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://clinicaltrials.gov/, which specifically identifies data to be disclosed, as mandated by US federal law.

Title of Study: A Phase 3, Randomized, Placebo-Controlled, Double-Blinded Trial Evaluating the Safety and Efficacy of Asenapine in Subjects Continuing Lithium or Valproic Acid/Divalproex Sodium for the Treatment of an Acute Manic or Mixed Episode

Studied Period: 30 May 2005 until 28 February 2007 | **Clinical Phase:** III

Objective(s): The primary objective of this trial was to demonstrate clinical and statistical superiority of asenapine compared with placebo in subjects who have not completely responded to continuing treatment with lithium or valproic acid (VPA) to treat acute manic or mixed episodes associated with bipolar I disorder. Secondary objectives included evaluating adjunctive treatment effects of asenapine compared with placebo with respect to Clinical Global Impressions Scale for use in Bipolar Disorder (CGI-BP); Montgomery-Asberg Depression Rating Scale (MADRS); Positive and Negative Syndrome Scale (PANSS); the Hamilton Anxiety (HAM-A) Scale; CNS Vital Signs cognition battery; Readiness to Discharge Questionnaire (RDQ); the General Activities subscale of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q); Short Form-36 Version 2.0 (SF-36v2) (acute form); and the Modified InterSePT Scale for Suicide Thinking (ISST-Modified); and safety and tolerability.

Methodology: This was a randomized, placebo-controlled, double-blind, multicenter trial.

Number of Subjects:

A total of 438 subjects were enrolled in the trial, of whom 324 subjects were randomized and took at least 1 dose of study medication:

- 166 subjects were in the placebo group,
- 158 subjects were in the asenapine (5-10 mg twice daily [BID]) group.

Diagnosis and Criteria for Inclusion: Subjects had a primary diagnosis of bipolar I disorder, current episode manic (DSM-IV 296.4x) or mixed (DSM-IV 296.6x). Subjects were men or women of at least 18 years of age with documented history of at least one previous moderate-to-severe mood episode with or without psychotic features (manic or mixed). Subjects were to have a Young-Mania Rating Scale (Y-MRS) score =20 at screening and at baseline, have a current manic or mixed bipolar I episode that must have begun no more than 3 months prior to the screening visit, and been continuously treated with lithium or VPA for at least 2 weeks immediately prior to screening.

Test Product, Dose, Mode of Administration: Asenapine 5 mg and asenapine 10 mg doses as white to off-white, fast-dissolving tablets .

Duration of Treatment: Double-blind, randomized period: 84 days

Reference Therapy, Dose, Mode of Administration: Matching fast-dissolving placebo tablets.

Criteria for Evaluation:

Efficacy:

Y-MRS for assessing the symptoms of mania (evaluated at screening and Days 1, 3, 7, 14, 21, 42, 63, and 84/study endpoint); CGI-BP for assessing the severity and change from preceding phase of illness of manic, depressive, and overall symptoms of bipolar disorder during treatment of an acute episode or in longer-term illness prophylaxis (evaluated at Days 1, 3, 7, 14, 21, 42, 63, and 84/study endpoint); PANSS for assessing psychotic or schizophrenic symptoms (evaluated at Days 1, 7, 21, 42, 63, and 84/study endpoint); MADRS for assessing the severity of symptoms of depression (evaluated at Days 1, 7, 14, 21, 42, 63, and 84/study endpoint); HAM-A for assessing anxiety symptoms (evaluated at Days 1, 7, 14, 21, 42, 63 and 84/study endpoint); RDQ to assess readiness for discharge (evaluated at Days 1, 3, and 7; Days 14, 21, 42, 63, and 84/study endpoint for inpatients only); InterSePT Scale for Suicide Thinking (ISST) for rating suicidality (evaluated at Days 1, 7, 14, 21, 42, 63, and 84/study endpoint); and CNS vital signs cognitive batter to characterize cognitive symptoms (evaluated at screening and Days 1, 21, and 84/study endpoint).

Health Outcomes: SF-36v2 to measure 8 health concepts (questionnaire administered on Days 1, 21, 42 and 84/study endpoint); and Q-LES-Q to assess subjects' quality of life (administered on Days 1, 21, 42, and 84/study endpoint).

