A Randomized Placebo-Controlled Trial of Asenapine for the Prevention of Relapse of Schizophrenia After Long-Term Treatment

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Objective: Long-term efficacy of asenapine in preventing schizophrenia relapse was assessed in a 26-week double-blind, placebo-controlled trial that followed 26 weeks of open-label treatment.

Method: Stable schizophrenia patients (*DSM-IV-TR* criteria) who were cross-titrated from previous medication to sublingual asenapine and remained stable during 26 weeks of open-label treatment were eligible for 26 weeks of double-blind treatment, with randomization to continued asenapine or switch to placebo. Time to relapse/impending relapse (primary endpoint, as usually determined by specific scores on the Positive and Negative Syndrome Scale and the Clinical Global Impressions-Severity of Illness Scale) and discontinuation for any reason (key secondary endpoint) were assessed by survival analyses for asenapine versus placebo. The study was conducted from May 2005 through June 2008.

Results: Of 700 enrolled patients treated with open-label asenapine, 386 entered (asenapine, n = 194; placebo, n = 192) and 207 completed (n = 135; n = 72) the double-blind phase. Times to relapse/impending relapse and discontinuation for any reason were significantly longer with asenapine than with placebo (both $P < .0001$). Incidence of relapse/impending relapse was lower with asenapine than placebo (12.1% vs 47.4%, $P < .0001$). The modal dosage of asenapine was 10 mg twice daily in both phases. During the double-blind phase, the incidence of adverse events (AEs) considered serious with asenapine and placebo was 3.1% and 9.9%, respectively; incidence of extrapyramidal symptom–related AEs was 3.1% and 4.7%, respectively. The most frequently reported AEs with asenapine versus placebo were anxiety (8.2%; 10.9%), increased weight (6.7%; 3.6%), and insomnia (6.2%; 13.5%). The incidence of clinically significant weight gain (≥ 7% increase from double-blind baseline) was 3.7% with asenapine and 0.5% with placebo.

Conclusions: Long-term treatment with asenapine was more effective than placebo in preventing relapse of schizophrenia and appeared to be safe and well tolerated.

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Relapse is common in schizophrenia when pharmacotherapy is discontinued.[1,2] Relapse may be due to factors such as noncompliance or discontinuation (for reasons including adverse events [AEs]), lack of efficacy, or loss of efficacy (as evidenced by relapse in patients taking depot medications[3]). Given that effective pharmacotherapy reduces relapse risk and its associated costs,[4] the continued development of novel pharmacotherapies is worthwhile.

Asenapine is a US Food and Drug Administration (FDA)–approved atypical antipsychotic indicated for treatment of schizophrenia and acute treatment, as monotherapy or adjunctive therapy to lithium or valproate, of manic or mixed episodes associated with bipolar I disorder[5]; asenapine is indicated in the European Union for treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.[6] In two 6-week, placebo- and active-controlled clinical trials, sublingual asenapine demonstrated superiority over placebo in the treatment of acute schizophrenia, as measured by changes from baseline in Positive and Negative Syndrome Scale (PANSS) total and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores.[7,8]

In this study, the long-term efficacy of asenapine was examined. The primary objective was to compare the efficacy of asenapine versus placebo in preventing time to relapse/impending relapse in schizophrenia patients who were stable on asenapine treatment after 26 weeks of open-label treatment.

METHOD

Study Design

This randomized, placebo-controlled, double-blind, phase III, multinational trial (A7501012; clinicaltrials.gov Identifier NCT00150176) was conducted at 61 centers (United States, n = 21; Russian Federation, n = 16; Ukraine, n = 9; India, n = 8; Latvia, n = 4; Croatia, n = 3) from May 2005 through June 2008. The study had 2 phases: a 26-week open-label flexible-dose phase and a 26-week randomized, double-blind, limited flexible-dose, placebo-controlled phase.

Open-label treatment began with cross-titration from prior antipsychotics to sublingual asenapine for ≤ 4 weeks. The starting asenapine dosage of 5 mg bid was increased to 10 mg bid after 1 week. Monotherapy with asenapine and placebo continued for ≥ 22 weeks, with dosage adjustment allowed. Asenapine and placebo sublingual tablets, which were identical in appearance, were coadministered (simultaneously placed under the tongue) in a blinded fashion during open-label treatment; neither patients nor sites were aware of the tablet identity. Coadministration of asenapine and placebo ensured that slight taste differences would not be associated with a specific treatment. (Note: placebo tablets were flavored to approximate the taste of asenapine tablets.)

Patients completing open-label treatment were not randomized to double-blind treatment if they experienced

a loss of stability (a PANSS total score[9] increase of ≥ 20% or 12 points from open-label baseline) or met any of these exclusion criteria: PANSS total score > 75; CGI-S score[10] > 3; PANSS item scores ≥ 4 on "unusual thought content," "conceptual disorganization," "hallucinatory behavior," "hostility," or "uncooperativeness"; or Modified International Suicide Prevention Trial Scale for Suicidal Thinking (ISST)[11] scores of 2 on items 7 (control over suicidal ideation), 10 (specific planning of suicidal acts), or 11 (anticipation or expectation of suicide).

