The study listed may include approved and non-approved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult prescribing information for the product approved in their country.

Results presented here may include different data from those shown on http://clinicaltrialsgov/, which specifically identifies data to be disclosed, as mandated by US federal law.

Title of the clinical trial

A Multicenter, Double-Blind, Flexible-Dose, 6-Month Trial Comparing the Efficacy and Safety of Asenapine With Olanzapine in Stable Subjects With Predominant, Persistent Negative Symptoms of Schizophrenia.

Studied period (years)

The trial was carried out from May 15, 2005 to June 13, 2007

Clinical phase

Phase III

Objectives

Primary
To compare the efficacy of 5-10 mg BID asenapine to that of 5-20 mg QD olanzapine in the treatment of predominant, persistent negative symptoms of schizophrenia.

Secondary
To compare the efficacy of asenapine with olanzapine in psychosocial function in subjects with schizophrenia and predominant, persistent negative symptoms.

Additional objectives included evaluating treatment effects of asenapine with olanzapine with respect to:

- Other dimensions of schizophrenia (positive, disorganized thought, hostility/excitement, anxiety/depression, and general psychopathology)
- Safety and tolerability, including ophthalmology testing at participating centers
- Quality of life and patient functionality
- Neurocognition

Methodology

A Phase III multicenter, randomized, double-blind study in schizophrenia subjects with predominant, persistent negative symptoms.

Number of subjects (total and for each treatment)

A total of 481 subjects were randomly assigned to treatment (241 subjects were assigned to asenapine and 240 subjects were assigned to olanzapine) and received at least 1 dose of double-blind trial medication. This set of subjects was defined as the All-Subjects-Treated (AST) Group. A total of 433 subjects (90.0% of those randomly assigned to treatment) received at least 1 dose of double-blind trial medication and had a least 1 post-baseline NSA evaluation (216 and 217 subjects in the asenapine and olanzapine groups, respectively). This set of subjects was defined as the ITT set. The number of subject in the ITT set was lower than in the AST set because it excluded repeat subjects and subjects from three sites where data irregularities were observed.

Diagnosis and criteria for inclusion

Subjects were eligible to participate in the study if they:

Demographic

1. were at least 18 years of age;
2. were a male, or a female who is not of childbearing potential (ie, surgically sterile, postmenopausal for at least 1 year) or non-pregnant, non-lactating, and using a method of birth control that was acceptable to the investigator;

Procedural

3. signed written informed consent after the scope and nature of the investigation had been explained to them before screening evaluations. Subjects unable or incapable of signing could participate if the legal representative provided consent and the subject affirms their participation;
4. were fluent in the language of the investigator, study staff (including raters), and the informed consent;
5. had a caregiver or an identified responsible person (eg, family member, social worker, caseworker, or nurse) considered reliable by the investigator in providing support to the subject to ensure compliance with study treatment, outpatient visits and protocol procedures;

Diagnoses

6. had a documented current diagnosis of schizophrenia of paranoid (295.30), disorganized (295.10), catatonic (295.20), residual (295.60), or undifferentiated (295.90) subtype (the MINI International Neuropsychiatric Interview [MINI] will be used);
7. had a minimum PANSS negative subscale score of 20 at screening and baseline, with a minimum score of 4 (moderate) on at least 3of the Marder factors for negative symptoms (blunted affect [N1], emotional withdrawal [N2], poor rapport [N3], passive social withdrawal [N4], lack of spontaneity [N6], motor retardation [G7], active social avoidance [G16]);
8. had a PANSS positive subscale (Marder factor) score <the PANSS negative subscale (Marder factor) score at screening and baseline; and
9. had demonstrated clinical stability for the past 5 months at time of screening, defined as:
    - no significant changes in schizophrenia symptomatology (changes in medication or medication dosing may be acceptable
    - no hospitalizations for the symptoms of schizophrenia during the past 5 months,
    - no increase in level of psychiatric care during the past 5 months due to worsening of symptoms of schizophrenia;
    - no jailing or imprisonment in the past 5 months due to worsening of symptoms of schizophrenia.