Safety: Treatment-emergent adverse events and serious adverse events (evaluated throughout the study); clinical laboratory analysis (evaluated at screening and Days 1, 21, 42 and 84); physical examination (evaluated at screening and study endpoint); vital signs, including sitting blood pressure, heart rate, and respiratory rate (evaluated at screening and Days 1, 3, 7, 14, 21, 42, 63, and 84/study endpoint); anthropometric measurements, including waist circumference, body weight, and body mass index (BMI) (evaluated at screening and Days 21, 42, and 84/study endpoint); and extrapyramidal symptoms (EPS) were assessed using the Simpson-Angus Rating Scale (SARS), the Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) (evaluated at screening and Days 1, 7, 21, 42, and 84/study endpoint).

Statistical Methods:

Efficacy: The primary efficacy variable was the Y-MRS. The primary efficacy endpoint was change from baseline to Day 21 on the Y-MRS total score, and was analyzed by a fixed-effects analysis of covariance (ANCOVA). The primary model used the baseline score as a covariate. Comparisons between treatment groups were made using the difference in the model based least square means (LSMEANs). Secondary analyses supportive of efficacy in mania included change from baseline in Y-MRS total score (all time points); Y-MRS responders (defined as a 50% decrease from baseline in Y-MRS score at any given visit); Y-MRS remitters (defined as a Y-MRS total score of 12 or lower at any given visit); change from baseline in CGI-BP severity in mania; and CGI-BP change from baseline in state of mania. In addition, secondary analyses of depressive symptom endpoints, overall bipolar state endpoints, psychotic symptom endpoints, and cognitive symptom endpoints were conducted.

Health outcomes: Secondary analyses for outcomes research endpoints were conducted for the following endpoints: change from baseline in each domain and subscale score of the SF-36v2 (acute form) and each domain score of the Q-LES-Q.

Safety: Investigator terms for treatment-emergent adverse events and serious adverse events were mapped to Medical Dictionary for Drug Regulatory Affairs (MedDRA) preferred terms. Treatment-emergent adverse events and serious adverse events were summarized and analyzed descriptively from standard reporting tables. Predefined criteria were used to define markedly abnormal and clinically important changes in clinical laboratory values and the clinical laboratories provided reference ranges for evaluation of clinical laboratory values. The percentages of subjects with clinically important changes in clinical laboratory values and with values that changed to above or below laboratory reference ranges during the trial were summarized by treatment group. Descriptive statistics were used to summarize baseline, study endpoint, and change from baseline in clinical laboratory values by treatment group. Adverse changes in physical exam findings and possibly clinically important changes in vital signs (including orthostatic changes) body weight, BMI, and waist circumference were summarized by treatment group and analyzed descriptively. The number and percentage of subjects assessed who met the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criterion for diagnosis of metabolic syndrome were summarized by treatment group. Extrapyramidal symptoms (Parkinsonism, dystonia, dyskinesia, and akathisia scales and CGI scales) data were tabulated by treatment group and summarized using descriptive statistics.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy:

The primary objective of this trial was to demonstrate the efficacy of asenapine compared with placebo in treatment of subjects with manic or mixed episodes associated with bipolar I disorder who have not completely responded to continuing treatment with lithium or VPA. Both treatment groups were comparable with respect to baseline characteristics such as demographics and diagnosis.

The primary efficacy endpoint LOCF analysis result was supported by the analysis of the CGI-BP, severity of mania and severity of overall bipolar illness, which also showed statistically significant improvements in the asenapine group over placebo at Day 21 and Day 84. Additionally, the percentage of subjects who were Y-MRS remitters (subjects with a Y-MRS total score of 12 or lower) was statistically significantly higher in asenapine-treated subjects compared with placebo-treated subjects at Day 21 and Day 84.

Asenapine at flexible doses of 5-10 mg BID, when administered concurrently with lithium or VPA, was statistically superior to placebo in reducing the symptoms of mania in subjects with manic or mixed episodes associated with bipolar I disorder as measured on the primary endpoint, the change from baseline in Y-MRS total score on Day 21 based on the LOCF analysis. The LOCF analysis also demonstrated statistical superiority of asenapine over placebo at Day 84.

