

# Post hoc analyses of asenapine treatment in pediatric patients with bipolar I disorder: efficacy related to mixed or manic episode, stage of illness, and body weight

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**Background:** Patient characteristics and disease progression may affect response to pharmacologic intervention in bipolar I disorder. Asenapine is approved for acute treatment of manic/mixed episodes of bipolar I disorder in patients 10–17 years old. Post hoc analyses assessed asenapine efficacy in pediatric patients by current manic or mixed episode, number of lifetime episodes, and baseline body mass index (BMI).

**Patients and methods:** Data were obtained from a 3-week, randomized, double-blind, placebo-controlled, parallel-group trial of asenapine 2.5, 5.0, or 10.0 mg twice daily (BID) in male or female patients (10–17 years) with bipolar I disorder (NCT01244815). Patients were stratified by current episode type (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition – defined mixed/manic), number of lifetime episodes (<3, 3–5, >5), and baseline BMI tertile. Changes from baseline to day 21 in Young Mania Rating Scale (YMRS) total score and Clinical Global Impressions Scale for use in Bipolar Illness (CGI-BP) were assessed in asenapine subgroups vs placebo.

**Results:** In patients with mixed episodes, differences in YMRS and CGI-BP scores were statistically significant for each asenapine dose vs placebo ( $P < 0.001$ ) at day 21; in patients with manic episodes, significant differences vs placebo were seen in all groups ( $P < 0.05$ ) except 2.5 mg BID on the YMRS. In patients with <3 previous mixed/manic episodes, significant differences in YMRS and CGI-BP scores were observed for all asenapine doses vs placebo ( $P < 0.05$ ). In patients with 3–5 or >5 previous episodes, asenapine 10 mg BID was significantly different than placebo ( $P < 0.05$ ) on both scales; differences vs placebo varied for lower doses. Baseline body weight or BMI did not appear to influence the efficacy of asenapine.

**Conclusion:** Asenapine was effective in the treatment of pediatric patients with bipolar I disorder. Efficacy did not appear to be influenced by the type of current episode, stage of disease progression, or baseline body weight/BMI.

**Keywords:** asenapine, child, adolescent, bipolar disorder, atypical antipsychotic, second-generation antipsychotic

## Introduction

Onset of bipolar disorder in childhood and adolescence is common, with large retrospective studies estimating that between 50% and 66% of adults had onset of bipolar illness before the age of 19; even earlier onset of illness (before the age of 13) was reported for 15%–28% of adults.<sup>1,2</sup> Early onset of illness and delay to first pharmacologic treatment are associated with high levels of dysfunction, decreased quality of

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life, and poor overall outcomes as patients mature.<sup>3–5</sup> Monotherapy with an atypical antipsychotic or a mood stabilizer, such as lithium, is recommended as a first-line treatment for pediatric patients with bipolar mania.<sup>6</sup> Given the wide range and dynamic nature of illness characteristics and body weight in children and adolescents, the possibility of tailoring the efficacy of antipsychotic treatment to individual patient characteristics is appealing.

Interest in factors associated with response to treatment in bipolar disorder increased with the discovery that the efficacy of lithium differed by baseline characteristics in adults.<sup>7,8</sup> Evidence in adult patients suggests that worse treatment response may be related to factors such as more advanced disease progression, characterized by the number of previous mixed or manic episodes,<sup>9,10</sup> and the type of current episode (mixed vs pure mania).<sup>11</sup> Specifically, mixed states may be associated with worse outcomes and prognosis, including elevated relapse rates, suicide, comorbidity, and treatment resistance.<sup>12,13</sup> However, in several subgroup analyses of atypical antipsychotics, no evidence of differential efficacy has been observed in groups defined by factors including sex, age, race, presenting syndromal characteristics, disease history, and comorbidity, with efficacy consistently being demonstrated in favor of drug vs placebo. Although evidence in support of differential efficacy for antipsychotics in adult patients with bipolar I mania may be confined to specific factors, characteristics that influence response to treatment in young patients have not been well studied<sup>14</sup> and deserve to be investigated to enhance best practices in this developing and maturing patient population.

Asenapine is a sublingual atypical antipsychotic approved as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients aged 10–17 years. In a randomized, double-blind, placebo-controlled trial in pediatric patients with acute manic or mixed episodes associated with bipolar I disorder,<sup>15</sup> asenapine 2.5, 5.0, and 10.0 mg twice daily (BID) were more effective than placebo on the Young Mania Rating Scale (YMRS)<sup>16</sup> total score, Clinical Global Impressions Scale for use in Bipolar Illness (CGI-BP),<sup>17</sup> and Children's Global Assessment Scale (CGAS).<sup>18</sup> Furthermore, differential efficacy based on several baseline characteristics was evaluated in patient subgroups defined by characteristics relevant to this patient population. Of note, asenapine was more effective than placebo in subgroups of patients with or without attention-deficit hyperactivity disorder (ADHD), with or without concomitant stimulant use, and without respect to age of onset (<11 years vs >11 years), or sex.