Patients randomized to double-blind treatment continued sublingual asenapine or were switched to sublingual placebo. During double-blind treatment, patients continued taking only 1 tablet—asenapine or placebo. The double-blind was maintained. The starting dosage for asenapine patients matched the final open-label treatment dosage, with further reductions allowed for tolerability only. Dose increases were not allowed.

All patients provided written informed consent before screening. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Patients

Men and women (≥ 18 years) with a primary *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, diagnosis of schizophrenia were eligible. Documented histories of ≥ 1 prior acute schizophrenia episode during the preceding 3 years and schizophrenia requiring continuous antipsychotic treatment for ≥ 1 year preceding screening were required. Patients had to be clinically stable (no antipsychotic dose increase, psychiatric hospital admission, emergency room visit, or psychiatric care increase owing to worsening schizophrenia; no arrest or imprisonment) for ≥ 4 weeks before study entry and have a caregiver/responsible person and access to appropriate supervision during treatment. Women of childbearing age could not be pregnant or breastfeeding and had to be using birth control for ≥ 1 month before screening.

Participants were excluded for any of the following reasons: diagnosis of a concurrent Axis I psychiatric disorder; mental retardation, organic brain syndrome, or substance abuse; current acute schizophrenia relapse; PANSS total score > 80 or scores ≥ 4 on "unusual thought content," "conceptual disorganization," "hallucinatory behavior," "hostility," or "uncooperativeness" at screening; CGI-S score > 4 (moderately ill); score of 2 on Modified-ISST items 7, 10, or 11; history (within preceding 2 y) or imminent risk of suicide attempt or violence; history of noncompliance with antipsychotic medication; clozapine use for schizophrenia within preceding 12 weeks; or unstable medical conditions.

Concomitant Medications

Concomitant medications, except single doses of acetaminophen, were not to be used without consultation. Chronic use of certain medications (eg, hormonal birth control, antihypertensives, diuretics, and oral hypoglycemics) was allowed if the condition and treatment regimen were stable before initiating open-label treatment. Clozapine, dopamine antagonist antiemetic, dopamine agonist, and medium- and long-acting benzodiazepine use was prohibited.

Short-acting benzodiazepines could be used for agitation (maximum dose: 6 mg/d lorazepam for the first 8 wk and 4 mg/d for the remainder of trial). A dosage increase was allowed (additional 2 mg/d lorazepam or equivalent) for up to 7 days to treat transient life stressors (excluding relapse/impending relapse) during the double-blind period. Partial benzodiazepine agonists or an equivalent short half-life non-benzodiazepine hypnotic could be used for insomnia and sleep disturbances. Short-acting benzodiazepines and partial benzodiazepine agonists were prohibited 12 hours before efficacy assessments.

Antidepressants, except fluvoxamine, or mood stabilizers could be used for depressive symptoms provided the treatment regimen was stable at screening and could be initiated only to treat depressive symptoms, measured on the Calgary Depression Scale in Schizophrenia (CDSS),[12] during open-label treatment. The initiation or increase in dosage of antidepressants or mood stabilizers during double-blind treatment was considered an intervention for relapse/impending relapse.

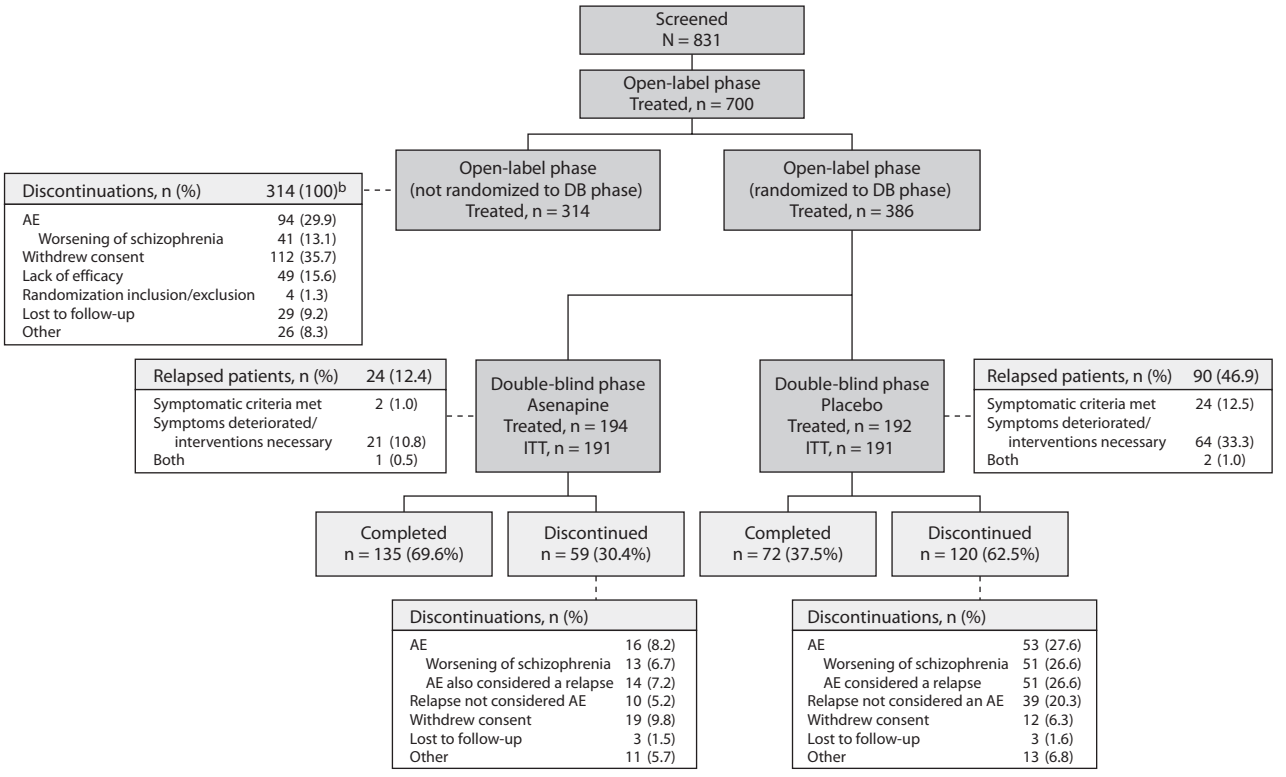
Concomitant treatment of extrapyramidal symptoms (EPS) could be continued following the initiation of open-label asenapine. After cross-titration to asenapine was completed, the dosage of EPS medication was gradually decreased; if EPS reappeared, dosage adjustments were allowed.

