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Research report

Asenapine for long-term treatment of bipolar disorder: A double-blind 40-week extension study

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ABSTRACT

Background: Asenapine is approved in the United States for acute treatment of manic or mixed episodes of bipolar I disorder with or without psychotic features. We report the results of long-term treatment with asenapine in patients with bipolar I disorder.
Methods: Patients completing either of two 3-week efficacy trials and a subsequent 9-week double-blind extension were eligible for this 40-week double-blind extension. Patients in the 3-week trials were randomized to flexible-dose asenapine (5 or 10 mg BID), placebo, or olanzapine (5–20 mg QD; included for assay sensitivity only). Patients entering the extension phase maintained their preestablished treatment; those originally randomized to placebo received flexible-dose asenapine (placebo/asenapine). Safety and tolerability endpoints included adverse events (AEs), extrapyramidal symptoms, laboratory values, and anthropometric measures. Efficacy, a secondary assessment, was measured as change in Young Mania Rating Scale (YMRS) total score from 3-week trial baseline to week 52 with asenapine or olanzapine; the placebo/asenapine group was assessed for safety only.
Results: Incidence of treatment-emergent AEs was 71.9%, 86.1%, and 79.4% with placebo/asenapine, asenapine, and olanzapine, respectively. The most frequent treatment-emergent AEs were headache and somnolence with placebo/asenapine; insomnia, sedation, and depression with asenapine; and weight gain, somnolence, and sedation with olanzapine. Among observed cases, mean ± SD changes in YMRS total score at week 52 were −28.6 ± 8.1 and −28.2 ± 6.8 for asenapine and olanzapine, respectively.
Limitations: The study did not have a long-term placebo group.
Conclusions: In this 52-week extension in patients with bipolar mania, asenapine was well tolerated and long-term maintenance of efficacy was supported.

1. Introduction

Bipolar disorders are highly prevalent chronic conditions, heterogeneous in phenomenology and pathoetiology (Bauer and Pfennig, 2005; Judd and Akiskala, 2003; Merikangas et al., 2007; Shastry, 2005). During the past decade, there have been substantial developments in the pharmacologic treatment of various phases of bipolar disorder, notably acute mania (Gajwani et al., 2006; Ketter et al., 2006; Weisler et al., 2006). However, relatively few long-term studies have evaluated relapse prevention or the maintenance of acute efficacy and tolerability of pharmacologic treatments during long-term extensions of short-term studies (Vieta et al., 2008a,b). The pertinacity of this deficiency is underscored by prospective naturalistic longitudinal studies that have

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documented substantial rates of nonrecovery, subsyndromal symptomatology, relapse/recurrence rates, and psychosocial impairment during the maintenance phase of bipolar disorder (Judd et al., 2008a,b).

Asenapine is an atypical antipsychotic approved in the United States for the acute treatment of schizophrenia in adults and of manic or mixed episodes of bipolar I disorder with or without psychotic features in adults (Saphris® (asenapine) sublingual tablets. Full Prescribing Information, 2009). It has been developed in a fast-dissolving sublingual formulation. Asenapine has a unique human receptor-binding profile characterized by high affinity for serotonergic, dopaminergic, α-adrenergic, and histaminergic receptor subtypes but no appreciable affinity for muscarinic cholinergic receptors (Shahid et al., 2009).

The short-term efficacy, tolerability, and safety of asenapine in treating acute mania in bipolar I disorder were assessed in two similarly designed 3-week randomized, double-blind, double-dummy, placebo- and active-controlled trials (A7501004, trial registration number NCT00159744; A7501005, NCT00159796). The primary efficacy parameter was the change from baseline on the Young Mania Rating Scale (YMRS) total score at endpoint with asenapine versus placebo. Across both studies, 960 patients were assessed for efficacy after randomization to treatment with asenapine, placebo, or olanzapine (McIntyre et al., 2009a; McIntyre et al., 2010). In each study, asenapine was significantly more effective than placebo at endpoint in decreasing YMRS total scores; advantage was seen as early as treatment day 2. Similar results were observed with olanzapine versus placebo (assessed for assay sensitivity only).

Of the 680 patients who completed either of these 3-week efficacy trials, 504 were enrolled in a double-blind, double-dummy, 9-week extension study (A7501006, NCT00143182) to assess the efficacy and tolerability of asenapine over a longer time frame (McIntyre et al., 2009b). In this trial, asenapine was directly compared with olanzapine using a statistical analysis for noninferiority. An assessment of the change in YMRS total score from baseline to day 84 indicated that asenapine met the criteria for noninferiority to olanzapine. Furthermore, the incidence of treatment-emergent adverse events (AEs) was similar across treatment groups. Thus, asenapine remained efficacious and appeared to be well tolerated over a total of 12 weeks of treatment.