Although several pharmacologic treatment options for bipolar mania are available, efficacy varies in pediatric patients,<sup>19,20</sup> with greater treatment resistance reported for young patients than for adult patients.<sup>14</sup> To further characterize the efficacy profile of asenapine in pediatric patients, we conducted post hoc analyses to evaluate the efficacy of asenapine vs placebo in additional subgroups of pediatric patients from the prospective outcome study. Relevant to our interest in improving patient outcomes, we evaluated whether episode type (manic or mixed) or the stage of bipolar disorder (indicated by the number of previous mixed or manic episodes) affected the efficacy of asenapine in young patients. Additionally, as growth and development result in continuous changes that could influence drug effect in pediatric patients, we also conducted analyses in subgroups defined by the dynamic characteristics of weight and body mass index (BMI) to see if a weight-based dosing strategy could be beneficial for asenapine. Collectively with the prospective subgroup analyses, these results may provide a more complete clinical profile that could better inform clinicians about the efficacy of asenapine in pediatric patients.

## Patients and methods

### Study design

Data were obtained from the positive 3-week, randomized, double-blind, placebo-controlled, parallel-group trial of asenapine in pediatric patients with bipolar I disorder (NCT01244815). Detailed methods of the study have been published previously.<sup>15</sup> Briefly, the trial included a 2- to 14-day screening/tapering period followed by a 21-day double-blind treatment period. Patients were randomized 1:1:1:1 to sublingual placebo or asenapine 2.5, 5.0, and 10.0 mg BID. Asenapine doses were up-titrated during the first week for patients in the 5.0 and 10.0 mg BID treatment groups. The primary and key secondary efficacy parameters were change from baseline to day 21 in YMRS total score and CGI-BP assessed at screening, baseline, and on days 4, 7, 14, and 21. Additional secondary parameters included the CGAS (screening, baseline, and day 21) and the Children's Depressive Rating Scale-Revised (CDRS-R)<sup>21</sup> (baseline and days 7, 14, and 21). The trial was conducted in accordance with Good Clinical Practice standards and applicable country and/or local statutes regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. Independent ethics committees (listed in Supplementary material) reviewed and approved the protocol and applicable amendments; written informed consent and subject assent were obtained at screening, and

additional informed consent was signed if a participant turned 18 years old during the trial.

## Patients

Male and female pediatric patients (10–17 years, inclusive) with a primary diagnosis of bipolar I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR)<sup>22</sup> and a current manic (296.4x) or mixed (296.6x) episode with or without psychotic features were included. The diagnosis was confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version.<sup>23</sup> The clinical measures required for inclusion were YMRS total score  $\geq 20$  and CGI-BP overall score  $\geq 4$ . Additionally, patients were required to have at least one mania-specific symptom (ie, elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, hypersexuality). Criteria for exclusion were typical of clinical studies in pediatric patients with bipolar disorder and included the presence of a pervasive development disorder, schizophrenia, schizoaffective disorder, posttraumatic stress disorder, obsessive-compulsive disorder, or psychosis due to a medical condition or prohibited concomitant medication. The presence of an uncontrolled, unstable, clinically significant medical condition was also exclusionary. Some concomitant medications were allowed during the study, including agents for agitation, irritability, restlessness, insomnia, and hostility (short-acting benzodiazepines such as lorazepam), ADHD (atomoxetine, methylphenidate, amphetamine, guanfacine), extrapyramidal symptoms (anticholinergics and short-acting benzodiazepines), and hormonal birth control.

## Post hoc analyses

Post hoc analyses were conducted to evaluate the relationship between efficacy and the type of current episode (mixed or manic), number of previous mixed or manic episodes ( $<3$ , 3–5, or  $>5$ ), and baseline body weight and BMI stratified by tertile. We hypothesized that asenapine would be effective vs placebo regardless of episode type (manic or mixed), the number of previous manic or mixed episodes, and baseline BMI in pediatric patients. The primary and secondary efficacy parameters from the clinical study (YMRS total score and CGI-BP overall score) were used as the measures for post hoc evaluation of patient subgroups. The all-patients-as-treated set consisted of all randomized patients who received at least one dose of study medication. All patients who received at least one dose of study drug and had a baseline and at least

one postbaseline efficacy assessment were included in the analyses (full analysis set).

Change from baseline to day 21 in YMRS total score and CGI-BP score was analyzed for each asenapine dose (2.5, 5.0, and 10 mg BID) vs placebo in the patient subgroups. Analyses were conducted using a mixed model for repeated measures (MMRM) for change from baseline values. The model for subgroup analyses by episode type and previous number of episodes included pooled site, treatment, visit, and treatment-by-visit interaction as factors, and baseline, episode group, baseline-by-visit interaction, treatment-by-episode group interaction, and treatment-by-episode group-by-visit as covariates. The model for subgroup analyses by BMI included pooled site, treatment, visit, and treatment-by-visit interaction as factors, and baseline, baseline-by-visit interaction, age, BMI, and treatment-by-BMI as covariates. Unstructured matrix was assumed for the repeated-measures variance-covariance and the model parameters were estimated using restricted maximum likelihood. In addition to analyses of efficacy within baseline BMI subgroups, the relationship between efficacy and baseline body weight, BMI, or BMI percentile was assessed by including the following continuous variables in separate MMRM models as covariates: 1) age, sex, baseline body weight, and the body weight-by-treatment interaction; 2) BMI, age, sex, and the BMI-by-treatment interaction; and 3) BMI percentile (for age and sex) and the BMI percentile interaction-by-treatment. Statistical tests were two-sided and conducted at the 0.05 level of significance.

