipolar illness was maintained through the course of the study and was similar across treatment groups. The LS mean change in OC CGI-BP-OS scores from acute baseline to the extension trial study endpoint were −2.3 in the PBO/ASN 5 mg group, −2.4 in the ASN 5 mg/ASN 5 mg group, and −2.3 in the ASN 10 mg/ASN 10 mg group.

An increase in OC CGI-BP-I overall response rates was seen in the PBO/ASN 5 mg treatment group, although there was little notable change from the extension trial baseline in the ASN 5 mg/ASN 5 mg or ASN 10 mg/ASN 10 mg treatment groups. Shifts in incidence of OC CGI-BP-I overall responders from extension trial baseline to study endpoint were as follows: PBO/ASN 5 mg, +13.2%; ASN 5 mg/ASN 5 mg, −6.4%; ASN 10 mg/ASN 10 mg, −10.0%.

In general, findings with the LOCF approach were similar to those using the above OC approach.

4. Discussion

Long-term treatment with fixed doses of ASN (5 mg bid and 10 mg bid) was generally safe and well tolerated in adults with an acute manic or mixed episode associated with bipolar I disorder treated for up to 29 weeks. No new or emerging safety/tolerability signals were observed in

Table 3
Summary of metabolic, lipid, and endocrine parameters (ATS).

Parameter	PBO/ASN 5 mg n=60		ASN 5 mg/ASN 5 mg n=53		ASN 5 mg overall n=113		ASN 10 mg/ASN 10 mg n=51	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Prolactin, ng/mL								
Acute Trial Baseline	58	11.9 (10.5)	53	13.6 (22.5)	111	12.7 (17.3)	50	9.4 (6.1)
Extension Baseline	58	8.6 (11.3)	50	21.4 (18.9)	108	14.5 (16.5)	51	23.8 (24.6)
Study Endpoint	55	15.1 (14.4)	50	17.6 (24.4)	105	16.3 (19.7)	49	22.3 (32.0)
Change[a]	55	3.2 (16.7)	50	3.6 (17.5)	105	3.4 (17.0)	49	12.7 (32.5)
Insulin, µU/mL								
Acute Trial Baseline	58	18.7 (13.7)	53	29.4 (42.0)	111	23.8 (31.0)	49	18.5 (19.9)
Extension Baseline	58	15.5 (17.6)	51	23.4 (30.8)	109	19.2 (24.9)	49	21.2 (27.1)
Study Endpoint	55	20.2 (14.5)	48	29.8 (40.7)	103	24.7 (30.0)	49	28.0 (55.4)
Change[a]	55	0.6 (19.0)	48	−1.2 (50.3)	103	−0.2 (36.8)	48	10.2 (49.8)
Total Cholesterol, mg/dL								
Acute Trial Baseline	58	186.7 (39.3)	53	198.7 (49.0)	111	192.5 (44.4)	50	197.9 (43.4)
Extension Baseline	58	181.3 (38.6)	50	197.2 (44.3)	108	188.6 (41.9)	51	192.3 (40.7)
Study Endpoint	55	180.1 (41.9)	50	201.3 (46.9)	105	190.2 (45.4)	50	195.8 (47.0)
Change[a]	55	−4.7 (30.7)	50	3.4 (35.3)	105	−0.9 (33.1)	50	−1.3 (32.8)
Fasting Triglycerides, mg/dL								
Acute Trial Baseline	51	133.8 (108.1)	47	140.4 (83.6)	98	137.0 (96.7)	45	133.5 (71.2)
Extension Baseline	54	94.8 (45.0)	44	132.5 (92.4)	98	111.7 (72.4)	48	127.1 (66.2)
Study Endpoint	52	122.4 (75.4)	43	146.7 (86.7)	95	133.4 (81.2)	46	145.9 (86.9)
Change[a]	49	−9.5 (80.3)	41	9.0 (75.9)	90	−1.1 (78.5)	45	10.6 (62.9)
Glucose, mg/dL								
Acute Trial Baseline	59	96.1 (14.6)	53	96.9 (18.1)	112	96.5 (16.3)	50	92.8 (15.8)
Extension Baseline	58	93.8 (16.5)	50	101.7 (32.3)	108	97.5 (25.3)	51	98.7 (18.3)
Study Endpoint	55	98.2 (15.0)	50	103.6 (31.4)	105	100.8 (24.2)	50	97.3 (15.5)
Change[a]	55	2.6 (14.9)	50	7.0 (29.4)	105	4.7 (23.0)	50	3.9 (16.3)
Glycosylated Hemoglobin, %								
Acute Trial Baseline	58	5.5 (0.5)	53	5.5 (0.5)	111	5.5 (0.5)	50	5.4 (0.5)
Extension Baseline	58	5.5 (0.5)	51	5.6 (0.6)	109	5.6 (0.6)	51	5.5 (0.5)
Study Endpoint	54	5.5 (0.4)	50	5.7 (1.3)	104	5.6 (1.0)	48	5.5 (0.4)
Change[a]	54	0.0 (0.3)	50	0.2 (1.1)	104	0.1 (0.8)	48	0.0 (0.4)