In the current study (A7501007, NCT00159783), treatment with asenapine and olanzapine was extended for an additional 40 weeks to provide safety and tolerability data over 1 year of treatment. The primary objective was to characterize the long-term safety and tolerability of asenapine in patients with manic or mixed episodes of bipolar I disorder for up to 52 weeks. Efficacy endpoints were considered secondary, and the trial was not powered to assess noninferiority or superiority of the active treatments.

2. Methods

2.1. Study design and participants

This 40-week, double-blind, double-dummy, multicenter, parallel-group extension study was conducted at 76 centers (United States, $n=32$; India, $n=10$; Russian Federation, $n=7$; Ukraine, $n=10$; Korea, $n=2$; Bulgaria, $n=4$; Philippines, $n=4$; Romania, $n=2$; Turkey, $n=2$; Malaysia, $n=3$). Patients who completed the 9-week extension of the 3-week efficacy trials were eligible for this double-blind 40-week study if they had no major protocol violations.

Principal inclusion and exclusion criteria were as described in the preceding trials (McIntyre et al., 2009a; McIntyre et al., 2010). All patients provided written informed consent. The study protocol was approved by the independent ethics committee/institutional review board at each center.

2.2. Treatment

Patients enrolled in the 40-week extension study were maintained on the treatment regimen established during the 3-week efficacy trials and the 9-week extension, with the blind maintained for all patients and investigators. Sublingual asenapine was started at 10 mg twice daily (BID) on day 1 of the 3-week efficacy trials and was flexible (5 or 10 mg BID) thereafter. Oral olanzapine was started at 15 mg once daily (QD) on day 1 of the 3-week trials and was flexible (5–20 mg QD) thereafter. The "placebo/asenapine" group comprised patients who received placebo during the 3-week efficacy trials and were switched to asenapine in the 9-week extension study (10 mg BID on day 1, with flexible dosing at 5 or 10 mg BID thereafter) with the blind unbroken. These patients were maintained on this regimen in the 40-week extension study but were included in the safety analyses only. Concomitant medications were allowed provided patients followed protocol guidelines established during the 3-week efficacy trials (McIntyre et al., 2009a, 2010).

2.3. Endpoints

Safety and tolerability endpoints included patient- and investigator-reported AEs, extrapyramidal symptoms (EPS) reported as AEs, and EPS measured using standard rating scales (Abnormal Involuntary Movement Scale [AIMS] (Munetz and Benjamin, 1988), Barnes Akathisia Rating Scale [BARS] (Barnes, 1989), and Simpson–Angus Scale [SAS] (Simpson and Angus, 1970)). Other safety and tolerability endpoints included laboratory measures (including glucose, lipids, prolactin, and hepatic enzymes), vital signs, anthropometric measures (body weight, abdominal girth, body mass index [BMI]), and electrocardiograms (ECG). Safety and tolerability data are reported from the start of the 3-week core trials, with baseline referring to baseline of the 3-week trials.

Efficacy assessments included changes from baseline of the 3-week efficacy trials on YMRS total score (Young et al., 1978), Clinical Global Impression for Bipolar Disorder (CGI-BP) mania severity (Guy, 1976), and Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery, 1979) total score. The percentages of responders (≥50% decrease in YMRS total score from baseline of the 3-week efficacy trials) and remitters (YMRS total score ≤12) were assessed at each visit. These response and remission criteria are consistent with those used in other published studies (Houston et al., 2009; McIntyre et al., 2009a,b, 2010; Patel et al., 2007) and are considered to be clinically meaningful by clinicians and

regulatory agencies. Time to response failure, defined as the number of days between a patient first achieving responder status (≥50% reduction in baseline YMRS total score) and then reverting to ≤30% reduction in baseline YMRS total score, was also assessed. Reported results are based on assessments in the intent-to-treat (ITT) population at study endpoint using last observation carried forward (LOCF) and at week 52 in observed cases (OC).

2.4. Statistical analysis

Safety analyses used data from the treated population (all patients who took ≥1 dose of study medication during the 40-week extension). Descriptive statistics are provided for all safety and tolerability measures.

Efficacy was assessed in the ITT population, which included all patients who took ≥1 dose of study medication and had ≥1 YMRS assessment during the 40-week extension. The placebo/asenapine group was not included in the efficacy analysis because of the shorter duration of treatment in this group.

Data collected from patients entering the extension study were combined across the two 3-week efficacy trials and the 9-week extension and analyzed together. Efficacy endpoints included change from baseline of the 3-week efficacy trials in YMRS total, CGI-BP mania severity, and MADRS total scores. Data from the ITT population with OC analysis at week 52 and with LOCF analysis at endpoint are presented. Summary statistics were provided for continuous and categorical endpoints. Fisher's exact tests were used for analyzing binary endpoints (eg, proportion of YMRS responders and remitters). Time to response failure was analyzed using a log-rank test based on Kaplan–Meier estimations.