## Results

A total of 403 patients were randomized and treated in the trial. Detailed demographic information has been previously published;<sup>15</sup> patient populations and baseline characteristics that are relevant to our post hoc analyses are presented in Table 1. The majority of patients (68.2%) were white with a mean age of 13.8 years. The percentage of females in each treatment group varied from 62 for the placebo group to 41 for the asenapine 10.0 mg BID group. The overall mean (SD) age of onset of bipolar I disorder was 11.0 (2.9) years. Based on standardized medical and psychiatric history intake questionnaires at screening, the most common comorbid Axis I disorder was ADHD, which was reported in 54.6% of patients overall. Baseline YMRS total and CGI-BP scores were similar between treatment groups (Table 1).

In prespecified analyses from the clinical study,<sup>15</sup> the least squares mean difference (LSMD) in change from baseline to day 21 was statistically significant in favor of all asenapine

**Table 1** Patient populations and characteristics and baseline efficacy scores

Characteristics	Placebo	Asenapine		
		2.5 mg BID	5.0 mg BID	10.0 mg BID
Patient populations, n				
All patients as treated	101	104	99	99
FAS	98	101	98	98
Completed study, n (%)	87 (86.1)	88 (84.6)	88 (88.9)	87 (87.9)
Patient subgroups, n (%)				
BMI subgroups (FAS)				
≤33rd percentile: ≤20.4 kg/m <sup>2</sup>	24 (24)	39 (39)	29 (30)	39 (40)
33rd to 66th percentile: >20.4 to ≤26.0 kg/m <sup>2</sup>	37 (38)	34 (34)	33 (34)	30 (31)
>66th percentile: >26.0 kg/m <sup>2</sup>	37 (38)	28 (28)	36 (37)	29 (30)
Current episode (FAS)				
Mixed <sup>a</sup>	55 (56)	61 (60)	55 (56)	55 (56)
Manic <sup>a</sup>	43 (44)	40 (40)	43 (44)	43 (44)
Number of previous episodes (FAS)				
<3	51 (63)	43 (61)	43 (59)	34 (47)
3–5	19 (23)	18 (25)	20 (27)	25 (34)
>5	11 (14)	10 (14)	10 (14)	14 (19)
Baseline efficacy scores, mean (SD) (FAS)				
YMRS	29.9 (5.5)	29.5 (5.7)	30.3 (5.9)	30.2 (5.6)
CGI-BP overall	4.3 (0.5)	4.5 (0.6)	4.4 (0.6)	4.4 (0.6)

**Note:** <sup>a</sup>DSM-IV-TR criteria.

**Abbreviations:** BID, twice daily; BMI, body mass index; CGI-BP, Clinical Global Impressions Scale for use in Bipolar Illness; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision; FAS, full analysis set; YMRS, Young Mania Rating Scale.

doses vs placebo in YMRS total score (2.5 mg BID, −3.2; 5.0 mg BID, −5.3; 10.0 mg BID, −6.2; all  $P < 0.01$  [adjusted]), CGI-BP overall score (2.5 mg BID, −0.6; 5.0 mg BID, −0.7; 10.0 mg BID, −0.7; all  $P < 0.001$  [adjusted]), and CGAS total score (2.5 mg BID, 4.3; 5.0 mg BID, 7.0; 10.0 mg BID, 5.1; all  $P < 0.01$ ). The LSMD for asenapine vs placebo on the CDRS-R at day 21 was only statistically significant for the 5.0 mg BID dose group (−2.2,  $P < 0.05$ ).