Efficacy

Primary efficacy measure. The primary efficacy measure was time to relapse/impending relapse during double-blind treatment according to rating-scale criteria or investigators' judgment. Relapse/impending relapse was judged to occur when a CGI-S score ≥ 4 (moderately ill) for ≥ 2 days within 1 week was accompanied by: a PANSS total score increase ≥ 20% from double-blind baseline (a ≥ 10-point increase if baseline total score was < 50), a PANSS item score ≥ 5 (moderately severe) on "hostility" or "uncooperativeness," or a PANSS item score ≥ 5 on 2 items of "unusual thought content," "conceptual disorganization," or "hallucinatory behavior." Relapse/impending relapse was also judged to occur if, in the investigators' opinion, schizophrenia, risk of violence to self/others, or suicide risk increased so ≥ 1 of the following was required: an additional ≥ 2 mg/d lorazepam (or equivalent) compared with the highest open-label dose for 1 week, addition of antipsychotic, addition or dosage increase of an antidepressant or mood stabilizer, increased psychiatric care, hospitalization or increased level of hospitalization, arrest or imprisonment, electroconvulsive therapy, or other relevant measure.

Secondary efficacy measures. The time to early discontinuation for any reason was a key secondary efficacy endpoint. Changes from baseline on PANSS total and Marder factor[13] scores, CGI-S, Clinical Global Impressions-Improvement

Figure 1. Patient Disposition[a]



[a]Relapse also includes impending relapse; all percentages are based on the treated population within each phase of the study.
[b]All patients who did not go on to randomization to double-blind treatment dropped out before the end of the open-label phase; all patients who completed the open-label phase went on to randomization.
Abbreviations: AE = adverse event, DB = double-blind, ITT = intent to treat.

(CGI-I), CDSS, and Modified-ISST were assessed during both phases.

Safety and Tolerability

Safety and tolerability were assessed with AEs, physical assessments, laboratory measures, electrocardiography, weight, and body mass index. EPS were assessed using patient reports of EPS-related AEs and standardized rating scales (Barnes Akathisia Rating Scale [BARS],[14] Abnormal Involuntary Movement Scale [AIMS],[15] and Simpson-Angus Scale [SAS][16]).

Statistical Analyses

The primary endpoint, time to relapse/impending relapse, was assessed using survival analysis in the intent-to-treat (ITT) population (patients randomized to double-blind therapy receiving ≥ 1 double-blind study medication dose; 4 patients previously enrolled in other asenapine trials were excluded). Survival time differences were assessed using a 2-sided log rank test with significance level set at $P < .05$.

The Kaplan-Meier estimate with confidence intervals (CIs), along with number at risk, number of events, and number of censored observations, were assessed at each time point. Point estimates with 95% CIs were calculated for survival curve quartiles when possible. Relative risk and relapse/impending relapse rates were also provided. Kaplan-Meier estimates and log-rank tests were used for time to relapse/impending relapse based on an independent endpoint review board (IERB) evaluation and time to early discontinuation for any reason.

Changes from baseline during the double-blind phase for other secondary efficacy endpoints were analyzed using analysis of covariance with treatment as a fixed effect and baseline as a covariate in observed cases. Safety was assessed in the treated population (patients receiving ≥ 1 study medication dose) and summarized using descriptive statistics.

RESULTS

Disposition and Study Population

Eighty-four percent of screened patients were treated in the open-label phase; of these, 44.9% discontinued (Figure 1). The most common reasons for open-label discontinuation were withdrawn consent and AEs/serious AEs (SAEs). Of the patients randomized to double-blind treatment, 53.6% completed the study (asenapine, 69.6%; placebo, 37.5%).

