Weight Change and Metabolic Effects of Asenapine in Patients With Schizophrenia and Bipolar Disorder

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ABSTRACT

Objective: To describe weight changes and metabolic effects of asenapine compared with placebo and olanzapine in adults.

Method: Post hoc analyses were performed using data from 17 asenapine trials (13 schizophrenia and 4 bipolar mania trials) with placebo (5–10 mg twice daily; n = 1,748; 1–6 weeks) and/or olanzapine (5–20 mg, once daily; n = 3,430; 3–100 weeks). Data were pooled based on treatment into placebo-controlled and olanzapine-controlled trials. For trials with placebo and olanzapine treatment groups, the asenapine population was included in both pools. Changes from baseline for weight, body mass index, and fasting lipid and glucose levels were determined. The Medical Dictionary for Regulatory Activities was used to define metabolic adverse events.

Results: Mean (standard error [SE]) weight change was greater with asenapine than with placebo (1.2 [0.2] vs 0.14 [0.2] kg; $P < .0001$) and similar in schizophrenia and bipolar disorder. Mean changes differed for asenapine versus placebo in triglycerides (1.8 [6.3] vs –12.2 [5.9] mg/dL; $P < .01$) and fasting glucose (1.9 [1.7] vs –1.6 [1.5] mg/dL; $P < .05$). In the olanzapine-controlled trials, weight change was significantly lower with asenapine than with olanzapine (0.9 [0.1] vs 3.1 [0.2] kg; $P < .0001$). Changes associated with asenapine were lower than those with olanzapine in fasting glucose (2.0 vs 3.3 mg/dL), total cholesterol (–0.4 [1.1] vs 6.2 [1.2] mg/dL; $P < .0001$), low-density lipoprotein cholesterol (–0.3 [1.1] vs 3.1 [1.2] mg/dL; $P < .01$), and triglycerides (–0.9 [5.4] vs 24.3 [5.8] mg/dL; $P < .0001$).

Conclusions: Asenapine was associated with greater weight gain and glucose changes than placebo and not associated with a meaningful change in triglycerides or cholesterol levels. Asenapine was not significantly different from olanzapine in change in glucose levels and lower than olanzapine with respect to triglycerides, weight gain, and increased cholesterol.

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Compared with the general population, people with schizophrenia and bipolar disorder have higher rates of obesity and metabolic syndrome, contributing to an increase in premature mortality.[1,2] Findings have confirmed that people with schizophrenia and bipolar disorder have a substantially reduced life expectancy due to excess deaths from somatic conditions, accounting for more lost years of life than from suicide or accidents.[1,3] In addition, cardiometabolic disorders have also been associated with greater psychopathology[4,5] and, in bipolar disorder, may portend a poorer response to mood-stabilizing treatments.[6] The presence of hypothalamic-pituitary-adrenal axis abnormalities and impaired insulin signaling among treatment-naive patients suggests an overlapping pathophysiology that may contribute to the development of cardiometabolic illness and mood or psychotic symptoms.[7–10]

Although lifestyle factors predispose patients with bipolar disorder to weight gain and metabolic disturbance,[11] there is also a notable contribution from the use of antipsychotic drugs.[12,13] The precise mechanisms by which these drugs exert metabolic adverse effects are unknown, but a central effect in the hypothalamic control of appetite regulation and energy expenditure has been proposed.[14] In schizophrenia, drug-specific metabolic abnormalities related to glucose and lipid regulation have been identified.[15,16] These adverse effects vary between different antipsychotics.[17,18] However, as long-term treatment is generally necessary for the management of schizophrenia and bipolar disorder, drugs with less metabolic burden offer advantages.

The risk of metabolic adverse effects also varies according to psychiatric diagnosis. A naturalistic cohort study identified a higher risk for metabolic syndrome and glucose dysregulation in patients with schizoaffective disorder compared with bipolar disorder.[19] Other studies[20] have found nearly a 2-fold increased risk of cardiovascular disease in people with schizophrenia and bipolar disorder than in the general population. Kilbourne and colleagues[21] showed that male patients with bipolar disorder were 18% more likely to have dyslipidemia, 19% more likely to have diabetes, and 44% more likely to have coronary artery disease than those with schizophrenia.

Asenapine is an antipsychotic drug indicated in the United States in adults for the treatment of schizophrenia and the acute treatment, as monotherapy or adjunctive therapy to lithium or valproate, of manic or mixed episodes of bipolar I disorder. It is approved in the European Union for the treatment of moderate to severe manic episodes in bipolar disorder in adults.[22] The receptor-binding profile of asenapine is characterized by high affinity for an array of serotonergic, dopaminergic, and α-adrenergic receptors but no appreciable affinity for muscarinic receptors.[23] Asenapine has been generally well tolerated in short- and long-term studies in adult schizophrenia or bipolar I disorder patients, with a limited risk for weight gain and metabolic disturbance compared with placebo.[24–35]

Clinical Points

- People with schizophrenia and bipolar disorder have higher rates of obesity and metabolic syndrome than the population without these disorders, and these states may be associated with the use of antipsychotic drugs.
- In studies over a year or longer in this population, asenapine was associated with less weight gain than patients receiving olanzapine.

At the request of the US Food and Drug Administration (FDA) to assess the potential risks of weight and metabolic changes associated with the use of asenapine in adults, we conducted detailed post hoc analyses of the pooled data from all available clinical trials of schizophrenia and bipolar disorder that included a placebo and/or an olanzapine control.