Post hoc analyses included assessment of the percentages of patients with shifts in MADRS scores from ≤8 at baseline to ≥16 at study endpoint or those with increases in YMRS total score of ≥25% from baseline at study endpoint. Additionally, the number needed to harm (NNH) for clinically significant weight gain and shifts in blood glucose and the number needed to treat (NNT) for YMRS response and remission were calculated. NNH and NNT were calculated as the reciprocal of the difference between outcomes with asenapine or olanzapine.

3. Results

3.1. Patient disposition and demographics

Of the 308 patients who completed the 9-week extension (placebo/asenapine, $n=50$; asenapine, $n=112$; olanzapine, $n=146$), 218 enrolled in the 40-week extension and received ≥1 dose of study medication (treated population). A total of 133 (61.0%) completed the 40-week extension (placebo/asenapine, $n=13$ [40.6%]; asenapine, $n=52$ [65.8%]; olanzapine, $n=68$ [63.6%]) (Fig. 1). Discontinuation rates due to AEs were highest in the placebo/asenapine group ($n=5$, 15.6%) but were comparable in the asenapine ($n=7$, 8.9%) and olanzapine ($n=9$, 8.4%) groups (Fig. 1). The discontinuation rate due to AEs among all patients who received asenapine (79 patients in the asenapine group plus 32 patients in the placebo/asenapine group) was 10.8% (12 of 111). Discontinuation rates due to lack of efficacy were 3.1% with placebo/asenapine ($n=1$), 2.5% with asenapine ($n=2$), and 2.8% with olanzapine ($n=3$); the rate of discontinuation for lack of efficacy among all patients treated with asenapine was 2.7% (3 of 111).

Some differences in demographic characteristics were noted across treatment groups (Table 1). The proportion of men was highest in the olanzapine group. In the placebo/asenapine group, the proportion of white patients was

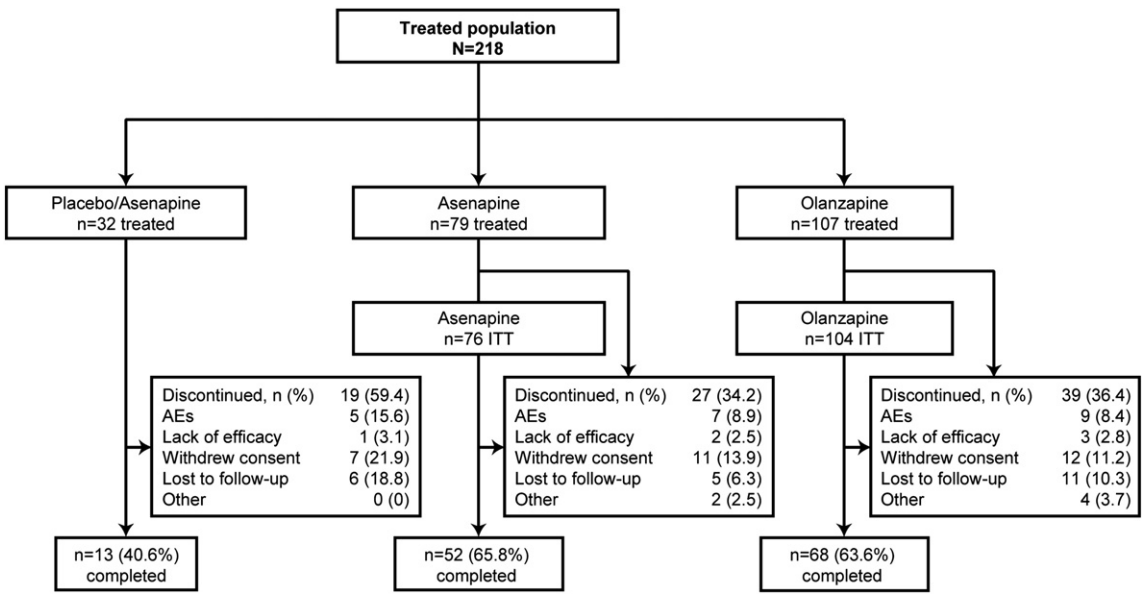

Fig. 1. Patient disposition in the 40-week extension. AE = adverse event; ITT = intent-to-treat.

Table 1
Baseline demographics and clinical characteristics in the treated population.