Table 1 summarizes demographics and clinical characteristics. In the open-label treated population (nonrandomized plus randomized patients), most patients were white (67.3%) and male (59.4%); mean ± SD age was 39.4 ± 12.1 years (range, 18–78 years).

Demographics were generally comparable between patients randomized to double-blind treatment and those not randomized and between patients randomized to

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Table 1. Demographic and Clinical Characteristics at Open-Label Baseline

Variable	Nonrandomized (n = 314)	Randomized	
		Asenapine (n = 194)	Placebo (n = 192)
Sex, n (%)			
Men	195 (62.1)	105 (54.1)	116 (60.4)
Women	119 (37.9)	89 (45.9)	76 (39.6)
Race, n (%)			
White	190 (60.5)	141 (72.7)	140 (72.9)
Black	60 (19.1)	22 (11.3)	18 (9.4)
Asian	53 (16.9)	30 (15.5)	33 (17.2)
Other	11 (3.5)	1 (0.5)	1 (0.5)
Age, y			
18–64, n (%)	308 (98.1)	189 (97.4)	188 (97.9)
≥65, n (%)	6 (1.9)	5 (2.6)	4 (2.1)
Mean ± SD	40.0 ± 12.1	39.2 ± 12.5	38.7 ± 11.6
Weight, mean ± SD, kg	80.3 ± 19.5	76.7 ± 19.4	76.4 ± 20.1
Body mass index, mean ± SD, kg/m^2	27.4 ± 6.1	27.0 ± 6.5	26.3 ± 6.7
Current schizophrenia diagnosis, n (%)			
Paranoid type	267 (85.0)	159 (82.0)	156 (81.3)
Disorganized type	2 (0.6)	0 (0.0)	1 (0.5)
Catatonic type	3 (1.0)	2 (1.0)	1 (0.5)
Undifferentiated type	36 (11.5)	26 (13.4)	26 (13.5)
Residual type	5 (1.6)	7 (3.6)	8 (4.2)
Schizoaffective disorder	1 (0.3)	0 (0.0)	0 (0.0)
Age at schizophrenia onset, mean ± SD, y	26.5 ± 8.9	26.9 ± 9.7	26.4 ± 8.9
Duration of disease, mean ± SD, y	14.0 ± 10.5	12.7 ± 10.6	12.8 ± 10.4
Previous hospitalization for schizophrenia, n (%)			
None	48 (15.3)	26 (13.4)	29 (15.1)
Unknown	1 (0.3)	1 (0.5)	1 (0.5)
1	35 (11.1)	32 (16.5)	22 (11.5)
2–3	69 (22.0)	47 (24.2)	56 (29.2)
≥4	161 (51.3)	88 (45.4)	83 (43.2)
Schizophrenia hospitalization within past year, n (%)			
None	178 (56.7)	124 (63.9)	120 (62.5)
Unknown	1 (0.3)	1 (0.5)	0 (0.0)
1	88 (28.0)	54 (27.8)	50 (26.0)
2–3	35 (11.1)	11 (5.7)	17 (8.9)
≥4	12 (3.8)	4 (2.1)	5 (2.6)
Length of most recent hospitalization, mean ± SD, d	60.7 ± 87.1	81.7 ± 120.6	121.1 ± 285.5

asenapine versus placebo. The percentage of white patients was higher and of black patients was lower in randomized patients versus nonrandomized patients. The percentage of women randomized to asenapine was higher than those randomized to placebo.

Open-Label Phase Results

Switching from other antipsychotics to asenapine. Among open-label treated patients, 548 switched from another antipsychotic to asenapine (eTable 1). The mean ± SD duration of the switch period was 12.6 ± 6.5 days (median, 14 days; range, 1–28 days).

Drug exposure. The mean ± SD asenapine dose was 15.5 ± 4.1 and 17.6 ± 3.2 mg/d in nonrandomized and randomized patients, respectively (modal dose in both groups, 20 mg/d). In nonrandomized and randomized groups, respectively, the total dose was 20 mg/d in 72.3% and 81.3% of patients; 75.8% and 79.5% of patients used this dose on the final day of open-label treatment. Mean exposure duration was 73 ± 57 days in nonrandomized and 183 ± 3 days in randomized patients.

Table 2. Adverse Events in the Treated Population[a]