METHOD

Data Source

To conduct the analyses as requested by the FDA, data from 17 double-blind, placebo- and/or active-controlled trials[24–30,32–38] were grouped into 2 pools (olanzapine or placebo controlled). Briefly, 13 of the 17 trials had an olanzapine control and comprised 9 schizophrenia (study duration range, 6–100 weeks)[30,32–36] and 4 bipolar mania (study duration range, 3–40 weeks) trials.[25,26,28,29] Five of the olanzapine-controlled studies included extension studies of ≥ 26 weeks' duration.[25,29,32,34] Placebo patients in short-term studies were moved to asenapine treatment in the extension studies. Overall, the 13 olanzapine-controlled trials included a total of 3,430 patients in the analysis: asenapine, 2,067; olanzapine, 1,363. The remaining 4 of the 17 trials were placebo controlled (2 schizophrenia trials,[24,27] 6 weeks' duration; 2 clinical pharmacology schizophrenia studies,[37,38] 1–2 weeks' duration). Two of the 9 olanzapine-controlled schizophrenia trials (6 weeks' duration)[33,34] and 2 of the 4 acute bipolar mania trials (3 weeks' duration)[25,28] also had a placebo control. These 8 placebo-controlled trials included a total of 1,748 patients in the analysis: asenapine, 989; placebo, 759. Trials on relapse prevention, adjunctive therapy, or comparators other than olanzapine or placebo were not included.

Asenapine was given sublingually at a dose of 5 or 10 mg twice daily (exception 2–20 mg twice daily in 2 clinical pharmacology studies). Olanzapine was given orally at doses of 5–20 mg once daily.

Pooling

The data were pooled into 2 populations: asenapine and placebo population (placebo-controlled population pool with schizophrenia and bipolar trials of 1–6 weeks' duration; data were also included for each disease state) and asenapine and olanzapine population (olanzapine-controlled population pool with schizophrenia and bipolar mania trials of 3–100 weeks' duration). For those trials with placebo and olanzapine treatment, the asenapine population was used in both pools. Data from the extension studies were pooled to the feeder studies for the same patient and same treatment group.

Assessments

Mean change from baseline to end point and other intermittent time points was calculated for weight, body mass index (BMI), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, fasting glucose, and triglycerides. All analyses using predefined categories were based on the FDA request. These analyses included predefined baseline categories for mean weight or BMI change, mean fasting glucose changes from baseline to end point or to the highest measurement as a function of baseline glucose level, incidence of prespecified weight changes at end point, and incidence of clinically relevant changes in serum lipid, fasting glucose, and glycosylated hemoglobin A_{1c} levels.

The Medical Dictionary for Regulatory Activities (MedDRA)[39] was used to define metabolic adverse events using high-level group terms (lipid metabolism disorders or lipid disorders analyses), high-level terms (diabetes mellitus, hyperglycemic conditions, or carbohydrate tolerance analysis), or preferred terms for weight issues.

Statistical Analysis

Inferential analyses based on analysis of variance, with fixed terms for protocol and treatment, were used for continuous variables; Fisher exact tests were used to compare incidence rates. Statistical comparisons were conducted to assess significance between treatment populations within pools. Thus, statistical comparisons of asenapine versus placebo and asenapine versus olanzapine were conducted independently (statistical significance, $P \leq .05$) in the treated populations. In the 2 data sets that were used, data were analyzed by visit observed cases and by treatment end point. The study or treatment end point was defined as the last observation for the patient during the treatment period in each data set.

RESULTS

Patient Demographics and Treatment Disposition

In the placebo-controlled population pool, subjects in the asenapine and placebo treatment groups were similar at baseline in age (mean = 40 years), gender distribution (male, 65%), racial distribution (white, 52% vs 55%), body weight (mean = 80 vs 82 kg), and BMI (mean = 27.1 vs 27.9). Mean treatment durations were similar for the 2 groups (24.8 and 25.1 days, respectively).

In the olanzapine-controlled population pool, mean values for subjects in the asenapine and olanzapine treatment groups were similar at baseline in age (39.1 vs 39.5 years), body weight (78 vs 80 kg), and BMI (26.6 vs 27.1). The percentages of female subjects and white subjects were higher in the asenapine than in the olanzapine treatment group

(40.2% vs 34.1% were women; 74.3% vs 66.5% were white). Mean and median treatment durations were longer for the olanzapine than the asenapine group (mean [median] = 226.2 [168] vs 207.3 [96] days).

The mean age of patients with schizophrenia and bipolar disorder was similar across the studies (range, 38.8–40.7 years); however, a higher percentage with schizophrenia were male (68.3% vs 52.7%, respectively) and black (37.8% vs 17.9%, respectively); the race difference in demographics is indicative of the high number of US patients included in the schizophrenia trials.