## Post hoc efficacy outcomes

### Efficacy by type of current episode (mixed or manic)

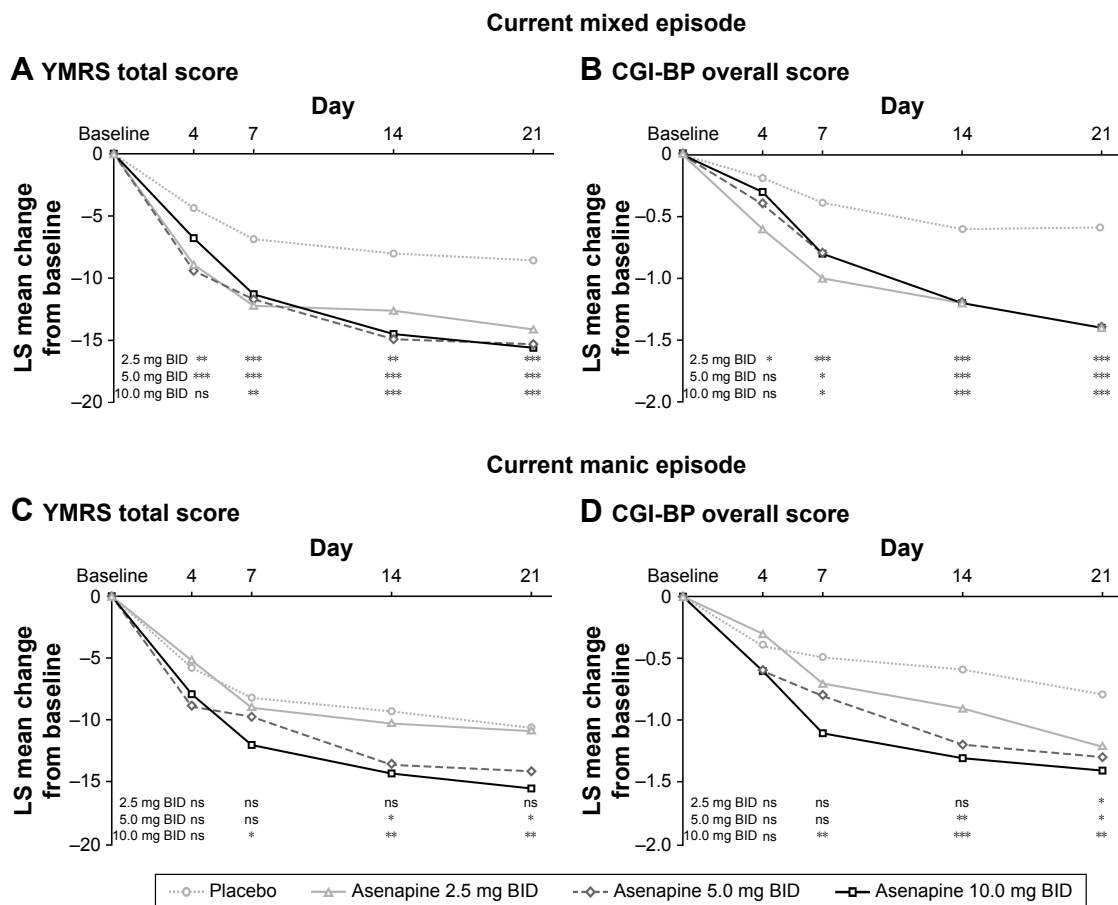
Baseline YMRS total scores were generally similar in patients with a current manic vs mixed episode (placebo, 29.4 vs 30.3; asenapine 2.5–10.0 mg BID, 30.6–31.3 vs 28.8–29.8). Baseline CGI-BP scores were also similar in patients with a current manic vs mixed episode (placebo, 4.4 vs 4.3; asenapine 2.5–10.0 mg BID, 4.4–4.6 vs 4.3–4.4). At baseline, 58% of patients overall were diagnosed with a current mixed episode according to DSM-IV-TR criteria. In patients currently experiencing a mixed episode, differences in total score change on the YMRS and CGI-BP were significantly greater for each asenapine dose group (2.5, 5.0, and 10.0 mg BID) compared to placebo, starting on day 7 and continuing to day 21 (Figure 1A and B). In patients currently experiencing a manic episode, the difference in YMRS total score was statistically significant in favor of asenapine 5.0 and 10.0 mg

BID vs placebo starting at day 14; no statistically significant difference from placebo was observed on the YMRS for patients with a current manic episode in the asenapine 2.5 mg BID group (Figure 1C). In patients experiencing a manic episode, the difference in CGI-BP overall scores was statistically significant for all asenapine doses vs placebo at day 21 (Figure 1D).

### Efficacy by number of previous episodes

The majority of patients experienced <3 previous manic or mixed episodes (Table 1). The LSMD in YMRS total score change was significantly different for all asenapine doses vs placebo in patients with <3 prior episodes (2.5 mg BID, −3.8; 5.0 mg BID, −3.9; 10.0 mg BID, −4.7 [ $P < 0.05$  for all doses]). In patients with 3–5 prior episodes, the LSMD vs placebo was significant for patients in the asenapine 5.0 and 10.0 mg BID dose groups (5.0 mg BID, −10.2; 10.0 mg BID, −7.7 [ $P < 0.01$  for both doses]); in patients with >5 prior episodes, the LSMD vs placebo was significant for the 2.5 and 10.0 mg BID dose groups (2.5 mg BID, −8.4; 10.0 mg BID, −11.6 [ $P < 0.05$  for both doses]; Figure 2A).

At day 21, the LSMDs were statistically significant in favor of asenapine vs placebo for change from baseline in CGI-BP overall score for all doses in pediatric patients with <3 prior episodes (2.5 mg BID, −0.7; 5.0 mg BID, −0.5; 10.0 mg BID, −0.6 [ $P < 0.05$  all doses]), for the



**Figure 1** (A) YMRS and (B) CGI-BP total scores for patients with a current mixed episode. (C) YMRS and (D) CGI-BP total scores for patients with a current manic episode (MMRM). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  (asenapine vs placebo). Analyzed by MMRM with terms for episode group (manic or mixed) and the interactions of episode group-by-treatment and episode group-by-treatment-by-visit as covariates.

**Abbreviations:** BID, twice daily; CGI-BP, Clinical Global Impressions Scale for use in Bipolar Illness; LS, least squares; ns, not significant; YMRS, Young Mania Rating Scale.

two higher doses in patients with 3–5 prior episodes (5.0 mg BID,  $-1.1$ ; 10.0 mg BID,  $-0.7$  [ $P < 0.05$  for both doses]), and for the 2.5 and 10.0 mg BID in those with  $>5$  prior episodes (2.5 mg BID,  $-1.0$ ; 10.0 mg BID,  $-1.5$  [ $P < 0.05$  for both doses]; Figure 2B).