AE Category	Open-Label Phase		Double-Blind Phase	
	Nonrandomized (n = 314)	Randomized (n = 386)	Asenapine (n = 194)	Placebo (n = 192)
Treatment-emergent AEs/SAEs	228 (72.6)	251 (65.0)	89 (45.9)	106 (55.2)
Treatment-emergent SAEs	39 (12.4)	3 (0.8)	6 (3.1)	19 (9.9)
Treatment-related AEs/SAEs	167 (53.2)	202 (52.3)	44 (22.7)	52 (27.1)
Treatment-related SAEs	8 (2.5)	1 (0.3)	2 (1.0)	8 (4.2)
Treatment-emergent AEs reported by ≥5% of patients				
Somnolence	54 (17.2)	63 (16.3)	1 (0.5)	2 (1.0)
Insomnia	42 (13.4)	57 (14.8)	12 (6.2)	26 (13.5)
Headache	19 (6.1)	35 (9.1)	6 (3.1)	2 (1.0)
Weight increased	11 (3.5)	30 (7.8)	13 (6.7)	7 (3.6)
Anxiety	34 (10.8)	23 (6.0)	16 (8.2)	21 (10.9)
Akathisia	21 (6.7)	22 (5.7)	4 (2.1)	3 (1.6)
Parkinsonism	12 (3.8)	20 (5.2)	1 (0.5)	3 (1.6)
Agitation	25 (8.0)	18 (4.7)	4 (2.1)	11 (5.7)
Schizophrenia	17 (5.4)	1 (0.3)	9 (4.6)	31 (16.1)
Weight decreased	3 (1.0)	14 (3.6)	7 (3.6)	16 (8.3)
Delusion	12 (3.8)	1 (0.3)	2 (1.0)	11 (5.7)
Hallucination	6 (1.9)	1 (0.3)	1 (0.5)	13 (6.8)

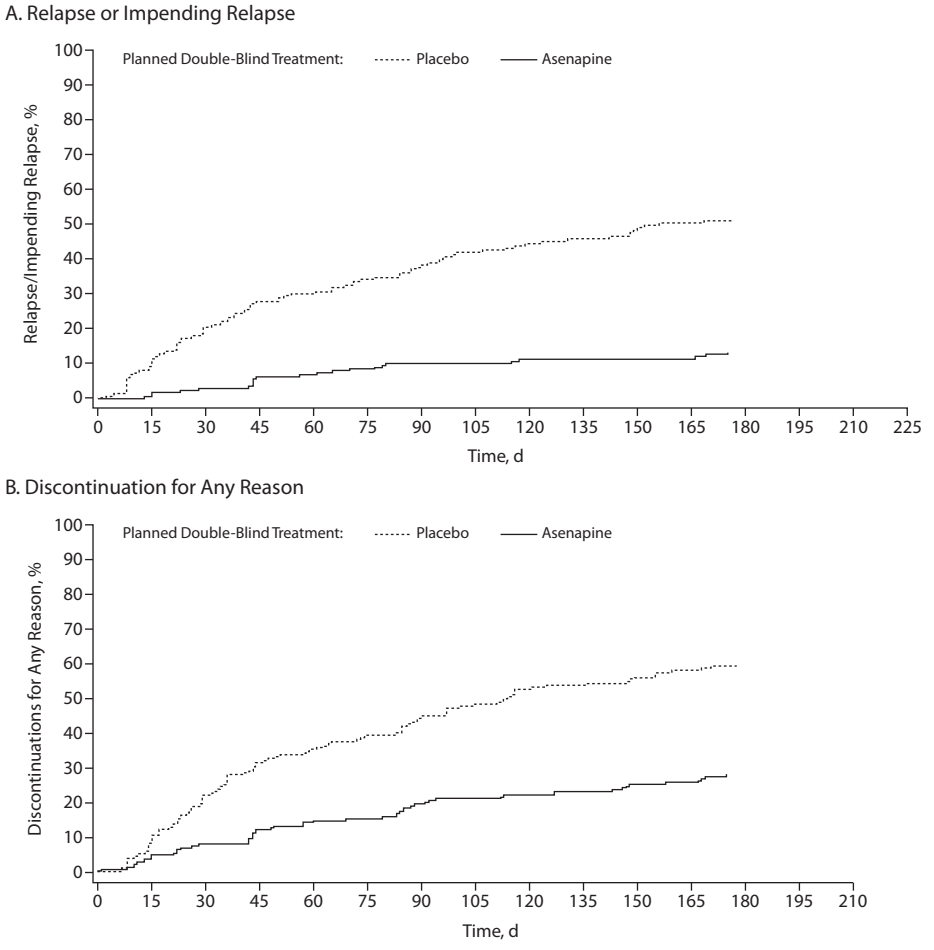
[a]All values shown as n (%). Open-label data represent AEs/SAEs reported as starting on or after the first dose of open-label trial medication through last dose date plus 7 days (AEs) or last dose date plus 30 days (SAEs) for patients who discontinued before randomization; or the day before randomization for patients randomized to double-blind trial medication (applies to AEs and SAEs). Double-blind data represent AEs/SAEs reported as starting on or after the date of randomization through last dose date plus 7 days (AEs) or last dose date plus 30 days (SAEs). Patients are counted only once within each preferred term.
Abbreviations: AE = adverse event, SAE = serious AE.

Concomitant medications. Concomitant medications were used by 89.7% of patients (initial 4 weeks, 87.9%; thereafter, 46.7%). The incidence of medication use to treat insomnia was 11.1% (initial 4 weeks, 6.0%; thereafter. 9.0%), to treat EPS was 6.7% (3.9%; 5.7%), and to treat agitation was 4.7% (2.6; 4.0%).

Efficacy. The mean ± SD PANSS total score change from baseline to the end of open-label treatment was −8.4 ± 7.9 among patients subsequently randomized to double-blind treatment (asenapine, −8.7 ± 7.9; placebo, −8.2 ± 7.8) versus 3.5 ± 13.7 among patients who were not randomized.