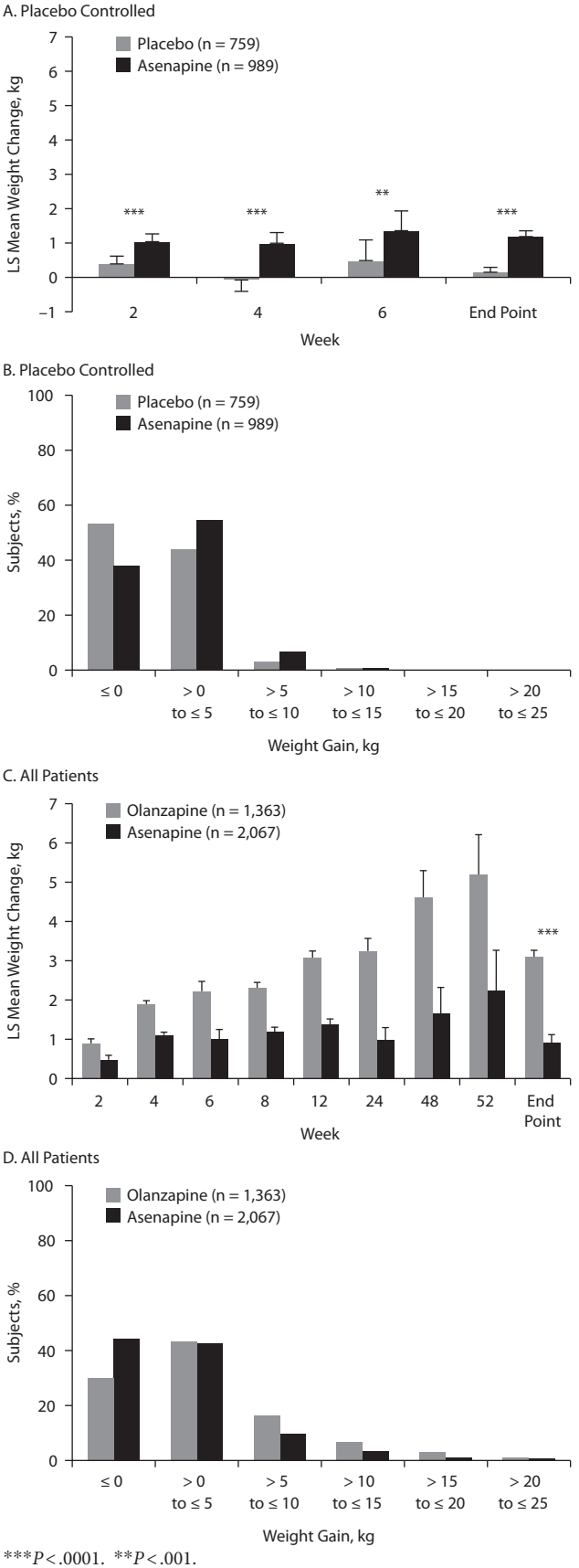
In the placebo-controlled population pool, the mean and modal asenapine dose was 16.2 mg/d and 20.0 mg/d, respectively. The mean duration of exposure for asenapine versus placebo was 25.1 versus 24.8 days, respectively. In asenapine and placebo groups, study discontinuations were attributed to any adverse event (14% vs 9%), to metabolic adverse event (0.3% vs 0.0%), or to lack of efficacy (12% vs 19%). Among asenapine-treated patients, the mean and modal asenapine dose for schizophrenia was 14.3 mg/d and 10.0 mg/d, respectively, and for bipolar disorder, 18.9 mg/d and 20.0 mg/d, respectively. The mean and median duration of study drug was 30.8 and 41.0 days, respectively, for patients with schizophrenia and 16.6 and 20.0 days, respectively, for bipolar disorder. Study discontinuations due to any adverse event were somewhat lower for patients with schizophrenia compared with bipolar disorder (12.4% vs 17.7%, respectively), whereas discontinuations due to lack of efficacy were somewhat higher for patients with schizophrenia versus bipolar disorder (13.6% vs 10.0%, respectively).

In the olanzapine-controlled population pool, the mean and modal dose was 15.3 mg/d and 20.0 mg/d, respectively, for asenapine compared with 15.0 mg/d and 20.0 mg/d, respectively, for olanzapine. The mean duration was 207.3 days for asenapine (median = 96 days; range, 1–1,065) and 226.2 days for olanzapine (median = 168 days; range, 1–996). Note the lower asenapine mean duration had 2 contributing factors: the olanzapine-controlled trials had a duration from 3 to 100 weeks, versus 1–6 weeks for the asenapine trials, and the asenapine group had higher early dropout rates compared to the olanzapine group. Study discontinuations were attributed to any adverse event (17% vs 11%), to metabolic adverse event (0.3% vs 1.5%), or to lack of efficacy (11% vs 7%) in asenapine- and olanzapine-treated patients, respectively.

Body Weight

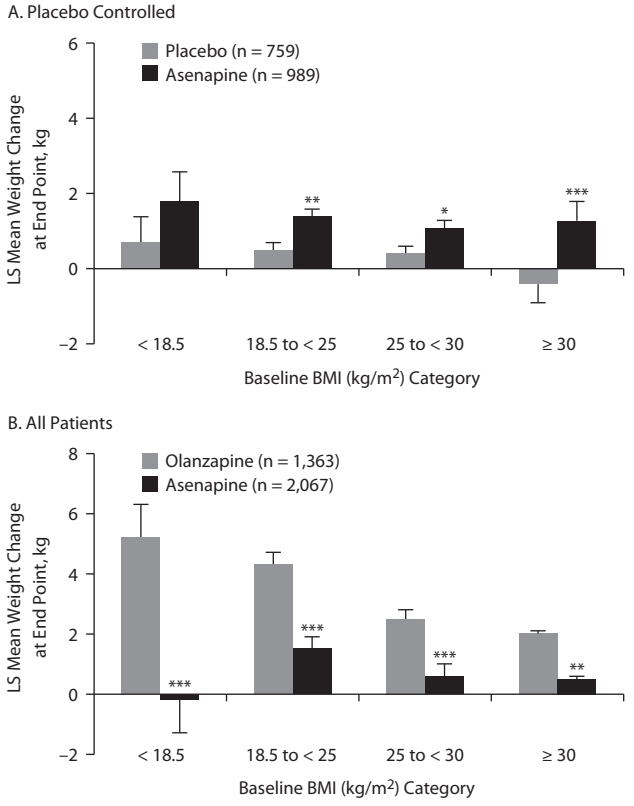
In the placebo-controlled population pool, least squares (LS) mean (standard error [SE]) weight changes in asenapine-treated patients were < 1.5 kg over time but were consistently higher than placebo-treated patients (1.2 [0.2] vs 0.14 [0.2] kg, $P < .0001$; Figure 1A). Overall, patients in both groups had a weight change, on average, of ≤ 5 kg from baseline to end point (Figure 1B); however, a larger percentage of placebo-treated patients versus asenapine-treated patients had weight change of ≤ 0 kg at end point (53% vs 38%,