	Number (%) of patients		
	Placebo/ asenapine	Asenapine	Olanzapine
	($n=32$)	($n=79$)	($n=107$)
Sex, *n* (%)			
Men	17 (53.1)	36 (45.6)	68 (63.6)
Women	15 (46.9)	43 (54.4)	39 (36.4)
Race, *n* (%)			
White	25 (78.1)	38 (48.1)	57 (53.3)
Black	2 (6.3)	5 (6.3)	4 (3.7)
Asian	3 (9.4)	34 (43.0)	44 (41.1)
Other	2 (6.3)	2 (2.5)	2 (1.9)
Age category, *n* (%)			
18–64 y	31 (96.9)	77 (97.5)	106 (99.1)
≥65 y	1 (3.1)	2 (2.5)	1 (0.9)
Age, y			
Mean ± SD age, y	38.8 ± 13.0	37.8 ± 13.3	38.7 ± 12.4
Range	19–65	18–73	18–67
Mean ± SD weight, kg (lb)	81.4 ± 19.9 (179.5 ± 44.0)	68.1 ± 17.2 (150.1 ± 38.0)	72.0 ± 20.0 (158.7 ± 44.0)
Mean ± SD BMI, kg/m^2	27.9 ± 5.7	24.6 ± 4.8	25.3 ± 5.7
Bipolar I diagnosis, *n* (%)			
Manic	23 (71.9)	63 (79.7)	85 (79.4)
Mixed	9 (28.1)	16 (20.3)	22 (20.6)

BMI = body mass index.

highest. Mean weight and BMI at baseline were higher in the placebo/asenapine group than in the other groups.

3.2. Drug exposure

The mean ± SD treatment duration was 250 ± 101 days in the placebo/asenapine group, 313 ± 88 days in the asenapine group, and 300 ± 98 days in the olanzapine group. The mean ± SD total daily dose taken was 15.7 ± 4.1 mg in the placebo/asenapine group, 16.3 ± 3.7 mg in the asenapine group, and 15.4 ± 4.0 mg in the olanzapine group. The total daily modal dose was 20 mg in all 3 treatment groups.

3.3. Concomitant medication use

Concomitant medications were used by 68.8%, 73.4%, and 71.0% of patients in the placebo/asenapine, asenapine, and olanzapine groups, respectively. Antiparkinson medications were used by 15.6%, 13.9%, and 8.4% of patients in the placebo/asenapine, asenapine, and olanzapine groups. Medications used by ≥10% of patients across all treatment groups were lorazepam (placebo/asenapine, 43.8%; asenapine, 34.2%; olanzapine, 37.4%), zolpidem (placebo/asenapine, 21.9%; asenapine, 25.3%; olanzapine, 15.9%), acetaminophen (placebo/asenapine, 25.0%; asenapine, 24.1%; olanzapine, 17.8%), and ibuprofen (placebo/asenapine, 21.9%; asenapine, 10.1%; olanzapine, 13.1%). Trihexyphenidyl use was reported by 10.1% of patients treated with asenapine and by 5.6% of patients treated with olanzapine.

3.4. Safety and tolerability

3.4.1. Adverse events

The incidence of treatment-emergent AEs (including serious AEs [SAEs]) was 71.9%, 86.1%, and 79.4% in the placebo/asenapine, asenapine, and olanzapine groups, respectively; the incidence of treatment-related AEs was 53.1%, 70.9%, and 61.7% (Table 2). The majority of AEs were rated as mild to moderate in all 3 treatment groups (59.4%, 77.2%, and 67.3% of AEs in the placebo/asenapine, asenapine, and olanzapine groups). The incidence of treatment-emergent SAEs was 6.3%, 11.4%, and 10.3% in the placebo/asenapine, asenapine, and olanzapine groups; the incidence of treatment-related SAEs was 0%, 3.8%, and 2.8% (Table 2).

Two deaths were reported during the study, 1 in the asenapine group that was considered possibly related to study medication by the investigator and 1 in the olanzapine group that was considered unlikely to be related to study medication by the investigator. The death in the asenapine group was a fetal death that occurred in a pregnant patient. The patient had previously experienced 3 miscarriages at 12 to 20 weeks of gestation and 1 cesarean section after 34 weeks due to fetal distress. She gave birth prematurely (31 weeks and 5 days of gestation), and the baby, who had no visible anomalies, died. In the olanzapine group, 1 patient committed suicide.

The most common treatment-emergent AEs (occurring in ≥10% of patients in any group) are summarized in Table 2. Headache, somnolence, insomnia, nausea, parkinsonism, tremor, and constipation were the most commonly reported AEs in the placebo/asenapine group; insomnia, sedation, depression, headache, somnolence, increased weight, dizziness, nausea, and akathisia in the asenapine group; and increased weight, somnolence, sedation, headache, insomnia, and akathisia in the olanzapine group.

Table 2
Incidence of adverse events in the treated population.