Safety and tolerability. At least 1 treatment-emergent AE was reported by 68.4% of patients (Table 2), with these AEs being higher in those who did not complete open-label treatment; incidence of treatment-related AEs was similar in both patient subsets. Among randomized and nonrandomized patients, the most frequently reported treatment-emergent AEs were somnolence and insomnia. Serious AEs reported

Figure 2. Kaplan-Meier Estimates of (A) Time to Relapse or Impending Relapse as Determined by the Investigator and (B) Time to Early Discontinuation Due to Any Reason, in the Intent-To-Treat Population



in >2% of all nonrandomized patients included worsening of schizophrenia (3.2%) and of paranoid schizophrenia (3.5%).

Incidence of ≥1 treatment-emergent EPS-related AEs (mostly akathisia and parkinsonism, Table 2) was 10.9% (nonrandomized, 8.9%; randomized, 12.4%); 4 (1.3%) and 2 (1.6%) patients discontinued due to akathisia and parkinsonism, respectively. Mean changes in BARS global, AIMS global, and SAS total scores were small (0.1, 0.1, and 0.9, respectively) and similar in randomized and nonrandomized patients. Among patients at risk for EPS (defined by BARS, AIMS, and SAS scores of <2, <2, and ≤3 at baseline), 7.1%, 1.5%, and 7.7%, respectively, reached threshold scores (≥2, ≥2, and >3) during treatment.

Mean ± SD weight change was 0.3 ± 3.8 kg (0.7 ± 8.3 lb) in nonrandomized patients and 0.7 ± 4.1 kg (1.5 ± 9.1 lb) in randomized patients. Incidences of clinically significant weight gain and weight loss (≥7% increase or decrease from baseline, respectively) were 5.5% and 3.3% in nonrandomized patients and 8.0% and 4.9% in randomized patients.

Laboratory assessments were unremarkable (eTable 2). Incidence of marked hyperprolactinemia (≥4 × upper limit of normal) was 3.5% in nonrandomized and 6.0% in randomized patients. Incidence of clinically significant abnormalities on physical examination (including vital signs) and electrocardiography was low.

Double-Blind Phase Results

Drug exposure. Among patients randomized to asenapine, mean ± SD dose was 17.6 ± 4.2 mg/d (modal dose, 20 mg/d). A dose of 20 mg/d was used by 78.9% of patients; 77.8% used this dose on the final day of double-blind treatment. Mean ± SD exposure duration was 151 ± 58 days with asenapine and 109 ± 70 days with placebo.

Concomitant medications. Concomitant medications were used by 46.4% of asenapine and 53.1% of placebo patients. Medications used by ≥5% of patients in either group included lorazepam, trihexyphenidyl, and zolpidem. Incidence of medication use to treat insomnia, EPS, and agitation, respectively, was 2.6%, 2.1%, and 1.0% with asenapine and 5.7%, 3.1%, and 3.1% with placebo.

In patients who experienced relapse/impending relapse, incidence of concomitant medication use from the date of relapse/impending relapse through study end was 16.7% with asenapine and 26.7% with placebo. In both groups, lorazepam (asenapine, 12.5%; placebo, 14.4%) was most commonly used; additional medications used by >1 placebo-treated patient included trihexyphenidyl, valproic acid, zolpidem, diazepam, propranolol, and antipsychotics.

Efficacy. Among treated patients, 114 (29.5%) experienced relapse/impending relapse (asenapine, 24/194 [12.4%]; placebo, 90/192 [46.9%]). Based on reports of relapse/impending relapse within ≤3 days of the last study medication dose (ITT population), incidence of relapse/impending relapse was 12.1% with asenapine and 47.4% with placebo ($P < .0001$). Relative risk of relapse/impending relapse with asenapine versus placebo was 0.26 over 6 months.

Determination of relapse/impending relapse was based on investigator judgment in 75%, rating scale criteria in 23%, and both criteria in 2% of cases. Only 1 patient was classified as relapsed by the IERB but not by the investigator; 6 were classified as relapsed by investigators but not by the IERB (κ coefficient, 0.9533; 95% CI = 0.9226 to 0.9881).

Table 3. Secondary Efficacy Measures During the Double-Blind Phase (observed cases, intent-to-treat population)[a]

	Asenapine (n = 191)		Placebo (n = 191)	
Measure	Double-Blind Baseline[b]	Change at Endpoint[c]	Double-Blind Baseline[b]	Change at Endpoint[c]
PANSS total score[d]	53.8 ± 0.9	1.3 ± 1.0*	53.3 ± 0.9	12.1 ± 1.0
Marder factors				
Positive symptom	13.3 ± 0.3	0.5 ± 0.3*	13.5 ± 0.3	3.9 ± 0.3
Negative symptom	15.3 ± 0.3	0.0 ± 0.3*	14.9 ± 0.3	1.7 ± 0.3
Disorganized thought	14.1 ± 0.3	0.0 ± 0.2*	13.6 ± 0.3	2.4 ± 0.2
Hostility/excitement	5.0 ± 0.1	0.4 ± 0.2*	5.2 ± 0.1	2.4 ± 0.2
Anxiety/depression	6.1 ± 0.2	0.4 ± 0.2*	6.1 ± 0.2	1.8 ± 0.2
CGI-S score	2.6 ± 0.04	0.2 ± 0.06*	2.7 ± 0.04	0.8 ± 0.06
CDSS total score	1.0 ± 0.1	0.4 ± 0.2**	1.0 ± 0.1	1.1 ± 0.2