Figure 1. Weight Change Over Time (A, C) and at End Point by Change Category (B, D) in Placebo- and Olanzapine-Controlled Pooled Data



***$P < .0001$. **$P < .001$.
Abbreviation: LS = least squares.

Figure 2. Weight Gain as a Function of Baseline Body Mass Index (BMI) in the Placebo- (A) and Olanzapine-Controlled (B) Pooled Data



*P < .01. **P < .001. ***P < .0001.
Abbreviation: LS = least squares.

respectively). Compared with placebo-treated patients, more asenapine-treated patients experienced weight change in the range of 0 to ≤ 5 kg (44% vs 55%; Figure 1B). Among those with schizophrenia or bipolar disorder, the LS mean (SE) weight changes were significantly greater with asenapine than with placebo (schizophrenia: 1.1 [0.1] vs 0.0 [0.2] kg, P < .0001; bipolar disorder: 1.3 [0.2] vs 0.2 [0.2] kg; P < .0001). However, asenapine-induced weight changes were similar between the disorders.

In the olanzapine-controlled population pool, LS mean [SE] weight changes at end point for asenapine were significantly less than for olanzapine (0.9 [0.1] vs 3.1 [0.2] kg, P < .0001; Figure 1C). On average, patients in both treatment groups showed ≤ 5 kg weight change from baseline to end point. However, a higher proportion of asenapine- versus olanzapine-treated patients had a weight change of ≤ 0 kg (44% vs 30%, respectively), whereas both groups showed a comparable weight change in the 0 to ≤ 5 kg category (42% vs 43%, respectively; Figure 1D). These results were consistent throughout the duration of the trials (24 weeks: asenapine 1.4 kg, olanzapine 3.8 kg; 52 weeks: asenapine 1.8 kg, olanzapine 4.8 kg). Overall, asenapine fared better than olanzapine in weight maintenance (≤ 0 kg) at end point (44% vs 30%).

There were 2 schizophrenia and 2 bipolar studies that included both olanzapine and placebo. Weight gain in patients from the 2 schizophrenia trials were significantly greater than placebo (0.17 kg) with asenapine (1.35 kg, P = .0002) or olanzapine (2.41 kg, P < .0001). Similarly, weight gain in the bipolar trials was also significantly greater than placebo (0.23 kg) with asenapine (1.26 kg, P = .0003) or olanzapine (2.27 kg, P < .0001).

Table 1. Incidence of Prespecified Body Mass Index (BMI) Changes at End Point in the Placebo- and Olanzapine-Controlled Data Sets

BMI Units (kg/m^2) Change Category, n (%)	Placebo-Controlled Studies		Olanzapine-Controlled Studies	
	Asenapine (n = 870)	Placebo (n = 616)	Asenapine (n = 1,843)	Olanzapine (n = 1,133)
BMI change ≤ 0	337 (38.7)	339 (55.0)	816 (44.3)	339 (29.9)
0 ≤ change ≤ 1	367 (42.2)	219 (35.6)	569 (30.9)	299 (26.4)
1 < change ≤ 2	124 (14.3)	44 (7.1)	244 (13.2)	224 (19.8)
2 < change ≤ 3	32 (3.7)	11 (1.8)	114 (6.2)	110 (9.7)
3 < change ≤ 4	6 (0.7)	2 (0.3)	50 (2.7)	65 (5.7)
4 < change ≤ 5	4 (0.5)	1 (0.2)	27 (1.5)	36 (3.2)
5 < change ≤ 6	0	0	14 (0.8)	25 (2.2)
6 < change ≤ 9	0	0	8 (0.4)	29 (2.6)
BMI change > 9	0	0	1 (0.1)	6 (0.5)

Body Mass Index

In the placebo-controlled population pool, LS mean (SE) changes for BMI (kg/m^2) at end point were significantly greater with asenapine than placebo (0.38 [0.05] vs 0.04 [0.06], P < .0001). In predefined BMI categories (< 18.5, 18.5 to < 25, 25 to < 30, and ≥ 30), baseline BMI was similar between treatment groups; however, at end point, LS mean changes were significantly greater with asenapine versus placebo in every category other than < 18.5 (Figure 2A). Among patients with schizophrenia or bipolar disorder, LS mean (SE) changes for BMI were greater with asenapine than with placebo (schizophrenia: 0.36 [0.05] vs 0.01 [0.06], P < .0001; bipolar disorder: 0.42 [0.05] vs 0.08 [0.07], P < .0001). However, mean changes were similar between disorders.

In the olanzapine-controlled population pool, LS mean (SE) changes in BMI were significantly less with asenapine versus olanzapine (0.31 [0.05] vs 1.06 [0.06], P < .0001). In predefined BMI categories (ranges: < 18.5 to ≥ 30), LS mean changes at end point were significantly less with asenapine versus olanzapine in every category (Figure 2B). These results were consistent throughout the duration of the trials (24 weeks: asenapine 0.5, olanzapine 1.3; 52 weeks: asenapine 0.6, olanzapine 1.7).