	Number (%) of patients		
	Placebo/ asenapine	Asenapine	Olanzapine
	($n=32$)	($n=79$)	($n=107$)
Treatment-emergent AEs/SAEs	23 (71.9)	68 (86.1)	85 (79.4)
Treatment-emergent SAEs	2 (6.3)	9 (11.4)	11 (10.3)
Treatment-related AEs/SAEs	17 (53.1)	56 (70.9)	66 (61.7)
Treatment-related SAEs	0 (0.0)	3 (3.8)	3 (2.8)
Common treatment-emergent AEs (≥10% of patients in any group)			
Insomnia	4 (12.5)	16 (20.3)	13 (12.1)
Sedation	3 (9.4)	13 (16.5)	17 (15.9)
Depression	3 (9.4)	12 (15.2)	8 (7.5)
Headache	5 (15.6)	11 (13.9)	15 (14.0)
Somnolence	5 (15.6)	11 (13.9)	17 (15.9)
Weight increased	3 (9.4)	11 (13.9)	19 (17.8)
Dizziness	3 (9.4)	10 (12.7)	6 (5.6)
Nausea	4 (12.5)	10 (12.7)	4 (3.7)
Akathisia	2 (6.3)	9 (11.4)	11 (10.3)
Parkinsonism	4 (12.5)	6 (7.6)	4 (3.7)
Tremor	4 (12.5)	6 (7.6)	5 (4.7)
Constipation	4 (12.5)	5 (6.3)	4 (3.7)

AE = adverse event; SAE = serious adverse event.

Among all patients treated with asenapine (asenapine group or placebo/asenapine group), AEs occurring at a rate of ≥10% and occurring at least twice as often as was seen with olanzapine included depression, dizziness, nausea, parkinsonism, tremor, and constipation; among patients treated with olanzapine, there were no commonly reported AEs occurring twice as often as was seen with asenapine (either group). Among patients in the placebo/asenapine group, there were no commonly reported AEs occurring twice as often as was seen with asenapine; nausea, parkinsonism, tremor, and constipation were reported at least twice as often with placebo/asenapine compared with olanzapine.

3.4.2. Extrapyramidal symptoms

As summarized in Table 3, EPS reported as an AE in >2% of patients in any group included akathisia, parkinsonism, bradykinesia, dystonia, gait disturbance, dyskinesia, and tardive dyskinesia. However, as assessed by formal rating scales, mean changes from baseline on the AIMS, BARS, and SAS were minimal and similar across treatment groups. During the study, the percentages of patients shifting to AIMS global scores ≥2 and SAS mean total scores >0.3 were slightly higher in the placebo/asenapine and asenapine groups than in the olanzapine group. The percentages of patients shifting to BARS global scores ≥2 were higher in the asenapine group compared with the placebo/asenapine and olanzapine groups.

Table 3
Extrapyramidal symptoms reported as adverse events and assessed by changes on EPS rating scale scores in the treated population.

	Placebo/ asenapine	Asenapine	Olanzapine
	(*n* = 32)	(*n* = 79)	(*n* = 107)
Reported as adverse events, n (%)			
Akathisia	2 (6.3)	9 (11.4)	11 (10.3)
Parkinsonism	4 (12.5)	6 (7.6)	4 (3.7)
Bradykinesia	0 (0.0)	3 (3.8)	2 (1.9)
Dystonia	1 (3.1)	3 (3.8)	1 (0.9)
Gait disturbance	0 (0.0)	2 (2.5)	0 (0.0)
Tardive dyskinesia	0 (0.0)	2 (2.5)	0 (0.0)
Dyskinesia	1 (3.1)	1 (1.3)	0 (0.0)
Masked facies	0 (0.0)	1 (1.3)	0 (0.0)
Parkinsonian rest tremor	0 (0.0)	1 (1.3)	0 (0.0)
Hypokinesia	0 (0.0)	0 (0.0)	2 (1.9)
Rating scale scores, mean ± SD			
AIMS 7 score, baseline	0.1 ± 0.25	0.1 ± 0.42	0.2 ± 0.64
Change from baseline [a]	0.4 ± 1.39	0.0 ± 0.41	−0.1 ± 0.6
BARS global score, baseline	0.3 ± 0.70	0.2 ± 0.66	0.2 ± 0.63
Change from baseline [a]	−0.1 ± 0.71	−0.1 ± 0.78	−0.1 ± 0.56
SAS total score, baseline	0.4 ± 0.91	0.3 ± 0.90	0.6 ± 1.84
Change from baseline [a]	0.2 ± 1.23	−0.1 ± 1.67	−0.3 ± 1.56
Shifts to worsening scores, n/number assessed [b] (%)			
AIMS global score ≥2	1/32 (3.1)	3/79 (3.8)	0/107 (0.0)
BARS global score ≥2	0/28 (0.0)	7/77 (9.1)	6/102 (5.9)
SAS mean total score >0.3	3/31 (9.7)	10/76 (13.2)	9/101 (8.9)

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; EPS = extrapyramidal symptoms; SAS = Simpson–Angus Scale.

