A Pilot Study of a Novel Monoamine Triple Reuptake Inhibitor, Centanafadine (EB-1020) SR, in the Treatment of Attention-Deficit Hyperactivity Disorder in Adult Males

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Background: this pilot study was designed to evaluate centanafadine (EB-1020) SR as a novel non-simulant stimulant treatment option for adult attention-deficit hyperactivity disorder (ADHD). Centanafadine SR is a norepinephrine-preferring triple reuptake inhibitor with IC50 values for human vascular smooth muscle norepinephrine uptake of 6 nM, 38 nM and 83 nM for norepinephrine (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 as blinded tablets titrated to a target dose of 500 mg daily over 10 days. Outcomes included assessed ADHD symptoms, executive function, and tolerability.

Results: 37 subjects completed the trial. Centanafadine SR produced a 21 point reduction on the adult ADHD Rating Scale IV (ADHD-RS-IV) (endpoint mean score change = -17, p<0.0001) and significant reductions in inattentive (p<0.0001) and hyperactive/impulsive symptoms (p<0.0001). Overall, 68% of subjects were considered responders using the CGI-I scale.

Conclusions: Centanafadine SR appears effective in treating ADHD and executive function deficits in adult males. The maximum dose studied appears well tolerated.

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 treatments, 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)-3-(4-naphthalen-2-yl)-4-hydroxy-3-(1H-tetrazol-1-yl)-4H-1,2,4-Benzothiazin-6-one 2HCl, may provide benefit for the treatment of adult patients with ADHD, because it combines robust NE reuptake inhibition with moderate DA uptake inhibition. Centanafadine SR, a sustained-release formulation developed for clinical use, is being investigated as a triple reuptake inhibitor with moderate DA uptake inhibition. Centanafadine SR, a sustained-release formulation developed for clinical use, is being investigated as a triple reuptake inhibitor with moderate DA uptake inhibition. Centanafadine SR, a sustained-release formulation developed for clinical use, is being investigated as a triple reuptake inhibitor with moderate DA uptake inhibition.

RESULTS

A total of 41 patients were enrolled at baseline to 37 adult males completed the study 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 score change = -17, p<0.0001) and a delayed return to baseline (Figure 2).

At the end of a single-blind placebo treatment, the ADHD-RS-IV with adult prompts was re-administered. Patients who showed 33% improvement over baseline values were removed from the study after an initial washout period. Data from the centanafadine SR treatment based on clinical judgment. Those who showed <30% improvement on placebo from baseline to week 2 were excluded from the study. All subjects completed informed consent including description of the inclusion criteria and whether or not the order of the study was active or sham.

Primary objective: To compare the change from Baseline-2 (start of centanafadine SR treatment) in ADHD symptoms to Week 4 after investigation product administration, as assessed by the adult ADHD-RS-IV.

Other important secondary outcomes: The change from Baseline-2 on the inattentive and hyperactivity/impulsivity subscales of the ADHD-RS-IV at Weeks 1, 2, 3, 4, and 6; change from Baseline-2 on the BRIEF-A at Week 4 and outcome as assessed by the responder rate using the Clinical Global Impressions-Self (CGI-I) and CGI-S scales at Weeks 1, 2, 3, and 4 and the follow-up visit (Week 6).

Safety and tolerability: Assessed by occurrence of adverse events throughout the study, clinical laboratory (hematology, blood chemistry, and urinalysis) tests results at Weeks 2 and 4 and the follow-up (Week 6), vital signs and 12-lead electrocardiograms (EKG) at each visit, and a Columbia Suicide Severity Rating Scale (CSSRS) at each visit.

DISCUSSION

This was a 4-week, Phase 2a, flexible-dose, single-blind, study with 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 considered for inclusion in the study, subjects were required to have an ADHD diagnosis characterized by inattentive symptoms and hyperactivity/impulsivity symptoms, Centanafadine SR also achieves efficacy 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 secondary efficacy endpoints are consistent with the findings from the primary endpoint. While a direct comparison to existing triple reuptake inhibitors was not performed in this study, an indirect review of data from the published literature indicates that centanafadine SR had comparable effectiveness to lisdexamfetamine in both symptom and executive function improvements. While the small sample size limited the ability to draw conclusions from this study, based on these results, randomized, controlled studies of centanafadine SR are warranted.

REFERENCES

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