Overall, the magnitude of weight gain with asenapine or olanzapine was inversely proportional to baseline BMI, with patients of underweight or normal BMI experiencing more weight gain than overweight or obese patients (Figure 2). In the placebo-controlled population pool, the incidence of prespecified changes in BMI categories of ≤ 0 and 0 to ≤ 1 was 39% and 42% for asenapine compared with 55% and 36% for placebo, respectively. In the olanzapine-controlled population pool, the incidence of prespecified changes in BMI categories of ≤ 0 and 0 to ≤ 1 was 44% and 31% for asenapine compared with 30% and 26% for olanzapine, respectively (Table 1).

Table 2. Incidence of Clinically Relevant[a] Lipid and Glucose Level Changes at End Point

	Asenapine 5 or 10 mg Twice Daily		Placebo		Asenapine 5 or 10 mg Twice Daily		Olanzapine 5–20 mg Once Daily	
Variable	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
Total cholesterol, mg/dL								
< 200 to ≥ 240	550	11 (2.0)	403	5 (1.2)	1,128	40 (3.5)	774	36 (4.7)
≥ 200 and < 240 to ≥ 240	202	31 (15.3)	149	20 (13.4)	506	96 (18.9)	332	85 (25.5)
< 240 to ≥ 240	752	42 (5.6)	552	25 (4.5)	1,634	136 (8.3)	1,106	121 (10.9)
< 200 to ≥ 200	550	102 (18.5)	403	57 (14.1)	1,128	220 (19.5)	774	234 (30.2)
LDL, mg/dL								
< 100 to ≥ 160	355	2 (0.6)	184	3 (1.6)	408	4 (1.0)	370	10 (2.7)
≥ 100 and < 160 to ≥ 160	378	37 (9.8)	244	11 (4.5)	513	66 (12.9)	489	74 (15.1)
< 160 to ≥ 160	733	39 (5.3)	428	14 (3.3)	921	70 (7.6)	859	84 (9.8)
< 100 to ≥ 100	355	102 (28.7)	184	63 (34.2)	408	146 (35.8)	370	155 (41.9)
HDL, mg/dL								
≥ 40 to < 40	588	73 (12.4)	338	33 (9.8)	754	98 (13.0)	679	144 (21.2)
Fasting triglycerides, mg/dL								
< 150 to ≥ 200	408	31 (7.6)	279	14 (5.0)	692	52 (7.5)	471	70 (14.9)
< 150 to ≥ 500	408	1 (0.2)	279	0	692	3 (0.4)	471	1 (0.2)
≥ 150 and < 200 to ≥ 200	88	21 (23.9)	68	15 (22.1)	185	39 (21.1)	107	57 (53.3)
≥ 150 and < 200 to ≥ 500	88	1 (1.1)	68	0	185	3 (1.6)	107	3 (2.8)
Fasting glucose, mg/dL								
< 100 to ≥ 126	400	19 (4.8)	331	13 (3.9)	867	25 (2.9)	537	23 (4.3)
≥ 100 and < 126 to ≥ 126	138	16 (11.6)	111	6 (5.4)	210	21 (10.0)	150	20 (13.3)
< 126 to ≥ 126	538	35 (6.5)	442	19 (4.3)	1,077	46 (4.3)	687	43 (6.3)
Hemoglobin A_{1c}, %								
< 6.1 to ≥ 6.1	687	30 (4.4)	391	20 (5.1)	913	73 (8.0)	847	85 (10.0)
< 6.1 to ≥ 8	687	1 (0.1)	391	0	913	2 (0.2)	847	4 (0.5)
< 6.1 to ≥ 10	687	0	391	0	913	0	847	2 (0.2)
< 6.1 to ≥ 12	687	0	391	0	913	0	847	1 (0.1)

[a]Categories were predefined according to the US Food and Drug Administration–proposed criteria.
[b]Total number assessed for each category.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Serum Lipids

In the placebo-controlled population pool, LS mean (SE) changes in total cholesterol, LDL cholesterol, and HDL cholesterol did not differ significantly between asenapine and placebo. Relative to baseline, LS mean (SE) triglyceride levels did not change substantially with asenapine but decreased with placebo (1.8 [6.3] vs –12.2 [5.9] mg/dL, $P < .01$ vs asenapine). The incidence of clinically relevant changes (categories predefined according to FDA criteria) in serum lipid values was numerically higher with asenapine than placebo, with the exception of LDL cholesterol, for which changes were similar for asenapine and placebo (Table 2). Among patients with either schizophrenia or bipolar disorder, serum lipid changes were similar for asenapine and placebo. At end point, mean fasting triglyceride levels in patients with schizophrenia decreased with placebo but not with asenapine (–7.6 vs 3.8 mg/dL), whereas in bipolar disorder, triglyceride levels decreased with both placebo and asenapine (–17.9 vs –3.5 mg/dL).

In the olanzapine-controlled population pool, LS mean (SE) changes in total cholesterol were statistically different for asenapine and olanzapine (–0.4 [1.1] vs 6.2 [1.2] mg/dL, respectively; $P < .0001$). There were significant statistical differences between asenapine and olanzapine in LS mean (SE) changes in LDL cholesterol (–0.3 [1.1] vs 3.1 [1.2] mg/dL, $P < .01$), HDL cholesterol (1.3 [0.4] vs –0.2 [0.4] mg/dL, $P < .01$), and fasting triglycerides (–0.9 [5.4] vs 24.3 [5.8] mg/dL, $P < .0001$). Relative to baseline, total cholesterol, LDL cholesterol, and fasting triglycerides decreased in response to asenapine treatment, whereas HDL cholesterol increased. Aside from patients with fasting triglycerides in the range 150 to 500 mg/dL, the incidence of clinically relevant changes in serum lipids with olanzapine numerically exceeded that of asenapine (Table 2).