ASN, asenapine; ATS, All Treated Set; PBO, placebo.
Acute Trial Baseline: last non-missing assessment prior to the first dose of acute trial medication.
Extension Baseline: last non-missing assessment prior to the first dose of extension trial medication.
Study Endpoint: last non-missing post-baseline assessment on or prior to the last dose date +7 days.
[a] Change from acute trial baseline to study endpoint.

Table 4
Efficacy parameters at acute trial baseline, extension trial baseline, and study endpoint (FAS).

	PBO/ASN 5 mg		ASN 5 mg/ASN 5 mg		ASN 10 mg/ASN 10 mg	
YMRS Total Score	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Acute Trial Baseline	59	29.8 (5.6)	52	28.3 (5.0)	50	31.4 (5.0)
Extension Trial Baseline	59	18.1 (10.7)	52	13.3 (8.6)	50	13.8 (8.9)
Endpoint	57	7.7 (7.1)	50	6.5 (7.2)	50	8.3 (7.7)
YMRS Responders	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Extension Trial Baseline	59	26 (44.1)	52	26 (50.0)	50	29 (58.0)
Endpoint	57	50 (87.7)	50	44 (88.0)	50	42 (84.0)
YMRS Remitters	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Extension Trial Baseline	59	20 (33.9)	52	23 (44.2)	50	25 (50.0)
Endpoint	57	44 (77.2)	50	43 (86.0)	50	34 (68.0)
CGI-BP-OS	**N**	**Mean Overall Score (SD)**	**N**	**Mean Overall Score (SD)**	**N**	**Mean Overall Score (SD)**
Acute Trial Baseline	59	4.4 (0.5)	52	4.5 (0.7)	50	4.7 (0.5)
Extension Trial Baseline	59	3.3 (1.1)	52	2.7 (0.9)	50	2.8 (1.1)
Endpoint	57	2.2 (1.1)	50	2.1 (1.1)	50	2.2 (1.2)
CGI-BP-I Responders	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Extension Trial Baseline	59	45 (76.3)	52	47 (90.4)	50	45 (90.0)
Endpoint	57	51 (89.5)	50	42 (84.0)	50	40 (80.0)

ASN, asenapine; CGI-BP-I, Clinical Global Impression-Bipolar Mania-Improvement; CGI-BP-OS, Clinical Global Impression-Overall Severity; FAS, Full Analysis Set; PBO, placebo; SD, standard deviation; YMRS, Young Mania Rating Scale.
Acute Trial Baseline: Last non-missing assessment prior to first dose of acute trial medication.
Extension Trial Baseline: Last non-missing assessment prior to first dose of extension trial medication.
Endpoint: Last non-missing post-baseline assessment on or prior to last dose date +3 days.
YMRS Responders: subjects who experienced at least 50% decrease from acute trial baseline in YMRS total score at that visit.
YMRS Remitters: subjects having YMRS total score ≤12 at that visit.

this long-term extension trial. The broad pattern of TEAEs and the discontinuation rate due to them were similar to those seen during a long-term trial of ASN in patients with schizophrenia or schizoaffective disorder (Schoemaker et al., 2010). Sedation and somnolence were the most commonly reported Tier 1 TEAEs, and may be treatment-limiting in a minority of patients. Together with akathisia, headache, dizziness, and oral hypoesthesia, these Tier 1 TEAEs occurred more frequently in those patients who received PBO during the acute trial and ASN 5 mg during the long-term extension compared with other treatment groups, and did not appear to be dose-dependent. This suggests that some TEAEs that occur upon treatment initiation may resolve over time. The rate of treatment discontinuation due to AEs was similar across all treatment groups suggesting that most patients are able to adhere to their treatment regimen even at the higher dose of ASN. AEs leading to discontinuation were most commonly Psychiatric and Nervous System Disorders and were observed across all groups. No deaths occurred during this long-term extension study, and most SAEs involved Psychiatric Disorders related to the patient's underlying condition of bipolar I disorder.