### Efficacy by baseline BMI

When results were stratified by baseline BMI, LS mean changes in YMRS total score significantly favored all asenapine doses within the middle tertile and the highest doses of asenapine within the highest tertile (Figure 3A). LS mean changes in CGI-BP score significantly favored all asenapine doses within the middle tertile (Figure 3B). Overall, however, no systematic patterns across BMI strata were evident.

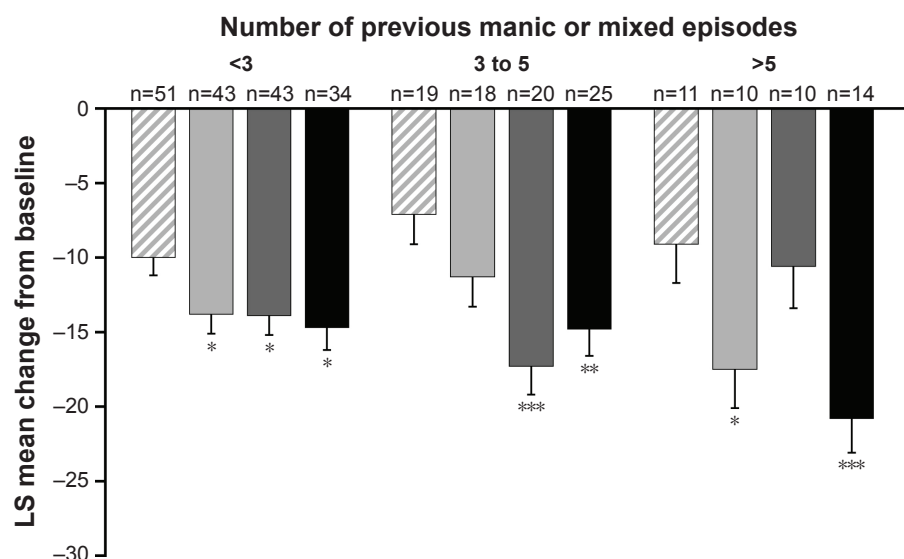
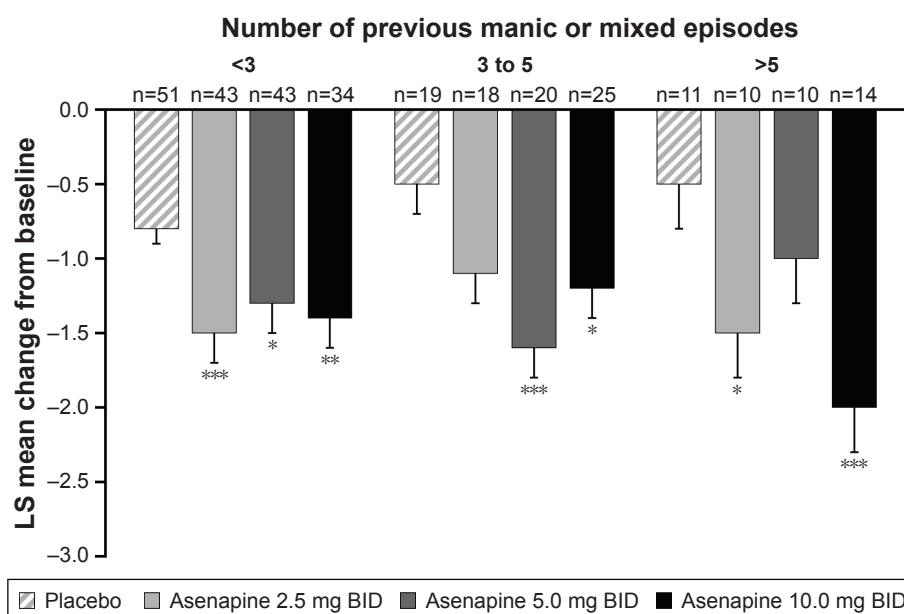
In analyses using continuous variables instead of subgroups, there were no statistically significant effects on efficacy for the continuous variables of baseline body weight, BMI, BMI percentile, or the interactions of dose with these variables ( $P > 0.10$  in all cases).

## Discussion

In these post hoc analyses, consistent efficacy was noted for asenapine vs placebo in the treatment of pediatric patients with bipolar I disorder regardless of the type of episode (mixed or manic) or the number of previous episodes. In patients experiencing a mixed episode, changes in YMRS and CGI-BP total score were significantly greater for each asenapine dose group compared to placebo starting on day 7 and continuing to day 21. In patients experiencing a current manic episode, the difference in YMRS total score was statistically significant in favor of asenapine 5.0 and 10.0 mg BID vs placebo starting at day 14, but no significant difference from placebo was observed in the asenapine 2.5 mg BID group, suggesting that higher asenapine doses may be the most beneficial in patients with solely manic symptoms. Significant improvement vs placebo in CGI-BP overall scores was also seen for all asenapine doses at day 21 in patients with a current manic episode.