Fasting Glucose and Hemoglobin A_{1c}

In the placebo-controlled population pool, mean baseline fasting glucose values were similar between placebo and asenapine. However, LS mean (SE) change at end point for fasting glucose was significantly different for asenapine compared with placebo (1.9 [1.7] vs –1.6 [1.5] mg/dL, respectively; $P < .05$). As with mean changes to end point in fasting glucose, LS mean (SE) change from baseline to subject's highest fasting glucose measurement was also greater for asenapine versus placebo (11.3 [1.7] vs 5.6 [1.5] mg/dL, respectively; $P < .001$). In a subanalysis of placebo-controlled trials, based on baseline levels, LS mean (SE) changes from baseline to highest fasting measurements were greater for asenapine versus placebo in patients with normal (14.3 [1.5] vs 10.3 [1.3] mg/dL; $P < .05$) and borderline (6.0 [3.5] vs –1.2 [3.2] mg/dL; $P < .05$) levels but not in high fasting glucose levels (2.2 [11.5] vs –28.1 [10.5] mg/dL]. The incidence of clinically relevant fasting glucose changes, based on the categories predefined according to FDA criteria, was numerically higher with asenapine than with placebo in most categories; however, there was no difference in the incidence of clinically relevant changes in hemoglobin A_{1c} (Table 2).

Table 3. Incidence of Clinically Relevant[a] Fasting Glucose Level Changes at End Point

Baseline-to-End Point Fasting Glucose Value, mg/dL	Schizophrenia Patients				Bipolar Disorder Patients			
	Asenapine 5 or 10 mg Twice Daily		Placebo		Asenapine 5 or 10 mg Twice Daily		Placebo	
	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
< 100 to ≥ 126	262	28 (10.7)	170	9 (5.3)	111	3 (2.7)	61	2 (3.3)
≥ 100 and < 126 to ≥ 126	95	17 (17.9)	51	7 (13.7)	35	4 (11.4)	23	0
< 126 to ≥ 126	357	45 (12.6)	221	16 (7.2)	146	7 (4.8)	84	2 (2.4)
Any value, increase ≥ 10	377	168 (44.6)**	232	68 (29.3)	156	28 (17.9)	89	26 (29.2)
< 100, increase ≥ 10	262	137 (52.3)**	170	56 (32.9)	111	22 (19.8)*	61	23 (37.7)
≥ 100 and < 126, increase ≥ 10	95	25 (26.3)	51	11 (21.6)	35	6 (17.1)	23	3 (13.0)
≥ 126, increase ≥ 10	20	6 (30.0)	11	1 (9.1)	10	0	5	0
< 140 to ≥ 140	366	28 (7.7)	224	10 (4.5)	150	4 (2.7)	86	2 (2.3)
< 200 to ≥ 200	373	5 (1.3)	230	0	155	0	88	1 (1.1)
< 300 to ≥ 300	376	1 (0.3)	231	0	156	0	89	0

[a]Categories were predefined according to US Food and Drug Administration–proposed criteria.
[b]Total number assessed for each category.
*$P < .05$ for asenapine versus placebo.
**$P < .001$ for asenapine versus placebo.

Least squares mean (SE) change for fasting glucose differed in schizophrenia, with increasing levels relative to placebo at end point (3.9 [1.4] vs −0.2 [1.7] mg/dL; $P = .0526$) but not in bipolar disorder. Comparison of the incidence of clinically relevant fasting glucose changes was similar for asenapine and placebo in bipolar disorder, with the exception that more placebo- than asenapine-treated patients (38% vs 20%; $P < .05$) with a normal baseline level had an increase of ≥ 10 mg/dL (Table 3). In schizophrenia patients with normal fasting glucose levels at baseline, more asenapine- than placebo-treated patients had an increase ≥ 10 mg/dL in fasting plasma glucose (52% vs 33%; $P < .001$).

In the olanzapine-controlled population pool, changes in fasting glucose levels were not significantly different between asenapine and olanzapine (2.0 vs 3.3 mg/dL, respectively). Least squares mean (SE) change from baseline to the highest fasting glucose measurement did not differ significantly for asenapine versus olanzapine (9.8 [1.5] vs 10.1 [1.6] mg/dL, respectively). The incidence of clinically relevant fasting glucose changes was comparable for asenapine and olanzapine; however, the incidence of clinically relevant hemoglobin A_{1c} changes was numerically higher with olanzapine (Table 2).

DISCUSSION

The post hoc analyses presented are based on a comprehensive set of available clinical studies with asenapine at effective doses and provide a characterization of asenapine's safety and tolerability profile with regard to weight gain and metabolic changes in patients with schizophrenia and in patients with manic or mixed episodes in bipolar disorder compared to placebo and olanzapine. On the basis of these analyses, asenapine is associated on average with more weight gain and adverse changes in lipids and fasting glucose than placebo and with less weight gain and adverse changes in lipids than olanzapine. Among patients with schizophrenia and bipolar disorder, changes in body weight and BMI in response to asenapine treatment reflected the changes observed in the entire placebo-controlled data set and did not differ according to diagnosis. However, asenapine treatment of schizophrenia, but not bipolar disorder, appeared to be associated with small increases in fasting triglyceride and glucose levels. On the basis of asenapine submission data from different studies (Merck data on file, 2008), the pattern of weight change in the asenapine and olanzapine groups did not appear to differ by race, gender, or geographic region.

