AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: AZD2327
ACTIVE INGREDIENT: AZD2327

Study No: D0880C00021
An Investigation of the Antidepressant Efficacy of a Selective, High Affinity Enkephalinergic Agonist in Anxious Major Depressive Disorder

Developmental Phase: Therapeutic exploratory (Phase II)
Study Completion Date: 19 December 2011
Date of Report: 7 September 2012

OBJECTIVES:

The primary aim of the study was to determine whether the highly selective δ-opioid receptor agonist AZD2327 given orally at a dose of 3 mg BID for 4 weeks is effective in the treatment of major depression (MDD) in adult men and women as assessed by the proportion who show a clinically significant change from baseline to endpoint in the Hamilton Rating Scale for Depression (HRSD17) or the Hamilton Rating Scale for Anxiety (HAM-A) total scores.

METHODS:

This was a randomized, double blind, placebo-controlled, parallel group, and single site inpatient and outpatient experimental study.

Per protocol, the primary outcome measures were the HAM-D and HAM-A. Item 10 (psychic anxiety) from the HAM-D was a secondary outcome measure. In an exploratory analysis, other individual items from the HAM-D and HAM-A were examined to understand specific effects of the drug. Change from baseline in the intent-to-treat sample was examined comparing drugs using repeated measures ANCOVA where post-treatment ratings were examined at each week for four weeks and the baseline rating was a covariate. Missing data was handled with the last observation carried forward. Cohen's d was calculated to understand the effect size for drug effects. An additional set of ANCOVAs examined the follow up ratings comparing drugs near hospital discharge where the initial baseline was the covariate. A logistic regression was used to compare the proportion of responders on each drug. Response was a 50 percent or greater decrease in ratings at four weeks. Additional planned analyses of time to relapse were

not performed due to insufficient sample size. Exploratory analyses examined changes in responders versus non-responders based on depression (HAM-D) as well as anxiety (HAM-A) changes. The significance criterion was set at .05, two-tailed. SPSS version 19.0.0.1 was used to conduct the analysis.

RESULTS:

Summary of efficacy results

For the overall HAM-D, the repeated measures ANCOVA showed no significant main effect for drug (F=0.77, df=1,19, p=.39; d=0.40) or interaction between drug and time (F=0.51, df=3,57, p=.68). An examination of the end point as the sole time point with baseline as the covariate also showed no significant drug difference (F=0.36, df=1,19, p=.56; d=0.28). A linear mixed model with drug and time as factors, baseline as a covariate, and restricted maximum likelihood estimation instead of last observation carried forward showed similar results. Further, A logistic regression showed no difference in response rates at end point as five (39%) patients responded to active drug and 4 (44%) to placebo (χ2=0.08, p=.78; OR=0.78).

For the HAM-A, the repeated measures ANCOVA showed no significant drug main effect (F=2.30, df=1,19, p=.15; d=.70) and no interaction between drug and time (F=0.32, df=3,57, p=.81). Using the end point as the sole time point with baseline as the covariate showed no significant drug difference (F=1.78, df=1,19, p=.20; d=0.61). Patients taking the active treatment had non-significantly lower scores than the group on placebo. A linear mixed model showed similar results. Seven (54%) patients responded to active drug and 3 (33%) to placebo. Response rates were not significantly higher with active drug than placebo at end point using logistic regression (χ^2=0.89, p=.35; OR=2.33).

For the psychic anxiety item of the HAM-D, the repeated measures ANCOVA showed a significant main effect for drug (F=2.32, df=1,19, p=.14; d=0.70) but no interaction between drug and time (F=0.35, df=3,57, p=.79). Patients taking the active treatment had significantly lower scores than the group on placebo. An examination of the end point as the sole time point with baseline as the covariate also showed no significant drug difference (F=2.25, df=1,19, p=.15; d=0.69). A linear mixed model showed similar non-significant results.

Exploratory analyses with the rest of the items on the HAM-D indicated that depressed mood was significantly lower on active drug (F=2.25, df=1,19, p=.15; d=0.69) and gastrointestinal symptoms were significantly higher on active drug (F=-3.82, df=1,19, p=.07; d=-0.90). All other items were not significantly different.

With items on the HAM-A, patients on active drug had significantly lower scores for autonomic symptoms (F=5.07, df=1,19, p=.04; d=1.03), respiratory symptoms (F=3.91, df=1,19, p=.06; d=0.91), concentration difficulties (F=2.12, df=1,19, p=.16; d=0.67), and depressed mood (F=1.91, df=1,19, p=.18; d=0.63). Also, there was a significantly interaction between time and drug for muscular symptoms (F=1.89, df=1,19, p=.14), where patients on active drug had fewer symptoms on day 7 only.

Summary of safety results

Completion rates were 85% (11/13) for active drug and 77% (7/9) for placebo ($\chi 2=0.17$, df=1, p=.68). With the active drug, one patient dropped out on the day of the drug infusion with dizziness, orthostatic hypotension, and emesis. A second patient dropped out on the last day of the study expressing concern over the transition to standard therapy following the study. With placebo, two patients dropped out after two weeks due to worsening depression, where one also had worsening anxiety.