AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Seroquel
ACTIVE INGREDIENT: quetiapine fumarate

Study No: Protocol No: AU-SEA-0006
A multicentre, parallel group, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of quetiapine fumarate as add-on therapy in patients with Post-Traumatic Stress Disorder

Developmental phase: Phase IV
Study Completion Date: Last subject last visit 27 August 2008
Date of Report: TBA

OBJECTIVES:

To evaluate the efficacy and safety of quetiapine fumarate as add-on therapy in a sample of subjects with PTSD.

METHODS:

Participants: 115 subjects consented and 69 subjects were randomized in to a double-blind trial according to the protocol to either a placebo or treatment arm of the trial. At 12 weeks the study was unblinded and participants on quetiapine were enrolled into a 1-year extensions study. In order to be included in the study, subjects between the ages of 18 and 65 were required to satisfy diagnostic criteria for PTSD. Subjects were excluded if they were acutely suicidal, or if there was a history of psychosis, seizures, or organic brain disease. In addition, exclusion criteria included the presence of cognitive and neurological deficits, malignancy, unstable or inadequately treated medical illness, and the use of medications that would affect the absorption, distribution, metabolism, or excretion of the study drug. Subjects were also ineligible to participate if they satisfied *DSM-IV-TR* diagnostic criteria for current substance abuse/dependence, or if a urine drug screen tested positive for illicit drugs. Females who were pregnant, breastfeeding, or not taking an adequate form of contraception were also excluded.

Assessments: The primary outcome of interest was change in PTSD symptomatology over the course of the study. To this end, the *Clinician Administered PTSD Scale* (*CAPS)* was employed to both confirm diagnosis prior to randomization (*CAPS* > 50, with sufficient number and severity of symptoms in each of the three symptom clusters), and monitor change in symptoms at each study visit. A *Mini Mental Status Examination* (*MMSE*) was also conducted at the initial subject visit, to confirm that no significant

cognitive deficits were present (i.e. score less than 27 resulted in exclusion). Secondary outcomes of interest were assessed at each visit using the following clinician- and self-rated instruments: (1) the *Hamilton Depression Scale* (*HAM-D*) (2) the *Hamilton Anxiety Scale* (*HAM-A)* (3) the *PTSD Checklist* (*PCL)* and (4) *Clinical Global Improvement* (CGI).

In addition, an ECG was performed, and blood and urine collected for the following laboratory analyses: electrolytes, urea, creatinine, liver function tests, thyroid stimulating hormone, glucose, cholesterol, triglycerides, urine drug screen and, if indicated, urine pregnancy test.

Randomised subjects initially attended on a weekly basis for 6 weeks, then fortnightly for the duration of the study. Study medication dose commenced at 25 mg/day at baseline, with the option to titrate up to 300 mg/day over the initial four weekly visits, depending on the clinicians' perception of participant response and the presence of side effects. Adverse events and additional safety data, including heart rate, blood pressure, and weight, were recorded at each visit. Adverse events were subsequently coded according to the preferred terminology outlined in the Medical Dictionary for Regulatory Activities (MedDRA).

Subjects who demonstrated a >30% reduction in CAPS score over the course of the double blind phase of the trial were offered the opportunity to enter a second, open label phase of the trial, in which all subjects were given the study medication. This period of the study lasted for a period of 12 months, with subjects attending clinical visits at 6 months and 12 months post double blind completion, and receiving a phone call at 3 months and 9 months post double blind phase completion. At each clinical visit, an independent rater administered the same measures outlined above, and a psychiatrist conducted a physical examination and recorded safety data.

Design: Prior to subject recruitment, it was determined that responders would be defined as those whose *CAPS* score reduced by $\geq$ 30% over the course of the study. Data were analysed using the *Statistical Package for the Social Sciences (SPSS)* version 16.0. The significance of change on each of the outcomes of interest was assessed in a multivariate analysis of variance, with time as the within-subject factor, and treatment arm as the between-subject factor. An intention to treat analysis, with last observation carried forward, ensured that each subject who was randomised according to the protocol was included in the analysis. A second analysis examined change in each outcome measure between the start and completion of the open label phase of the trial.

RESULTS:

Double blind study phase: In total, 86 subjects were randomised to the study, however of these, only 69 were randomised according to the protocol. Common reasons for protocol violations at the randomisation stage of the study included: subject did not meet diagnostic criteria for PTSD at screening and/or baseline (n = 9). age > 65 years (n = 3), and subject inadequately withdrawn from previous antipsychotic medication (n = 2). The

following information pertains to the sample of 69 subjects who were randomised according to the protocol.