The overall effects of asenapine on weight gain, BMI, and metabolic parameters in relation to placebo and olanzapine are consistent with the findings from individual clinical trials. In short- and long-term controlled studies, asenapine was associated with more weight gain than placebo but less than olanzapine in patients with schizophrenia or bipolar disorder, findings that are supported by the incidence of clinically significant (≥ 7% change from baseline) weight gain.[24–31] The greatest observable differences between asenapine and olanzapine treatment occurred in body weight and fasting triglycerides. A body weight change resulting in an increase of ≥ 2 BMI units occurred in 24% of olanzapine-treated patients compared with 12% of asenapine-treated patients, whereas an increase of ≥ 5 BMI units occurred in 5.3% and 1.2% of olanzapine- and asenapine-treated patients, respectively. Similarly, fasting triglyceride levels ≥ 200 mg/dL occurred in 22.0% and 10.4% of olanzapine- and asenapine-treated patients, respectively. Overall, asenapine produced minimal changes in serum lipids and glucose compared with placebo and is associated with decreases in triglycerides and total cholesterol compared with olanzapine.

In the current analyses, substantial decreases from baseline in total cholesterol, triglycerides, and fasting glucose were observed in the placebo group, most likely attributable to the switch from prior treatment with an antipsychotic. Although asenapine produced smaller increases in fasting glucose than olanzapine, both fasting glucose and hemoglobin A_{1c} changes did not differ significantly between treatment groups, suggesting that both short- and long-term measures of glycemic control can be used as markers of metabolic changes in nondiabetic patient populations. Given olanzapine's propensity to induce hyperglycemia,[40] LS mean changes in fasting glucose in this analysis (3.3 mg/dL) were smaller in magnitude than most reported changes

in other comparative studies.[41] Regardless of the magnitude of the effect, the tendency of olanzapine to produce weight gain and to negatively affect serum lipids is consistent with previous reports from clinical trials comparing olanzapine with other atypical antipsychotics.[42]

Although it is unknown why asenapine and olanzapine differ in their impact on weight gain, one may conjecture that the basis of this difference may be the greater affinity of asenapine for serotonin receptors relative to histaminic receptors,[23] as compared to the olanzapine receptor profile: activity at serotonergic, histaminic, and adrenergic receptor subtypes has been implicated in antipsychotic-induced weight gain.[39,43] Although asenapine is an antagonist of serotonin-7 receptors in the thalamus and hypothalamus,[44] it is not yet known whether this confers any advantage for weight or metabolic changes. Changes in lipids and glucose may arise secondary to weight gain[12,45] or occur independently of weight change during treatment with antipsychotics. Little is known about how individual antipsychotics may differentially impact weight and metabolic changes in patients with schizophrenia and bipolar disorder. Among patients with schizophrenia or bipolar disorder, asenapine-related changes in body weight and BMI were significantly greater than placebo, reflecting the changes observed in the entire placebo-controlled data set. Additionally, we also observed higher fasting triglyceride and glucose levels with asenapine in patients with schizophrenia than in those with bipolar disorder.

The findings of these post hoc analyses are compelling because of the large number of patients assessed; however, there are limitations. Interpretations of the safety and tolerability of asenapine versus placebo should be viewed cautiously because the duration of treatment was relatively brief (1–6 weeks). It should be also cautioned that, on average, olanzapine had longer treatment exposure than asenapine in olanzapine-controlled data. As with any post hoc analysis, there are limitations arising from the potential for type I errors.

In conclusion, in the placebo-controlled population pool, asenapine was associated with greater weight gain and glucose changes compared with placebo. Further, changes in serum lipids did not differ significantly between asenapine and placebo. Although triglyceride levels did not change substantially with asenapine treatment, levels decreased with placebo. In the olanzapine-controlled population pool, asenapine had a lower propensity than olanzapine to induce weight gain or increase triglycerides or serum lipids, indicating a more favorable metabolic profile than olanzapine in studies of a year or more.

Drug names: asenapine (Saphris), lithium (Lithobid and others), olanzapine (Zyprexa and others).

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Potential conflicts of interest: **Dr Kemp** has been a consultant to Bristol-Myers Squibb, Corcept, Janssen, and Teva; is on the speakers' bureau for AstraZeneca; has served on speakers' bureau for Pfizer; and his spouse is a former minor stock shareholder in Sanofi and Abbott. **Dr Zhao** was an employee of Merck at the time of research. **Dr Cazorla** was an employee and stock shareholder of Merck at the time of research. **Drs Landbloom** and **Mackle** and **Ms Snow-Adami** are employees of Merck. **Dr Szegedi** is an employee and stock shareholder of Merck.