[a] Positive change indicates worsening symptoms.

[b] Restricted to patients with an AIMS global score <2, BARS global score <2, and SAS mean total score ≤0.3 at baseline.

3.4.3. Laboratory, endocrine, and anthropometric measures

Changes from baseline in metabolic chemistries and laboratory values were generally small and not considered clinically relevant (Table 4). Shifts from low or normal fasting blood glucose levels to high levels were observed in 10% (2/20) of placebo/asenapine, 26.0% (13/50) of asenapine, and 22.2% (14/63) of olanzapine patients, respectively. Post hoc analysis indicated that the NNH value for shifts to high levels of fasting glucose was 27 [95% CI, range −∞ to −8 and 5 to ∞] for asenapine relative to olanzapine.

Aspartate aminotransferase levels >3 times the upper limit of normal (ULN) were documented in 3.1%, 3.8%, and 1.9% of the placebo/asenapine, asenapine, and olanzapine groups, respectively. Alanine aminotransferase levels >3 times the ULN occurred in 6.3%, 5.1%, and 7.5% of the placebo/asenapine, asenapine, and olanzapine groups.

Prolactin levels >4 times the ULN occurred in 0%, 6.5%, and 2.9% of the placebo/asenapine, asenapine, and olanzapine groups, respectively; abnormal prolactin levels were not reported as an AE in any treatment group. Shifts to high prolactin levels in patients with normal or low prolactin levels at baseline at any time during treatment occurred in 33.3% of placebo/asenapine-treated patients, 34.3% of asenapine-treated patients, and 61.9% of olanzapine-treated patients. The mean ± SD and median changes in prolactin levels in ng/mL [converted from micro-International Units/L (Ahmad and Beckett, 2004)] from baseline to last assessment were 0.58 ± 14.84 and 2.27 ng/mL in the placebo/asenapine group, 5.29 ± 28.43 and 0.47 ng/mL in the asenapine group, and 6.04 ± 17.66 and 4.20 ng/mL in the olanzapine group. The incidence of AEs that could be attributable to elevated prolactin levels (ie, hyperinsulinemia, amenorrhea, dysmenorrhea, dysfunctional uterine bleeding, irregular menstruation, metrorrhagia, or erectile dysfunction) was 6.3%, 5.1%,

Table 4
Summary of laboratory results.

	Mean change from baseline		
	Placebo/ asenapine	Asenapine	Olanzapine
	(*n* = 32)	(*n* = 79)	(*n* = 107)
Total cholesterol, mmol/L (mg/dL)	0.197 (7.61)	−0.118 (−4.56)	0.440 (16.99)
HDL, mmol/L (mg/dL)	0.092 (3.55)	−0.028 (−1.08)	−0.062 (−2.39)
LDL, mmol/L (mg/dL)	0.225 (8.69)	−0.077 (−2.97)	0.348 (13.44)
Triglycerides, fasting, mmol/L (mg/dL)	−0.504 (−44.60)	0.068 (6.02)	0.362 (32.04)
Glucose, fasting, mmol/L (mg/dL)	0.137 (2.47)	−0.035 (−0.63)	0.395 (7.12)
HbA_{1C}, %	0.16	0.01	0.23
AST, U/L	−0.4	−1.6	1.5
ALT, U/L	−0.2	−2.4	1.2

AST = aspartate aminotransferase; ALT = alanine aminotransferase; HbA_{1C} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Triglycerides and glucose are based on fasting blood samples; all other results are based on randomly obtained samples.

and 6.5% in the placebo/asenapine, asenapine, and olanzapine groups.

Clinically significant weight gain (≥7% increase from baseline) occurred in 21.9%, 39.2%, and 55.1% of patients in the placebo/asenapine, asenapine, and olanzapine groups, respectively. Post hoc analysis indicated that the NNH for clinically significant weight gain for olanzapine relative to asenapine was 7 (95% CI, 3 to 63). The mean ± SD increase in weight from baseline to study endpoint was 1.7 ± 6.0 kg (3.7 ± 13.1 lb), 3.5 ± 6.7 kg (7.7 ± 14.7 lb), and 6.0 ± 6.6 kg (13.2 ± 14.5 lb) in the placebo/asenapine, asenapine, and olanzapine groups.