Test product, dose and mode of administration

Asenapine (Org 5222) and placebo for asenapine (Org 5222) dosage forms were prepared as indistinguishable white to off-white fast dissolving tablets, which disintegrate in less than 10 seconds. Each fast dissolving tablet contained asenapine 5 mg, asenapine 10 mg, or placebo. The flat side of the tablets may occasionally contain a slightly raised surface. This is normal and is of no cause for concern.

Code Name:	Asenapine (Org 5222)
Active Substance:	trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz (2,3:6,7) oxepino-(4,5-c)pyrrole(Z)-2-butenedioate (1:1)
Supplier:	Organon USA Inc.
Dosage Form:	Asenapine (Org 5222) and placebo dosage forms were prepared as indistinguishable fast dissolving tablets
Dose:	Asenapine (Org 5222) was provided in identical fast dissolving tablets containing 5 or 10 mg of asenapine (Org 5222)

Duration of treatment

Subjects received the initial dose of either 5 mg BID asenapine or 10 mg once daily (QD) olanzapine as the active dose matched with the comparator placebo for 1 week. After 1 week, doses could be increased, decreased, or held constant at the discretion of the investigator only. Decisions to change the dose were to be made at the subject's visit, and based on the subject's symptomotology and tolerability. Dose changes could only be made between visits if intolerable adverse events (AEs) prohibit a delay.

Reference therapy, dose and mode of administration

Olanzapine 10 mg and its matching placebo were prepared as indistinguishable film-coated tablets. Each tablet contained olanzapine 5 mg, olanzapine 10 mg, or placebo.

Code Name:	Olanzapine
Active Substance:	2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno(2,3-b)(1,5) benzodiazepine
Dosage Form:	Olanzapine and placebo dosage forms was prepared as indistinguishable film-coated tablets
Dose:	Olanzapine was provided in film-coated tablets containing 5 or 10 mg of olanzapine

Criteria for evaluation

All efficacy assessments were to be performed 1 to 10 hours after the morning dose. Efficacy assessments are described below:

Efficacy assessments:

- NSA: A 16-item clinician-rated instrument for rating the negative symptomatology of schizophrenia;
- PANSS: A 30-item clinician-rated instrument for assessing the symptoms of schizophrenia;
- CGI-S: A 7-point clinician-rated scale for assessing the global severity of schizophrenia;
- CGI-I: A 7-point clinician-rated scale for assessing the global improvement of schizophrenia;
- CDSS: A 9-item clinician-rated scale for assessing depressive symptoms in schizophrenia patients;
- CNS Vital Signs Neurocognitive Test Battery: A computerized cognitive testing battery consisting of neuropsychological tests which measure cognitive domains of working memory, visual and verbal memory and learning, speed of processing, attention, vigilance, reasoning, and problem solving and social cognition.

Quality-of-Life assessments:

- QLS: A 21-item clinician-rated scale for rating psychosocial functioning (subscalesInterpersonal Relations, Instrumental Role, Intrapsychic Foundations, and Common Objects and Activities
- LOF: A 9-item clinician-rated scale for rating functional outcomes;
- PETiT: A 30-item patient-completed questionnaire assessing a patient's subjective experience with treatment including a subscale for assessing a patient's attitude toward their medicine
- Q-LES-Q (Leisure Time Activities and Social Relations Subscales): Two patient-completed subscales of the Q-LES-Q assessing a patient's involvement in leisure activities and their interaction with others
- CSRI: An interview-based instrument which site personnel use to assess patient resource use over the past 3 months.

Safety: Was to be assessed through concomitant medication use, (S)AE monitoring, weight, abdominal girth, vital signs (heart rate, blood pressure, and respiration), physical exam, electrocardiogram (ECG), and clinical laboratory evaluations (hematology, biochemistry, and urinalysis) including prolactin levels and measures of glucose metabolism (including hemoglobin A_{1C} and insulin) and lipid panel (total cholesterol, HDL, LDL, triglycerides). EPS was to be assessed with the Extrapyramidal Symptom Rating Scale (Abbreviated) (ESRS-A).

