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Enclosure:

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Executive Function Symptom Outcomes in Adults With ADHD Treated With Centanafadine: A Pooled Post Hoc Analysis of Two Phase 3 Trials

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in adults and is frequently associated with impairments in executive functions such as organization, planning, time management, and working memory[1-3]
- Executive dysfunction in adults with ADHD contributes to substantial impairment in work, social relationships, and daily functioning and is associated with greater risk-taking (leading to lower rates of self-care), and increased mortality[4,5]
- Despite available treatments that manage core symptoms, substantial unmet need remains in adults with ADHD, particularly for associated features such as executive functioning[6-8]
- Centanafadine, a norepinephrine-dopamine-serotonin reuptake inhibitor (NDSRI), was studied in two large-scale, phase 3 trials for the treatment of ADHD in adults aged 18–55 years, demonstrating efficacy and safety[9]

Objective

- Evaluate the effect of centanafadine on patient-reported assessment of executive functioning using the adult ADHD Self-Report Scale (ASRS) Expanded Version in adults after 6 weeks of treatment

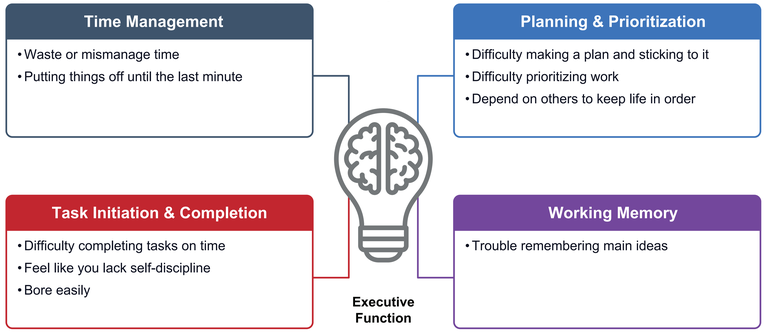
Methods

- **Studies:** Two identically designed phase 3, multicenter, randomized, double-blind, placebo-controlled trials conducted in the US (NCT03605680 and NCT03605836)
- **Participants:** Adults (18–55 years) with a primary diagnosis of ADHD (of any presentation) according to *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria, as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS)
- **Treatment:** Patients were randomized (1:1:1) to receive centanafadine 200 mg, centanafadine 400 mg, or placebo for up to 6 weeks
- **Post hoc endpoints:** Change from baseline in the ASRS Expanded Version Executive Function (EF) subscale scores and individual EF items at Week 6
  - The ASRS is a validated, self-administered questionnaire used to screen for and assess ADHD symptoms and their severity, including 9 items assessing aspects of executive dysfunction (**Figure 1**)[10]
  - Response choices consist of 0 (never), 1 (rarely), 2 (sometimes), 3 (often), and 4 (very often)[10]
- **Analysis:** Post hoc endpoints were analyzed using a mixed-effect model for repeated measures, with trial site, treatment group, visit, and treatment group-by-visit interaction as factors and baseline-by-visit interaction as a covariate; used "unstructured" covariance matrix
  - Endpoints were not controlled for multiplicity
  - Effect sizes were calculated using Cohen's d method based on mixed models for repeated measures estimates

Results

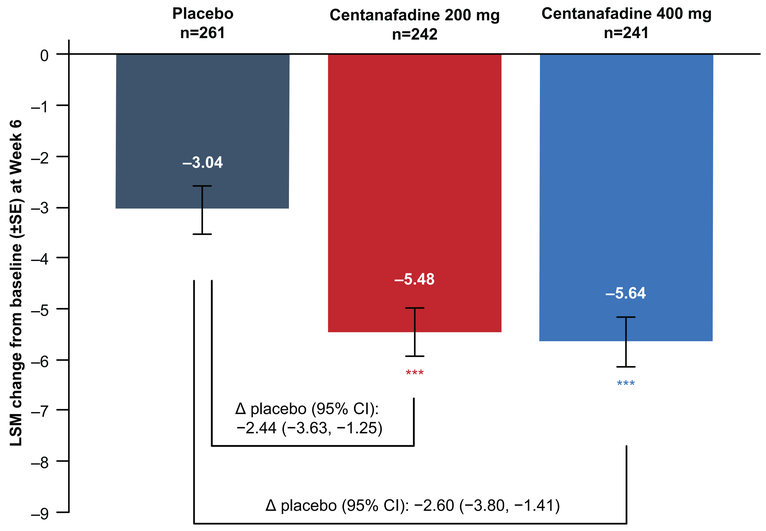
- Of the 859 treated adults in the pooled population, 744 participants with available ASRS Expanded Version data were included in these analyses (centanafadine 200 mg, n=242; 400 mg, n=241; placebo, n=261)
- At baseline, the mean ± standard deviation ASRS Expanded Version EF subscale score was 26.6 ± 6.0, consistent with a substantial burden of symptoms
- At Week 6, adults treated with centanafadine reported improvements from baseline in the ASRS EF subscale compared with placebo, reflecting reductions in the frequency of patient-reported executive functioning difficulties assessed by the scale (**Figure 2**)
- Effect sizes for the EF subscale were 0.36 for centanafadine 200 mg and 0.38 for 400 mg, and were comparable in magnitude to those for core symptom subscales assessing Inattention (0.42 and 0.45, respectively) and Hyperactivity/Impulsivity (0.30 and 0.42, respectively)
- Consistent with the subscale-level findings, improvements from baseline versus placebo were observed across individual ASRS EF items at Week 6, including those related to time management, planning and prioritization, task initiation and completion, and working memory–related difficulties (**Figure 3**)
- In the pooled analysis, centanafadine was also associated with improvements from baseline at Week 6 in ASRS 18-item total score ($P<0.001$), with effect sizes of 0.38 and 0.42 for the 200 mg and 400 mg doses, respectively