Additionally, when efficacy by number of prior manic or mixed episodes was evaluated, significantly greater changes



**A YMRS total score****B CGI-BP overall score**

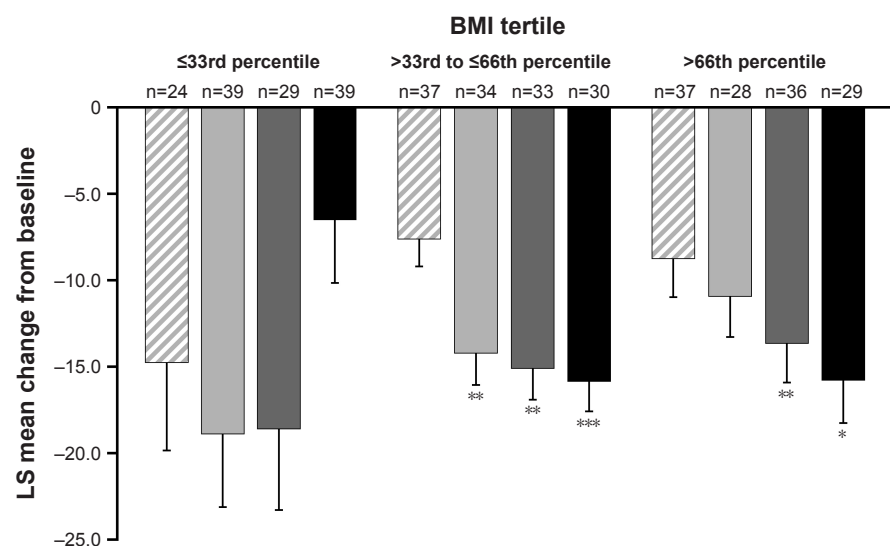
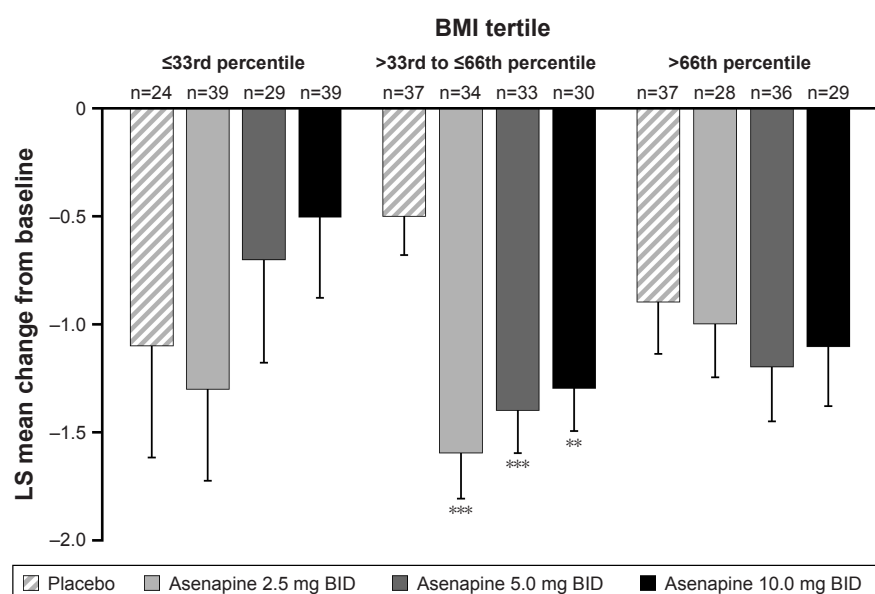
**Figure 2** Efficacy by number of previous episodes as measured by LS mean (SE) change from baseline to day 21 in (A) YMRS total score and (B) CGI-BP overall score. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  (asenapine vs placebo within episode group). Analyzed by MMRM with terms for number of previous episode and the interactions of episode group-by-treatment and episode group-by-treatment-by-visit as covariates.

**Abbreviations:** BID, twice daily; CGI-BP, Clinical Global Impressions Scale for use in Bipolar Illness; LS, least squares; MMRM, mixed-model for repeated-measures; SE, standard error; YMRS, Young Mania Rating Scale.

in YMRS total score and CGI-BP overall score, indicating symptomatic and global improvement, were seen for all asenapine doses vs placebo in patients with <3 prior episodes. Data were less consistent in patients with  $\geq 3$  prior mixed or manic episodes, which may have been due to small sample sizes in these subgroups. In patients with 3–5 prior episodes, change in YMRS total score and CGI-BP overall score was significantly greater for asenapine 5.0 and 10.0 mg BID than for placebo, but in patients with >5 prior episodes,

YMRS total score and CGI-BP overall score changes were significantly greater than placebo for asenapine 2.5 and 10.0 mg BID.

