ABSTRACT

Background: This pilot study was designed to evaluate centanafadine (EB 1020) SR as a novel non-sedating stimulant treatment option for adult attention-deficit hyperactivity disorder (ADHD). Centanafadine SR is a nor-epinephrine-prefering triple reuptake inhibitor with IC50 values for human transporter reuptake inhibition of 6 nM, 38 nM, and 83 nM for noradrenaline (NE), dopamine (DA), and serotonin (5HT), respectively.

Methods: A total of 41 adult males with well-characterized ADHD enrolled in this 4-week, single-blind study with a 1-week placebo run-in. Centanafadine SR was given twice daily for 4 weeks and titrated to a target dose of 500 mg daily over 10 days. Outcomes assessed included ADHD symptoms, executive function, and tolerability.

Results: 37 subjects completed the trial. Centanafadine SR produced a 21-point reduction in the adult ADHD Rating Scale-IV (ADHD-RS-IV) endpoint mean total score (5.7, p<0.001) including significant reductions in inattentive (p<0.001) and hyperactive impulsivity (p<0.001). Overall, 68% of subjects were considered responders using the Clinical Global Impressions-Improvement Scale (CGI-I) (much/very much improved). 21 subjects (54%) met the minimum Level 2 criteria for statistically significant improvements in overall and specific domains of executive function using the Behavioral Rating Inventory of Executive Function—Adult Version (BRIEF-A) (overall p<0.001). No clinically meaningful trends in adverse events, laboratory values, vital signs, or ECG parameters were noted.

Conclusions: Centanafadine SR appears effective in treating ADHD and executive function deficits in adult males. The maximum dose studied appears well-tolerated. Based on the results, randomized, controlled studies of centanafadine SR are warranted.

INTRODUCTION

Despite the availability of both FDA-approved and other agents for the treatment of ADHD, a number of individuals either cannot tolerate or do not respond optimally to existing agents, necessitating the development of alternative agents. Interest has arisen in the role of monoamine triple reuptake inhibitors in the treatment of ADHD.

One monoamine transport inhibitor, centanafadine (1R,5S)-1-(2-ethyl-6-methylpyridin-2-yl)-3-(azabicyclo[3.1.0]hexane HCl) may provide benefit for the treatment of adult patients with ADHD, because it combines robust NE uptake inhibition with moderate DA uptake inhibition. Centanafadine SR, a sustained-release formulation developed for clinical use, is being investigated as a potential treatment for ADHD in adult males. This pilot study was to evaluate centanafadine SR as a novel treatment for ADHD in adults. We hypothesized that significant improvement in both primary ADHD and ADHD/executive function endpoints would be observed, as well as tolerability, variability and observability, in patients on the medication after 4 weeks of treatment compared to baseline.

METHODS

This was a 4-week, Phase 2a, flexible-dose, single-blind, study with a one-week placebo run-in. A total of 41 adult males aged 18-55 years with well-characterized ADHD were enrolled in the trial. To be included for inclusion in this study, subjects were requiring medication and labor and no other major medical or current psychiatric comorbidity. Centanafadine SR was given twice daily and titrated to a target dose of 500 mg daily over seven days. The trial was randomized in a 1:1:1 ratio and no subjects were withdrawn from the trial. All subjects were informed of the exact timing of the centanafadine SR vs. placebo treatment to maintain the blinded nature of the placebo treatment and reduce potential placebo effects while on active study drug. The relatively short duration of the trial was chosen because of limitations in supportive toxicological testing available at the initiation of the trial.

RESULTS

A total of 41 patients were enrolled at baseline-2 and 37 adult males completed this trial and were considered evaluable for efficacy (Table 1). The ADHD-RS-IV scores for the patients were stable during the screening and the two baseline visits with only 1 patient being dropped during the placebo run-in (Figure 1). Centanafadine SR produced a 21-point reduction on the ADHD-RS-IV (endpoint mean total score = 11.7, p<0.001) and a delayed return to baseline (Figure 2). Treatment with centanafadine SR also resulted in significant reductions in inattentive (p<0.001) and hyperactive impulsivity (p<0.001) (Figure 3). The average % of the standard error of the mean divided by the mean total score was about 11%, a low level of variability, indicating that the mean reduction in scores was driven by a few patients. Overall, 68% of subjects were considered responders using the CGI-I (much/very much improved) (Figure 4). Clinically and statistically significant improvements in overall and specific domains of executive function using the BRIEF-A were also found (overall p<0.001) (Figure 5). Clinically and statistically significant improvements in emotional dysregulation using the Children’s Global Impression Scale (CGI) were observed (p<0.001) (Figure 6). No clinically meaningful findings in adverse events, laboratory values, vital signs, or ECG parameters were noted (Table 2). No notable increases in suicidality were observed at any of the dose levels studied.

DISCUSSION

For this study of the triple reuptake inhibitor centanafadine SR in the treatment of adult males with ADHD, the study met the primary endpoint of change from Baseline-2 (start of centanafadine SR treatment) in ADHD symptoms to Treatment Week 4 there was a statistically significant decrease in the mean (SD) score for ADHD symptoms. Similar decreases were observed for the mean (SD) scores in the subscales of inattentive symptoms and hyperactive impulsivity symptoms. Centanafadine SR also appeared to be effective in treating executive function in adult males at the maximum dose studied, and appears to be well tolerated with no increase in suicidality observed at any of the dose levels studied. Results from the primary and secondary endpoints were consistent with the findings from the primary endpoint. While a direct comparison of centanafadine SR with other agents was not performed in this study, an indirect review of data from the published literature indicates that centanafadine SR had comparable effectiveness to efensidintamine in both treatment-naive and treatment-experienced patient groups. Based on these results, randomized, controlled studies of centanafadine SR are warranted.

REFERENCES


DISCLOSURES