Overall, 12.8% of patients taking ASN experienced potentially clinically significant weight gain (≥7% increase in body weight at endpoint compared with the acute trial baseline). There was a trend towards a greater incidence of ≥7% weight increase in patients who received ASN 10 mg/ASN 10 mg (16.3%) compared with other treatment groups (PBO/ASN 5 mg group, 8.9%; ASN 5 mg/ASN 5 mg, 13.7%; ASN 5 mg overall, 11.2%). Among those who had weight gain meeting the PDLC, the increase in weight was reported as a TEAE for 2 patients. From the extension trial baseline to endpoint, increases in mean glucose and prolactin levels were seen for all treatment groups. Prolactin increases were greatest in the ASN 10 mg/ASN 10 mg group, although there was wide variability in these measurements as evidenced by the large standard deviations. Despite the observed increases in mean prolactin levels, a low percentage of patients (1.8%, 3 of 164 patients) had values that met PDLC levels, and no TEAEs related to prolactin abnormalities were reported in this study. Mean increases also were observed in some groups with respect to fasting triglycerides and insulin, whereas total cholesterol was increased in the ASN 5 mg/ASN 5 mg group alone.

Over the course of this 26-week, double-blind, uncontrolled extension trial, the results of measures of mania and overall severity of illness indicated improvement over time. However, the conclusiveness of such results is confounded by the uncontrolled nature of the trial design.

4.1. Limitations

This study had noteworthy strengths, including a relatively large sample size, double-blind treatment, extended treatment duration, and long-term TEAE monitoring. However, this study also had noteworthy limitations, including the absence of a comparator group throughout the 26-week extension period, restricting conclusions, arguably more with respect to efficacy than with respect to safety/tolerability. Moreover, this trial was not powered for direct comparisons of ASN 5 mg bid versus 10 mg bid, making conclusions regarding dose-dependency of outcomes particularly challenging. Pharmacokinetic data was not collected, so plasma levels of the drug following long-term treatment are not available. Clinically significant weight gain (≥7% increase) was not evaluated from extension trial baseline to endpoint which prohibits drawing conclusions related to the potential stabilization of weight change. Further, an extension study tends to include patients who responded to the drug and in whom the drug was tolerated and reasonably safe.

It should also be noted that our findings may not be applicable to more general bipolar disorder populations, owing to the trial's inclusion and exclusion criteria. Furthermore, it needs to be kept in mind that patients were enrolled based on the DSM-IV-TR diagnostic criteria, which have since been updated in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), limiting interpretation of our findings with respect to DSM-5 nosology. For example, DSM-IV-TR defined mixed states as the simultaneous presence of both threshold major depressive and manic episodes (DSM-IV-TR., 2000), whereas DSM-5 has replaced the diagnosis of mixed episode with the more inclusive mixed features (≥3 opposite pole symptoms) specifier that can be applied to threshold episodes of mania, hypomania, and even major depression (American Psychiatric Association, 2013). Although it is unclear how results of a clinical study conducted using DSM-IV criteria for manic and mixed episodes should be interpreted in the context of DSM-5 (which would diagnose manic episodes without and with mixed features, but not mixed episodes), the emphasis of the current study on safety/tolerability rather than efficacy may mitigate this limitation.

5. Conclusion

Long-term treatment with ASN 5 and 10 mg bid was generally safe and well tolerated in adults with an acute manic or mixed episode associated with bipolar I disorder treated for up to 29 weeks. No dose-dependence for predefined TEAEs was apparent, and SAEs were primarily due to patients' underlying bipolar I disorder. In addition, the metabolic effects of ASN in this uncontrolled trial appear to be consistent with findings from earlier trials.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2016.09.037.

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