[a]All values shown as least squares mean ± SE. Period endpoint is the last nonmissing postbaseline assessment on or before last double-blind dose date plus 3 d.
[b]Analysis of variance with treatment as a fixed effect.
[c]Analysis of covariance with treatment as a fixed effect and baseline as a covariate.
[d]Mean ± SD values at baseline (asenapine, 62.6 ± 10.7; placebo, 61.3 ± 11.2).
*P < .0001, **P = .027; asenapine vs placebo.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

Time to relapse/impending relapse in the ITT population was significantly longer with asenapine versus placebo (log rank test, P < .0001; Figure 2A). With asenapine, the first quartile and above for time to relapse/impending relapse could not be estimated. With placebo, the first quartile of the time to relapse/impending relapse was 41 days (95% CI = 30 to 69); the median was 156 days (95% CI = 113, upper limit could not be estimated).

Rates of early discontinuation for any reason were 30.4% with asenapine and 62.5% with placebo; relative risk of discontinuation with asenapine versus placebo was 0.47. Time to early discontinuation was longer with asenapine versus placebo (log rank test, P < .0001; Figure 2B). With asenapine, the first quartile of the time to discontinuation was 148 days (95% CI = 91.0, upper limit could not be estimated); median time to discontinuation could not be estimated. With placebo, the first quartile of the time to discontinuation was 35 days (95% CI = 29–46) and the median was 113 days (95% CI = 89–155).

Statistically significant differences in favor of asenapine were observed in the change from baseline of the double-blind period to endpoint for PANSS total and Marder factor scores, CGI-S, and CDSS total score (Table 3; all P < .0001 except CDSS, P = .027).

Safety and tolerability. Treatment-emergent AEs reported by > 5% of patients included anxiety, increased weight, and insomnia with asenapine and schizophrenia, insomnia, anxiety, decreased weight, hallucinations, agitation, and delusions with placebo; no AEs were reported in ≥ 5% of patients treated with asenapine that occurred at twice the rate of placebo (Table 2). Serious AEs reported by > 2% of patients treated with either asenapine or placebo included worsening of schizophrenia (asenapine, 1.0%; placebo, 4.7%) or of paranoid schizophrenia (asenapine, 1.0%; placebo, 3.6%).

AEs occurring at 7, 14, and 42 days postrandomization were assessed to determine if abrupt withdrawal from asenapine could be associated with an increased incidence of particular AEs; no AEs could be definitively attributed to asenapine withdrawal.

Incidence of EPS-related AEs was 3.1% with asenapine and 4.7% with placebo. Akathisia was most common with asenapine; akathisia, parkinsonism, and dyskinesia were most common with placebo (Table 2). No asenapine patients discontinued due to EPS-related AEs; 1 placebo patient discontinued due to tardive dyskinesia.

Mean changes in BARS global, AIMS global, and SAS total scores were similar with asenapine and placebo (0.1, 0.1, and 0.6, respectively, in both groups). Percentages of asenapine- and placebo-treated patients, respectively, at risk for EPS who reached threshold scores were 1.1% and 3.3% on the BARS, 1.1% and 3.8% on the AIMS, and 5.6% and 4.0% on the SAS.

Mean ± SD weight change from baseline of the double-blind phase was 0.0 ± 3.4 kg (0.0 ± 7.5 lb) with asenapine and –1.2 ± 4.0 kg (–2.6 ± 8.7 lb) with placebo. Incidences of clinically significant weight gain and weight loss, respectively, were 3.7% and 3.2% with asenapine and 0.5% and 9.6% with placebo.

Incidence of marked hyperprolactinemia was 2.8% with asenapine and 4.2% with placebo. There were few abnormalities on other laboratory tests (eTable 2) or electrocardiography.

DISCUSSION

This study evaluated the time to relapse/impending relapse in stable schizophrenic patients maintained on open-label asenapine for 26 weeks and subsequently randomized to placebo or continued asenapine. The results demonstrated that asenapine (modal dose, 10 mg BID) is significantly more effective than placebo in delaying the time to relapse/impending relapse. Patients tended to remain stable or show mild improvement on asenapine treatment during the open-label phase. After randomization, relapse/impending relapse was nearly 4-fold greater with placebo versus asenapine. The significantly greater risk for relapse/impending relapse after switching to placebo indicates that clinical stability deteriorated after cessation of asenapine treatment. Time to discontinuation for any reason was also significantly shorter with placebo compared with asenapine.

Asenapine appeared to be generally well tolerated, with the most common reasons for discontinuation during both study phases being withdrawn consent and AEs.

It should be noted that overall assessment of the long-term efficacy and safety of asenapine is limited because only patients who could be stabilized on asenapine treatment entered the double-blind treatment phase of the study. Clearly, this aspect of the study design was necessary to determine if asenapine was superior to placebo in clinically stable patients.