Differential efficacy for antipsychotics in patients with manic vs mixed episodes has been attributed to the presence of depressive features instead of pure mania.<sup>11</sup> Our results suggest that asenapine may be an appropriate treatment option for pediatric patients with either manic or mixed episodes, which is consistent with previous efficacy findings in favor

**A YMRS total score****B CGI-BP overall score**

**Figure 3** Efficacy by baseline BMI tertile. Efficacy by BMI tertile as measured by LS mean (SE) change from baseline to day 21 in (A) YMRS total score and (B) CGI-BP overall score. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  (asenapine vs placebo within tertile). Analyzed by MMRM with terms for BMI tertile and the interactions of BMI tertile-by-treatment and BMI tertile-by-treatment-by-visit as covariates. BMI tertiles: ≤33rd percentile is ≤20.4 kg/m<sup>2</sup>, 33rd to 66th percentile is >20.4 kg/m<sup>2</sup> and ≤26.0 kg/m<sup>2</sup>, and >66th percentile is >26.0 kg/m<sup>2</sup>.

**Abbreviations:** BID, twice daily; CGI-BP, Clinical Global Impressions Scale for use in Bipolar Illness; LS, least squares; LSMD, LS mean difference; MMRM, mixed-model for repeated-measures; SE, standard error; YMRS, Young Mania Rating Scale.

of asenapine vs placebo in adult patients with acute manic or mixed episodes.<sup>24–26</sup> Of additional interest for asenapine, the presence of depressive symptoms in adult patients with mixed mania did not appear to predict inferior efficacy. In a pooled post hoc analysis of two studies in adults, asenapine was compared with placebo in patients with acute manic or mixed episodes who also met proxy criteria for a moderate-to-severe mixed major depressive episode; olanzapine was used as an active comparator in these studies.<sup>24</sup> Asenapine- vs

placebo-treated patients had significant improvement in both manic and depressive symptoms as shown by change from baseline in YMRS total score and Montgomery–Åsberg Depression Rating Scale (MADRS) total score;<sup>27</sup> no significant differences in manic or depressive symptoms were observed for olanzapine vs placebo in patients meeting mixed criteria.

Improvement in depressive symptoms with asenapine was supported in another pooled post hoc analysis showing

significant differences in MADRS total score in favor of asenapine over placebo in adult patients experiencing an acute bipolar manic or mixed episode with clinically relevant depressive symptoms.<sup>26</sup> Finally, asenapine findings of efficacy in mixed episodes are in accordance with a meta-analysis investigating second-generation antipsychotic efficacy in the treatment of acute mixed episodes in adult patients with bipolar disorder.<sup>28</sup> Antipsychotic monotherapy was significantly more effective than placebo in treating acute mixed episodes, with effect sizes for mixed episodes (0.44) and pure manic episodes (0.56) both in the medium range, suggesting efficacy for these agents in both mixed and manic episodes. Although these findings pertain to adult patients and asenapine is not approved for the treatment of bipolar depression, these results support the effects of asenapine in patients with mixed affective symptoms and may be instructive for clinicians treating mixed affective symptoms in pediatric patients.

Illness progression, defined in our analyses as the number of previous episodes, has also been related to differential efficacy in patients with bipolar mania. Decreased antimanic response to lithium has been noted in association with an increasing number of manic episodes,<sup>9</sup> with parallel results observed with at least one atypical antipsychotic. In a pooled analysis that included mania studies with olanzapine in adults, data from individuals categorized as having had 0, 1–5, 6–10, or >10 prior episodes of illness were analyzed.<sup>10</sup> Response rates ranged from 52% to 69% for individuals with 1 to 5 previous manic episodes, and from 29% to 59% for individuals with >5 previous episodes. The rate of response was significantly higher for the 1–5 episode group compared to the >5 episode group, with an up to twofold increase in the chance of responding for those with fewer previous episodes.

Alternatively, in pediatric patients in our subgroup analyses, efficacy for asenapine vs placebo was observed at some dose levels regardless of the number of previous episodes. This is an important finding because bipolar disorder may not be immediately recognized and diagnosed in pediatric patients,<sup>29</sup> and treatment may be commensurately delayed. In a retrospective review of youths treated in a community mental health outpatient clinic, the mean time from onset of symptoms to a diagnosis of bipolar disorder was 5 years,<sup>30</sup> suggesting that delayed diagnosis may be common in pediatric patients with bipolar disorder and efficacy in cases with a greater number of previous episodes may be an important aspect of treatment.

In our post hoc analyses examining efficacy by baseline BMI, changes in YMRS total score were significantly greater

for all asenapine doses in the middle BMI tertile (>33rd and ≤66th percentile) and for the highest dose of asenapine in the highest BMI tertile (>66th percentile); no dose was significantly different than placebo in the lowest BMI tertile (≤33rd percentile). Changes in CGI-BP score were also significantly greater for all asenapine doses in the middle BMI tertile, but no significant differences from placebo were noted for any dose in the low or high BMI tertiles. When weight characteristics were analyzed using continuous variables instead of subgroups, there were no statistically significant effects for baseline body weight, BMI, BMI percentile, or the interactions of dose with these variables. In pediatric patients where growth and development are often times changing, the impact of body weight on medication efficacy and safety is an important clinical consideration. As such, weight-based dosing is common in pediatric patients because pharmacokinetic parameters may be affected by several factors such as weight and BMI.<sup>31</sup> Consistent with results from our post hoc analyses showing that asenapine was effective across BMI tertiles and irrespective of body weight, a previous population pharmacokinetics study of asenapine found no statistically significant differences or clinically meaningful changes in asenapine exposure when BMI was analyzed as a covariate in the model.<sup>32</sup> Together, these findings indicate that no asenapine dose adjustments based on patient weight or BMI are required.