The OC and MMRM analyses of the primary efficacy endpoint could not confirm the statistical superiority of asenapine over placebo at either Day 21 or Day 84. Based on the OC analysis, the mean change from baseline

to Day 21 in Y-MRS total score in the asenapine group of -12.2 is similar to what has been observed in previous asenapine monotherapy trials in bipolar subjects. However, the mean change in the placebo group of -11.2 is greater than what has been observed previously. The larger placebo response observed in the OC analysis may have several explanations. First, in this study all subjects in both the placebo and asenapine treatment groups were receiving concurrent therapy with lithium or VPA. Therefore, the placebo group was not a "true" placebo group in that they were receiving some treatment for bipolar I disorder. Additionally, during the second week of the study more subjects in the placebo group (19.9%, 6.0% due to lack of efficacy) than in the asenapine group (8.9%, 1.9% due to lack of efficacy) discontinued from the study. These unbalanced dis continuation rates carried forward to Day 21 and up to Day 84. These subjects who discontinued, especially those who discontinued due to lack of efficacy and presumably had poor Y-MRS responses, would not have had their higher (less improved) Y-MRS scores available for the Day 21 OC analysis. However, their higher Y-MRS scores were carried forward for the LOCF analysis. Additionally, approximately 21% of subjects in both treatment groups discontinued due to withdrawal of consent, and no further information is known for these subjects.

Based on the LOCF analysis, statistically significant differences from placebo were evident from Day 14 until the end of the trial. Previous studies of asenapine monotherapy in subjects with bipolar I disorder have shown an onset of action starting at Day 2. As stated previously, in this study all subjects in both the placebo and asenapine treatment groups were receiving concurrent treatment for bipolar I disorder. This may help explain the perceived delayed asenapine response in this study compared with monotherapy studies.

Safety:

There were no deaths during this study. The frequency of serious adverse events was similar between the placebo (14.5%) and asenapine (13.3%) groups. In many of the subjects with serious adverse events (11/21 in the asenapine group and 14/24 in the placebo group), the event involved an exacerbation of the underlying disease.

Sedation (asenapine 13.3%, placebo 6.0%), *somnolence* (asenapine 11.4%, placebo 4.2%), *hypoaesthesia oral* (asenapine 5.7%, placebo 0.6%), and *weight increased* (asenapine 5.1%, placebo 0.6%) occurred in at least 5% of subjects in the asenapine group and with an incidence twice that of placebo. There were no notable differences between the treatment groups for any other treatment-emergent adverse events.

In both treatment groups, most treatment-emergent adverse events were mild or moderate in intensity with 8.9% of asenapine-treated subjects and 12.7% of placebo-treated subjects experiencing at least 1 severe treatment-emergent adverse event.

The incidence of withdrawals due to treatment-emergent adverse events was higher in the asenapine group (15.8%) than in the placebo group (10.8%). The most common treatment-emergent adverse event that led to discontinuation in both treatment groups was *mania* (asenapine 4.4%, placebo 5.4%).

The incidence of EPS-related treatment-emergent adverse events was similar between the asenapine and placebo groups. The only EPS treatment-emergent adverse event that was reported by >2% of asenapine-treated subjects was *akathisia* (3.2% asenapine, 5.4% placebo) The incidence of treatment-emergent EPS based on rating scale scores was also similar between the groups.

In general, mean changes in laboratory variables and vital signs were small in magnitude and not notably different between the treatment groups. Furthermore, the incidences of post-baseline markedly abnormal clinical laboratory values and vital signs and the incidences of treatment-emergent adverse events related to clinical laboratory and vital sign findings were low in both groups.

The incidence of clinically relevant weight gain (asenapine 19.5%, placebo 5.2%) and the mean increase in weight from baseline to study endpoint (asenapine 2.3 kg, placebo 0.7 kg) were greater in the asenapine group than in the placebo group. Despite being higher than in the placebo group, both the incidence of clinically relevant weight gain and the mean change in weight in the asenapine group were similar to what has been observed in previous asenapine monotherapy studies in subjects with bipolar I disorder.

The percentage of subjects who developed risk factors during the trial such that they met NCEP criteria for metabolic syndrome at study endpoint was similar between the asenapine (6.8%) and placebo (6.7%) groups.

CONCLUSIONS:

In this trial, the efficacy of asenapine at flexible doses of 5-10 mg BID compared with placebo in treatment of subjects with manic or mixed episodes associated with bipolar I disorder being concurrently treated with lithium or VPA was demonstrated. Asenapine was statistically superior to placebo in reducing the symptoms of mania as measured on the primary endpoint, the change from baseline in total Y-MRS score on Day 21 based on the

LOCF analysis. The LOCF analysis also demonstrated statistical superiority of asenapine over placebo at Day 84.

Asenapine at flexible doses of 5-10 mg BID (with a beginning dose of 5 mg BID) was safe and well tolerated in subjects with bipolar I disorder, current episode mixed or manic, being concurrently treated with lithium or VPA. The safety profile of asenapine administered with lithium or VPA in this study was generally similar to what has been observed in previous studies of asenapine monotherapy in both bipolar I disorder and schizophrenia.

Date of the Report: 24-Mar-2008