However, it removes patients who could not be stabilized and those who experienced unacceptable AEs during the open-label phase from the overall assessment of efficacy and safety.

Schizophrenia requires effective and well-tolerated long-term treatments. Here, we demonstrate that long-term asenapine is significantly more effective than placebo in preventing or delaying relapse/impending relapse in schizophrenia patients, with safety findings indicating that asenapine appears to be well tolerated. Given that maintenance treatment plays a critical role in preventing or delaying relapse after acute treatment in schizophrenia patients, the results of this study suggest that asenapine is useful in the long-term management of schizophrenia.

Drug names: acetaminophen (Ofirmev and others), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), diazepam (Diastat, Valium, and others), fluvoxamine (Luvox and others), lithium (Lithobid and others), lorazepam (Ativan and others), propranolol (Inderal, InnoPran, and others), valproic acid (Depakene, Stavzor, and others), zolpidem (Ambien, Edluar, and others).

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Potential conflicts of interest: **Dr Kane** has served as a consultant or advisory board member for Bristol-Myers Squibb, Otsuka, Eli Lilly, Janssen, Johnson & Johnson, MDS Pharma Services, Pfizer Inc, Targacept, Solvay, Wyeth, Lundbeck, Vanda, Astra-Zeneca, Cephalon, Dainippon Sumitomo, GlaxoSmithKline, Intracellular Therapeutics, PGxHealth, Proteus, Takeda, and Schering-Plough, now Merck; and has received honoraria from Boehringer Ingelheim and Bristol-Myers Squibb. **Drs Mackle**, **Zhao**, and **Szegedi** and **Ms Snow-Adami** are full-time employees of Merck. **Dr Panagides** was an employee of Schering-Plough (formerly Organon), now Merck, New Jersey, when this trial was conducted.

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Supplementary material: Available at PSYCHIATRIST.COM

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Supplementary Material

Article Title: A Randomized Placebo-Controlled Trial of Asenapine for the Prevention of Relapse of Schizophrenia After Long-Term Treatment

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List of Supplementary Material for the article

1. eTable 1 Characteristics of Switched-Therapy Patients

2. eTable 2 Mean ± SD Changes in Laboratory Results From Baseline (Treated Population)

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eTable 1. Characteristics of Switched-Therapy Patients*

	Number (%) of Patients			
Switched-therapy patients	548 (78.3)†			
Prior antipsychotics used by ≥5% of switched-therapy patients				
Risperidone	179 (25.6)			
Olanzapine	106 (15.1)			
Quetiapine	68 (9.7)			
Haloperidol	67 (9.6)			
Trifluoperazine	59 (8.4)			
Aripiprazole	39 (5.6)			
	Open-Label Phase		**Double-Blind Phase**	
	Nonrandomized (n=235)	**Randomized (n=313)**	**Asenapine (n=155)**	**Placebo (n=158)**
Discontinuations	235 (100.0)	–	45 (29.0)	102 (64.6)
Most common reasons for discontinuation				
Withdrawal of consent	83 (35.3)	–	15 (9.7)	9 (5.7)
AEs	73 (31.1)	–	10 (6.5)	43 (27.2)

AE=adverse event.
*Defined as switched from previous antipsychotic therapy to open-label treatment with asenapine.
†Based on open-label treated population (n=700).

eTable 2. Mean ± SD Changes in Laboratory Results From Baseline* (Treated Population)

	Open-Label Phase				Double-Blind Phase			
	Nonrandomized (n=314)		Randomized (n=386)		Asenapine (n=194)		Placebo (n=192)	
HbA_{1C}, %	0.11±0.50		0.09±0.47		0.05±0.40		–0.06±0.67	
AST, U/L	1.4±10.2		2.0±20.7		2.3±24.5		0.1±9.5	
ALT, U/L	0.1±16.4		3.7±34.8		–2.2±26.9		–2.0±14.8	
	mmol/L	**mg/dL**	**mmol/L**	**mg/dL**	**mmol/L**	**mg/dL**	**mmol/L**	**mg/dL**
Total cholesterol	–0.036±0.731	–1.39±28.2	–0.027±0.739	–1.04±28.5	0.024±0.718	0.927±27.7	–0.145±0.673	–5.60±26.0
HDL	–0.013±0.235	–0.502±9.07	–0.031±0.216	–1.20±8.34	0.005±0.214	0.193±8.26	0.006±0.212	0.232±8.19
LDL	–0.028±0.564	–1.08±21.8	0.023±0.568	0.888±21.9	–0.009±0.573	–0.347±22.1	–0.097±0.575	–3.75±22.2
Triglycerides†	–0.105±1.184	–9.29±104.8	0.042±0.785	3.72±69.5	0.010±0.995	0.885±88.1	–0.127±0.743	–11.2±65.8
Glucose†	0.302±1.633	5.44±29.4	0.159±1.146	2.86±20.6	0.116±1.480	2.09±26.7	0.001±1.146	0.018±20.6

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

*Data from open-label phase are changes from open-label phase baseline, and data from double-blind phase are changes from double-blind phase baseline.

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