While there is research investigating efficacy and patient characteristics in adults with bipolar disorder, very few studies have investigated whether illness or patient factors are related to efficacy in mixed or manic episodes in young patients with bipolar disorder. A small naturalistic study in children and adolescents with manic or mixed episodes associated with bipolar disorder found that most of the evaluated clinical characteristics (eg, mean age, sex, inpatient vs outpatient, duration of follow-up, manic vs mixed index episode) did not differentiate treatment responders from nonresponders.<sup>14</sup> However, the study did find that comorbidity with conduct disorder or ADHD, and higher baseline CGI-Severity score were predictors of nonresponse. This is an interesting finding given that there was a high rate of comorbid baseline ADHD in our pediatric population (55%) but no differences in efficacy were observed in asenapine-treated patients with or without ADHD.<sup>15</sup> Collectively, prospective asenapine subgroup analyses in pediatric patients, in conjunction with our post hoc analyses, contribute to the literature on differential response in pediatric patients with bipolar I disorder. Namely, asenapine has been shown to be effective regardless of the type of episode (mixed or manic)



and the level of disease progression, without regard to patient BMI and weight, in patients with and without ADHD and without concomitant stimulant use, and regardless of age of onset or sex.

## Limitations

Limitations of our analyses include their post hoc nature and the short-term duration of the clinical study. Given the scope of these post hoc investigations, our analyses were limited to factors that we considered salient based on prior results in adult patients or of particular relevance in pediatric patients. As our analyses were exploratory, there is risk for both type I error (false positive findings) due to multiple comparisons and type II errors (false negative findings) due to the small sample size of the subgroups. Additionally, these results may not be generalizable to a wider population of child and adolescent patients with bipolar I disorder beyond the inclusion and exclusion criteria that were used in the clinical study. Finally, patients in the clinical trial were enrolled based on criteria described in the DSM-IV-TR; it is unknown whether efficacy by type of episode (mixed or manic) would have differed had mixed episodes been defined using DSM-V diagnostic criteria.

## Conclusion

In these post hoc, exploratory analyses, asenapine 2.5, 5.0, and 10.0 mg BID were more effective than placebo in the treatment of pediatric patients with bipolar I disorder regardless of the type of episode (mixed or manic) or the number of previous mixed or manic episodes. Change from baseline in YMRS and CGI-BP total was significantly greater than placebo for at least one dose of asenapine in each patient subgroup that was evaluated by episode type (mixed or manic) and number of previous episodes; in most cases, multiple asenapine doses were more effective than placebo. Significant differences vs placebo on the YMRS and CGI-BP were not seen in all BMI subgroups; however, when all weight variables were considered, body weight did not appear to influence the efficacy of asenapine, obviating the need for weight-based dosing in this population. Due to small patient subgroup numbers and the vagaries of post hoc analysis, it was not possible to detect specific by-dose patterns of statistical significance vs placebo in most subgroups.

## Acknowledgments

Writing assistance and editorial support were provided by Krystina Neuman, PhD, of Prescott Medical Communications

Group (Chicago, IL), a contractor of Allergan. The study was sponsored by Merck & Co., Inc. This manuscript was supported by funding from Allergan (Madison, NJ).

## Author contributions

Robert L Findling, Willie Earley, Trisha Suppes, Mehul Patel, and Roger S McIntyre contributed to the concept/design of these analyses and data analyses/interpretation. Xiao Wu and Cheng-Tao Chang were involved in the statistical analysis and interpretation of data. All authors contributed toward data analyses/interpretation, drafting and critically revising the paper, and they agree to be responsible for all aspects of the work.

## Disclosure

Dr Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Aevi, Akili, Alcobra, Amerex, American Academy of Child & Adolescent Psychiatry, American Psychiatric Press, Bracket, Epharma Solutions, Forest, Genentech, Guilford Press, Ironshore, Johns Hopkins University Press, KemPharm, Lundbeck, Merck, NIH, Neurim, Nuvelution, Otsuka, PCORI, Pfizer, Physicians Postgraduate Press, Purdue, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, Teva, Tris, TouchPoint, Validus, and WebMD.

Dr Suppes has reported grants from National Institute of Mental Health, VA Cooperative Studies Program, Pathway Genomics, Stanley Medical Research Institute, Elan Pharma International Limited, and Sunovion Pharmaceuticals; consulting fees from A/S H. Lundbeck, Sunovion, Merck & Co., and Astra Zeneca; honoraria from Medscape Education, Global Medical Education, and CMEology; royalties from Jones and Bartlett and UpToDate.

Dr McIntyre has received research grant support from Lundbeck, AstraZeneca, Pfizer, Shire, Otsuka, Bristol-Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. He has also received speaker/consultant fees from Lundbeck, Pfizer, AstraZeneca, Eli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol-Myers Squibb, and Shire.

Drs Earley and Patel acknowledge potential conflicts of interest as employees of Allergan.

Drs Wu and Chang acknowledge potential conflicts of interest as former employees of Allergan.

The authors report no other conflicts of interest in this work.

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## Supplementary material

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