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REFERENCES

1. Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. *PLoS ONE*. 2011;6(9):e24597.
2. Hoang U, Stewart R, Goldacre MJ. Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999–2006. *BMJ*. 2011;343:d5422.
3. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.
4. Arango C, Bobes J, Aranda P, et al; CLAMORS Study Collaborative Group. A comparison of schizophrenia outpatients treated with antipsychotics with and without metabolic syndrome: findings from the CLAMORS study. *Schizophr Res*. 2008;104(1–3):1–12.
5. Thompson KN, Phillips LJ, Komesaroff P, et al. Stress and HPA-axis functioning in young people at ultra high risk for psychosis. *J Psychiatr Res*. 2007;41(7):561–569.
6. Kemp DE, Gao K, Chan PK, et al. Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. *Bipolar Disord*. 2010;12(4):404–413.
7. Pariante CM, Dazzan P, Danese A, et al. Increased pituitary volume in antipsychotic-free and antipsychotic-treated patients of the AEsop first-onset psychosis study. *Neuropsychopharmacology*. 2005;30(10):1923–1931.
8. Dasgupta A, Singh OP, Rout JK, et al. Insulin resistance and metabolic profile in antipsychotic naïve schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(7):1202–1207.
9. Guest PC, Schwarz E, Krishnamurthy D, et al. Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia. *Psychoneuroendocrinology*. 2011;36(7):1092–1096.
10. Rush AJ, Giles DE, Schlesser MA, et al. The dexamethasone suppression test in patients with mood disorders. *J Clin Psychiatry*. 1996;57(10):470–484.
11. Taylor V, MacQueen G. Associations between bipolar disorder and metabolic syndrome: a review. *J Clin Psychiatry*. 2006;67(7):1034–1041.
12. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry*. 2006;51(8):480–491.
13. Megna JL, Schwartz TL, Siddiqui UA, et al. Obesity in adults with serious and persistent mental illness: a review of postulated mechanisms and current interventions. *Ann Clin Psychiatry*. 2011;23(2):131–140.
14. Le Hellard S, Theisen FM, Haberhausen M, et al. Association between the insulin-induced gene 2 (INSIG2) and weight gain in a German sample of antipsychotic-treated schizophrenic patients: perturbation of SREBP-controlled lipogenesis in drug-related metabolic adverse effects? *Mol Psychiatry*. 2009;14(3):308–317.
15. Orešič M, Tang J, Seppänen-Laakso T, et al. Metabolome in schizophrenia and other psychotic disorders: a general population-based study. *Genome Med*. 2011;3(3):19.
16. Kaddurah-Daouk R, McEvoy J, Baillie RA, et al. Metabolomic mapping of atypical antipsychotic effects in schizophrenia. *Mol Psychiatry*. 2007;12(10):934–945.
17. Kemp DE, Karayal ON, Calabrese JR, et al. Ziprasidone with adjunctive mood stabilizer in the maintenance treatment of bipolar I disorder: long-term changes in weight and metabolic profiles. *Eur Neuropsychopharmacol*. 2012;22(2):123–131.
18. Kemp DE, Calabrese JR, Tran QV, et al. Metabolic syndrome in patients enrolled in a clinical trial of aripiprazole in the maintenance treatment of bipolar I disorder: a post hoc analysis of a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2010;71(9):1138–1144.

19. van Winkel R, van Os J, Celic I, et al. Psychiatric diagnosis as an independent risk factor for metabolic disturbances: results from a comprehensive, naturalistic screening program. *J Clin Psychiatry*. 2008;69(8):1319–1327.
20. Birkenaes AB, Opjordsmoen S, Brunborg C, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. *J Clin Psychiatry*. 2007;68(6):917–923.
21. Kilbourne AM, Brar JS, Drayer RA, et al. Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. *Psychosomatics*. 2007;48(5):412–417.
22. Gerrits MG, de Greef R, Dogterom P, et al. Valproate reduces the glucuronidation of asenapine without affecting asenapine plasma concentrations. *J Clin Pharmacol*. 2012;52(5):757–765.
23. Shahid M, Walker GB, Zorn SH, et al. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol*. 2009;23(1):65–73.
24. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68(10):1492–1500.
25. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disord*. 2009;11(7):673–686.
26. McIntyre RS, Cohen M, Zhao J, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study. *Bipolar Disord*. 2009;11(8):815–826.
27. Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010;30(2):106–115.
28. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2010;122(1–2):27–38.
29. McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *J Affect Disord*. 2010;126(3):358–365.
30. Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010;43(4):138–146.
31. Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349–355.
32. Buchanan RW, Panagides J, Zhao J, et al. Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia. *J Clin Psychopharmacol*. 2012;32(1):36–45.
33. Study 041021. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. http://clinicaltrials.gov/ct2/show/NCT00156117?term=NCT00156117&rank=1. Updated October 9, 2009. Accessed August 21, 2013.
34. Study 041022. A multicenter, randomized, double-blind, flexible-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. http://clinicaltrials.gov/ct2/show/study/NCT00151424?term=NCT00151424&rank=1. Updated August 25, 2008. Accessed August 21, 2013.
35. Study 041512. A multicenter, randomized, double-blind, flexible-dose, long-term extension trial of the safety and maintenance of effect of asenapine using olanzapine positive control in subjects who complete protocols 041021 or 041022. http://clinicaltrials.gov/ct2/show/study/NCT00156091?intr=%22Asenapine%22&rank=34. Updated October 2, 2009. Accessed August 21, 2013.
36. Study 25520. Long- term efficacy and safety evaluation of asenapine (10–20 mg/day) in subjects with schizophrenia or schizoaffective disorder, in a multicenter trial using olanzapine (10–20 mg/day) as a control. http://www.clinicaltrials.gov/ct2/show/NCT00212771?term=P05846&rank=1. Updated October 2, 2009. Accessed August 21, 2013.
37. Study A41012. A single-center randomized, double-blind, placebo-controlled, titration study to evaluate the tolerability of sublingual org 5222 up to 20 mg twice daily in subjects with schizophrenia or schizoaffective disorder. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022117s000_ClinPharmR_P2.pdf. Accessed August 21, 2013.
38. Chapel S, Hutmacher MM, Haig G, et al. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. *J Clin Pharmacol*. 2009;49(11):1297–1308.
39. MedDRA MSSO. Medical Dictionary for Regulatory Activities. http://www.meddra.org/faq. Accessed August 21, 2013.
40. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs*. 2007;21(11):911–936.
41. Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(3):CD006654.
42. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. *Life Sci*. 2000;68(1):29–39.
43. Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology*. 2003;28(suppl 1):83–96.
44. Stahl SM. The serotonin-7 receptor as a novel therapeutic target. *J Clin Psychiatry*. 2010;71(11):1414–1415.
45. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry*. 2007; 68(suppl 1):20–27.