Most patients in each treatment group remained in the same BMI category from baseline to study endpoint. The mean ± SD increase in waist circumference from baseline to study endpoint was 3.0 ± 6.8 cm (1.2 ± 2.7 in), 2.6 ± 6.9 cm (1.0 ± 2.7 in), and 5.0 ± 7.9 cm (2.0 ± 3.1 in) in the placebo/asenapine, asenapine, and olanzapine groups, respectively.

3.4.4. Electrocardiographic findings

Clinically significant ECG findings were not reported in the placebo/asenapine group but were reported in 1 patient in the asenapine group (nonspecific ST-T change and right bundle branch block) and in 3 patients in the olanzapine group (isolated premature atrial and ventricular contractions; ST-T change and ischemia; and right bundle branch block).

3.5. Efficacy

The mean ± SD change (95% confidence interval) in YMRS total score from baseline in the ITT population at week 52 (OC data) was –28.6 ± 8.1 (−30.9 to −26.2) for asenapine ($n = 45$) versus −28.2 ± 6.8 (−29.9 to −26.5) for olanzapine ($n = 63$). The mean ± SD change in YMRS total score at endpoint (LOCF data) was −25.8 ± 10.3 (−28.1 to −23.4) for asenapine ($n = 76$) versus −26.1 ± 8.4 (−27.7 to −24.5) for olanzapine ($n = 104$).

Rates of YMRS response and remission at week 52 (OC) were the same (97.8% for asenapine, 98.4% for olanzapine). At endpoint (LOCF), they were also the same (93.4% for asenapine, 95.2% for olanzapine). Fisher's exact tests did not report statistically significant differences between the asenapine and olanzapine groups for YMRS response or remission rates at week 52 or study endpoint. Post hoc analyses indicated that the estimated NNT values for olanzapine relative to asenapine for YMRS response and remission were 158 (95% CI, range −∞ to −21 and 16 to ∞) at week 52 (OC) and were 33 (95% CI, range −∞ to −23 and 9 to ∞) at endpoint (LOCF). Worsening of mania, as measured by an increase of ≥25% in YMRS total score from baseline to study endpoint, was reported in 2.6% (2/76) of asenapine patients and 1.9% (2/104) of olanzapine patients.

Mean ± SD change from baseline in CGI-BP mania severity score was −3.6 ± 1.1 with asenapine versus −3.5 ± 0.9 with olanzapine at week 52 (OC) and −3.2 ± 1.3 versus −3.2 ± 1.1 at endpoint (LOCF).

Mean ± SD change from baseline in MADRS total score was −4.8 ± 5.8 for asenapine versus −4.4 ± 5.4 for olanzapine at week 52 (OC) and −4.8 ± 6.5 versus −3.2 ± 8.6 at endpoint (LOCF). Post hoc analysis of shifts in MADRS scores from ≤8 at baseline to ≥16 at study endpoint was reported in 0% (0/76) of asenapine and 3.0% (3/101) of olanzapine patients.

A log-rank test based on a Kaplan–Meier estimation indicated that the time to response failure was significantly longer with asenapine compared with olanzapine ($P = 0.0127$). Median times to response failure could not be calculated because high proportions of patients continued to meet criterion for YMRS response at study endpoint.

4. Discussion

In this 40-week extension trial, flexible-dose asenapine (5 or 10 mg BID) was well tolerated in the long-term treatment of patients with mania associated with bipolar I disorder. In addition, rates of discontinuation specifically attributed to AEs or to lack of efficacy were relatively low, suggesting that asenapine provided adequate long-term tolerability and sustained the efficacy observed with acute treatment. The overall AE profile of asenapine compared favorably with that of olanzapine.

Weight gain is commonly reported with atypical antipsychotic treatment. In a 48-week olanzapine maintenance therapy trial in bipolar I patients, mean weight gain averaged 4.1 kg after 48 weeks of treatment (Tohen et al., 2006). Mean weight gain after 26 weeks of risperidone treatment was 3.2 kg in patients with bipolar mania (Vieta et al., 2004). In this study, weight gain was the most frequently reported AE for olanzapine and clinically significant weight gain was more common with olanzapine. Based on the NNH, it is estimated that 7 patients need to be treated with olanzapine to see 1 additional case of clinically significant weight gain compared with asenapine. This NNH value, which is slightly lower than the previously reported NNH value of 9 after 12 weeks of treatment (McIntyre et al., 2009b), appears to indicate that differences in risk for clinically significant weight gain with olanzapine relative to asenapine increase with extended treatment. However, the degree of weight change over the course reported in this study should be interpreted cautiously because the number of patients completing 52 weeks of treatment was relatively low with both asenapine ($n = 52$) and olanzapine ($n = 68$).