Overall, 95.7% (n = 66) of the sample was male. Of the three female participants, one was using appropriate contraception, and two were not of childbearing age. The average age of the sample was 56.74 years (SDage = 6.78: Range = 28-65 years), and the majority were from a veteran (n = 61: 88.4%) rather than a civilian (n = 8: 11.6%) population, with an average length of time since PTSD diagnosis of 9.48 years (SD = 7.65; Range = 0.08 – 40.33 years). A comparison on each of the demographic measures noted above, and baseline psychometrics, reveals that the two treatment arms of the study did not differ significantly from each other in either demographic characteristics, or baseline symptomatology.

Of the 69 subjects who were randomised according to the protocol, 54 (78.3%) completed the 12 week study. Reasons for discontinuation included: serious adverse event (n = 1); adverse event (n = 9); and withdrew consent/failed to return (n = 5). The average time spent in the study was 75.30 days, however for those who discontinued, average time spent in the study was 37.46 days (SD = 22.90; Range = 6-69 days). Analysis revealed that subjects in the treatment arm of the study were significantly more likely to discontinue before the end of the 12 week period (n = 11) than those on placebo (n = 4) (p = .025).

Results of the Intention to Treat Analysis with Last Observation Carried Forward (ITT, LOCF) (N = 69) showed significant reductions in PTSD, depression, anxiety, and clinical global impression between randomisation and the conclusion of the double blind phase of the study. However, there were no differences between the treatment arms of the study, with participants in both ‘quetiapine’ and ‘placebo’ arms reporting similar symptom improvement across the 12-week period. A division of the treatment groups by response status yielded similar results, as the proportion of responders in treatment and placebo arms of the study did not differ significantly (57.6% vs. 42.9%; p = .225). In line with the protocol, study drug dose at visit 8/study discontinuation visit ranged from 25 to 300 mg/day (M = 109.06; SD = 73.01). However, for those in the treatment arm of the study, both mean dose and dose range were significantly lower than those on placebo (p = .001). Indeed, the mean dose for those taking seroquel was only 78.79 mg/day (SD = 54.53; Range = 25 -200 mg/day). Over 30% of this subject group completed the double blind phase of the study on a dose of 25 mg/day, with only six of 33 subjects titrated to a dose of $\geq$ 50 mgs/day at some stage of the trial.

Open label study phase: Of the 69 subjects who were randomized according to the protocol, 38 entered the open label phase of the trial, with 26 (68.4%) completing this additional 12 month phase of the study. The average time spent in the open label phase of the study was 294.66 days, however for those who discontinued, the average time spent in the study was 115.33 days (SD = 107.88; Range = 1-260 days). Reasons for discontinuation included: subject failed to return (n = 5); adverse event (n = 4); insufficient therapeutic response (n = 1); withdrew consent (n = 1), and protocol violation (n = 1).

Results of the Intention to Treat Analysis with Last Observation Carried Forward (ITT, LOCF) (N = 38) revealed significant differences on each outcome measure between randomization and trial completion, however score reduction between completion of the double blind phase and completion/discontinuation from the open label phase was not significant ($p > .05$). Even when the sample was restricted to subjects who completed the 15 months of the trial, the only significant change between week 12 and trial completion was Clinical Global Impression – the clinician's perception of the severity of the subject's presentation ($p = .005$).

Safety data: The collection of safety data included the recording of vital signs and adverse events at each study visit. Analysis of subjects in the study treatment group revealed no significant change in heart rate, and no increase in postural drop, between baseline and week 12 ($p > .05$). Of further note is that weight gain over the 12 week period was non-significant, with those allocated to the seroquel arm of the study gaining less than 0.5 kgs, on average ($p = .483$).

An overview of adverse events revealed that 45 participants (65.21%) experienced one or more adverse events which were deemed by the clinician to be in some way related to the study drug ($M = 2.12$; $SD = 2.64$; Range = 0 – 13). Of the 145 adverse events recorded, four were classified by the clinician as serious: (1) tremor; (2) pneumonia; (3) abnormal liver function test, and (4) deterioration of mental state. However, there were no significant differences between treatment and placebo groups in either the number of adverse events reported ($p = .916$), or the incidence of serious adverse events ($p = .285$). Subjects taking seroquel more frequently experienced dry mouth, fatigue, and sedation/somnolence, while those on placebo reported higher rates of headache, nausea/vomiting, and sensory disturbance.