Visual acuity, visual field and color vision testing were to be performed on subjects at selected sites throughout the trial. Testing was to be performed at Baseline (or during Observation period) and Day 182. All visual testing was to be supervised by a local ophthalmologist.

Post-treatment evaluation:
Subjects who did not participate in the extension trial were to be asked to return for a follow-up visit 7 days after their End of Treatment visit. At this time, all concomitant medications and new and continuing AEs were to be recorded. Thirty days after the last treatment visit, subjects were to be contacted to determine whether any SAEs occurred and for follow-up of continuing SAEs.

Statistical methods

Primary efficacy endpoints: The primary efficacy endpoint was defined as the change from baseline to week 26 in NSA total score. This analysis compared asenapine with olanzapine using a mixed model for repeated measures (MMRM) analysis. All statistical tests were two-sided with $\alpha = 0.05$ significance level.

Additionally, two separate sensitivity analyses were performed using analysis of covariance (ANCOVA) on the change from baseline in NSA total score at each visit with baseline NSA total score and duration of predominant, persistent negative symptoms as covariates. In the first analysis, the missing data were imputed by the last observation carried forward (LOCF). In the second analysis, only the observed cases (OC) were used.

Secondary endpoints: The key secondary endpoint, the change from baseline in QLS total score, was analyzed using mixed model for repeated measures (MMRM). Furthermore, two sensitivity analyses were performed using analysis of covariance (ANCOVA) on the change from baseline in QLS score at each visit with baseline QLS score and duration of predominant, persistent negative symptoms as covariates. In the first analysis, the missing data were imputed by the last observation carried forward (LOCF). In the second analysis, only the observed cases (OC) were used.

Other secondary endpoints included the following: PANSS, CDSS, CNS vital signs, PETiT, LOF, and Q-LES-Q as well as CGI-S, CGI-I, CGI-I responders (defined as "very much improved" and "much improved") and time to first

CGI response. The differences between asenapine with olanzapine on PANSS, CDSS, and CGI-S were analyzed using a mixed model for repeated measures (MMRM) analysis, and were further examined with LOCF and OC approaches. The other secondary endpoints, CNS vital signs, PETiT, LOF, and Q-LES-Q, were analyzed using LOCF and OC. Descriptive statistics were produced for CGI. The treatment groups were compared with respect to CGI responder ratesusing Cochran Mantel-Haentzel test. Both treatment groups were compared with respect to time to first CGI response using Kaplan-Meier (KM) product limit method and the Cox's proportional hazard model. Analyses were stratified by duration of persistent negative symptoms (2 year duration strata).

Summary

Efficacy:
The results of the current trial showed that asenapine (5 mg-10 mg BID) was not significantly different from olanzapine (5mg-20mg QD) on the primary efficacy endpoint, the change from baseline to Day 182 in NSA total score ($p = 0.7869$). The mean change from baseline over time on the NSA total score was comparable between the two groups. The results of the primary analysis, using MMRM, were corroborated by the LOCF and OC analyses.

A number of secondary analyses confirmed the results of the primary efficacy analysis. Secondary analyses, such as the NSA global scores, QLS total score, PANSS total score, CGI-S scores and CGI response rates showed no differences between asenapine and olanzapine. Some small differences between the two treatment groups were observed with PANSS sub scores and CDSS total score.

Safety: Overall, 74.7% of asenapine-treated subjects and 68.8% of olanzapine-treated subjects experienced at least one treatment-emergent adverse event. Treatment-emergent adverse events considered related to study treatment were reported for 55.2% of asenapine-treated subjects and 54.6% of olanzapine-treated subjects. Most adverse events were mild or moderate in intensity. Overall, 12.4% of asenapine-treated subjects and 6.7% of olanzapine-treated subjects experienced at least one severe treatment-emergent adverse event.

Overall, 14.9% of asenapine-treated subjects and 7.1% of olanzapine-treated subjects discontinued from the study due to an adverse event. The proportion of subjects who discontinued due to drug-related adverse events was 12.4% in the asenapine treatment group and 6.3% in the olanzapine treatment group.