There were some differences in the safety and tolerability profiles in the placebo/asenapine and asenapine groups. Treatment-emergent and treatment-related AEs and SAEs were less frequent in the placebo/asenapine group, possibly owing to the shorter duration of active treatment. Specific AEs reported less frequently in the placebo/asenapine group included insomnia, sedation, depression, and akathisia; AEs reported more frequently included parkinsonism, tremor, and constipation. There is no apparent reason why particular AEs would be more likely to occur with less exposure.

After up to 52 weeks of treatment, the overall incidence and severity of most treatment-emergent and treatment-related AEs did not change appreciably from the results obtained after shorter exposure (McIntyre et al., 2009a,b, 2010). Both treatments were associated with increased reports of weight gain as an AE compared with the rates reported in previously published 3- and 9-week trials (McIntyre et al., 2009a,b, 2010). Additionally, reports of insomnia, depression, and akathisia as AEs also increased in asenapine-treated patients in the current study, whereas

reports of tremor as an AE increased in olanzapine-treated patients. However, it is worth noting that the overall AE profiles described in this study are similar to the profile reported in a year-long trial of flexible-dose asenapine in patients with schizophrenia or schizoaffective disorder (Schoemaker et al., 2010).

The incidence of individual EPS-related AEs with asenapine and olanzapine was generally low, with akathisia and parkinsonism reported most frequently. The incidence of EPS-related AEs reported here compares favorably with the incidence reported in the year-long study in patients with schizophrenia or schizoaffective disorder (Schoemaker et al., 2010). The incidence of EPS diagnosed by formal rating scales was lower than the incidence reported as AEs, a common pattern in clinical trials of atypical antipsychotics.

Changes in laboratory parameters were similar across treatment groups and not clinically meaningful. Based on the post hoc analysis of NNH for risk of increased fasting glucose, it is estimated that 27 patients need to be treated with asenapine to see 1 additional case compared with olanzapine. This value contrasts with the previously reported NNH value of 10 for asenapine relative to olanzapine (incidence with asenapine, 22.1%; incidence with olanzapine, 11.5%) observed after 12 weeks of treatment (McIntyre et al., 2009b) and appears to indicate that differences in risk for elevated glucose levels with asenapine compared with olanzapine may dissipate with extended treatment.

Depression and depressed mood were infrequently reported as AEs with asenapine and olanzapine. Consistent with this finding, MADRS scores decreased in both groups over the course of the study, suggesting that long-term treatment did not cause or worsen depressive symptoms in this population.

Among secondary assessments, the efficacy of asenapine was generally maintained for up to 52 weeks of treatment. Manic symptoms declined throughout the 40-week extension, with improvements being most pronounced during the initial 12 weeks of treatment (McIntyre et al., 2009a,b, 2010). Post hoc estimation of NNT values for YMRS response and remission for olanzapine relative to asenapine using OC (both 158) and LOCF (both 33) indicate that a relatively large number of patients need to be treated with olanzapine to see 1 additional case of response or remission relative to asenapine. These NNT values with OC analysis exceed those reported after 12 weeks of treatment (ie, NNT values of 40 and 48 for YMRS response and remission [OC analysis], respectively) (McIntyre et al., 2009b) and further support the continued efficacy of asenapine relative to olanzapine.

Although the efficacy seen with asenapine appeared comparable to that of olanzapine, suggesting that the benefits of asenapine represent a true treatment effect, this conclusion needs to be considered in light of several study limitations. First, there was no long-term placebo treatment group in this extension. Without such a comparison group, it is difficult to ascertain the amount of treatment effect directly attributable to active treatment. Second, the 9-week extension study (McIntyre et al., 2009b) used as a feeder trial for this study was designed to assess noninferiority, but this 40-week extension was designed primarily to assess safety and tolerability. As a result, the study was not powered for formal assessments of efficacy. As such, any comparisons of efficacy between asenapine and olanzapine in this study should be considered primarily descriptive. The lack of formal statistical assessments of efficacy also precludes the assessment of regional differences in the efficacy of active treatment. The interpretation of efficacy in this study is also limited by the small number of patients who completed 52 weeks of treatment.

In conclusion, asenapine appeared to be well tolerated in patients with manic symptoms associated with bipolar I disorder treated for up to 52 weeks.

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Conflict of interest

Roger McIntyre has served as a consultant or speaker for AstraZeneca, Eli Lilly, Janssen-Ortho, Schering-Plough, Wyeth, Lundbeck, GlaxoSmithKline, Oryx, Biovail, Pfizer, Prestwick, Merck, and Shire and has received research funding from Wyeth, GlaxoSmithKline, Merck, Servier, and AstraZeneca. Miriam Cohen, Jun Zhao, and John Panagides are employees of Merck. Larry Alphs and Thomas Macek were employed at Pfizer Global R&D at the time the study was conducted. The authors have no other commercial associations that might pose a conflict of interest in connection with the manuscript.

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