There were 3 deaths reported during the study; 2 in the asenapine treatment group (*completed suicide*, judged by the investigator as possibly related to study drug and *lung cancer*, judged by the investigator not to be related to study drug) and 1 in the olanzapine treatment group (*completed suicide*, judged by the investigator not to be related to study drug). The incidence of serious adverse events was 10.8% in asenapine-treated subjects and 5.8% in olanzapine-treated subjects, whereas 4.1% of asenapine-treated subjects and 2.5% of olanzapine-treated subjects discontinued from the study due to a serious adverse event, the majority of whom discontinued as a result of psychiatric disorders.

The most common adverse events, occuring in more than 10% of asenapine-treated subjects, were: *insomnia* (15.8% asenapine; 10.8% olanzapine); *headache* (12.9% asenapine; 9.6% olanzapine); and *somnolence* (12.4% asenapine; 11.3% olanzapine); only *agitation* occurred in at least 5% of asenapine-treated subjects and had an incidence of at least twice that of olanzapine (6.2% asenapine; 1.3% olanzapine). The three most common adverse events in the olanzapine group, occuring in more than 10% of subjects, were: *weight increased* (4.6% asenapine; 21.3% olanzapine); *somnolence* (12.4% asenapine; 11.3% olanzapine); and *insomnia* (15.8% asenapine; 10.8% olanzapine).

Overall, the percentage of subjects reporting EPS adverse events was 8.3% and 3.3% in the asenapine and olanzapine groups, respectively. EPS or movement disorder AEs that were reported by >2% of asenapine-treated subjects were akathisia (2.9% of asenapine-treated subjects and 1.3% of olanzapine-treated subjects) and parkinsonism (2.1% of asenapine-treated subjects and 1.7% of olanzapine-treated subjects). All EPS adverse events were mild or moderate in intensity and no subjects discontinued due to EPS adverse events.

In general, changes in laboratory variables and vital signs were small in magnitude and not notably different between the treatment groups. Furthermore, the incidence of post-baseline markedly abnormal clinical laboratory values and vital signs was low in both treatment groups. Small mean increases in ALAT, ASAT, CK, and prolactin were observed in both treatment groups.

Clinically relevant weight gain (≥7%) from baseline to study endpoint occurred in 7.9% of asenapine-treated subjects and 24.6% of olanzapine-treated subjects. Clinically relevant weight loss (≥7%) from baseline to study endpoint occurred in 11.6% of asenapine-treated subjects and 3.3% of olanzapine-treated subjects. Weight increase was reported as adverse events in 4.6% of subjects in the asenapine group and in 21.3% of subjects in the olanzapine group. The mean (median) change in weight from baseline to study endpoint was -0.4 kg (0 kg) in the asenapine group and 2.9 kg (2 kg) in the olanzapine group.

Conclusions

No statistically significant differences for asenapine 5-10 mg BID compared with olanzapine 5-20 mg QD were observed on the primary efficacy endpoint, the change from baseline to endpoint in the NSA total score after 26 weeks of treatment, using either MMRM, LOCF, or OC analyses; similarly, no statistically significant differences were observed on the QLS. Secondary efficacy parameters were supportive of the primary efficacy result. Both asenapine and olanzapine were associated with clinically relevant beneficial treatment effects on negative symptoms, as evidenced by improvements on the total NSA score and a number of secondary endpoints, such as NSA global scores, PANSS negative subscale and PANSS Marder factor negative subscale scores and CGI. Both treatments had minimal effects on depressive and positive symptoms, suggesting that the therapeutic effects on negative symptoms were not indirect.

Asenapine at 5-10 mg BID was safe and well tolerated in these subjects with predominant, persistent negative symptoms of schizophrenia. Asenapine, as compared to olanzapine, demonstrated a better tolerability profile with respect to weight gain and shift to metabolic syndrome. Both asenapine and olanzapine did not increase prolactin values over time. In addition, both asenapine and olanzapine were associated with a low incidence of EPS.