Figure 1. Aspects of EF captured by the ASRS Expanded Version EF subscale



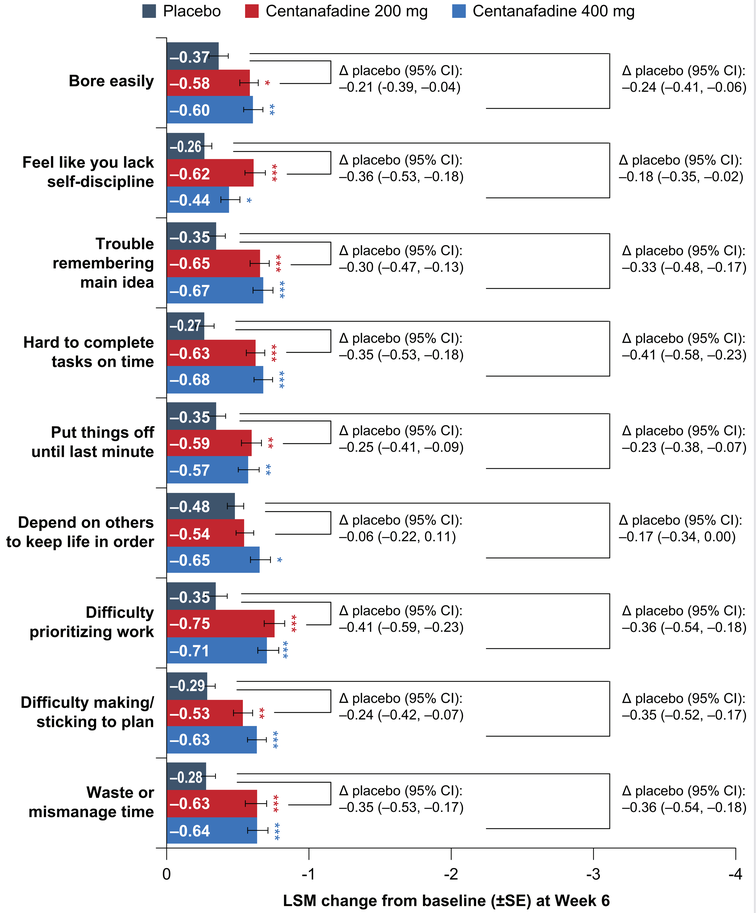
ASRS, adult ADHD Self-Report Scale; EF, Executive Function.

Figure 2. Change from baseline in ASRS EF subscale score at Week 6



***P<0.001 versus placebo.
Δ placebo, change from placebo; ASRS, Adult ADHD Self-Report Scale; CI, confidence interval; EF, Executive Function; LSM, least squares mean; SE, standard error.

Figure 3. Change from baseline in the ASRS Expanded Version EF item scores at Week 6



*P<0.05, **P<0.01 , ***P<0.001 versus placebo.
Δ placebo, change from placebo; ASRS, Adult ADHD Self-Report Scale; CI, confidence interval; EF, Executive Function; LSM, least squares mean; SE, standard error.

Conclusions

- In this post hoc analysis, centanafadine was associated with improvements in patient-reported executive functioning in adults with ADHD, as assessed by the ASRS Expanded Version, which were of similar magnitude to those observed for core ADHD symptom domains
- Improvements were observed across a broad range of executive function items, including time management, planning and prioritization, task initiation and completion, and working memory–related difficulties
- These results support further investigation into centanafadine's potential to address impairments beyond core symptoms, including emotional difficulties and executive function deficits frequently experienced by adults with ADHD

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At Otsuka, we hold a deep respect for the value of every mind. We will not rest until mental illnesses and brain diseases are approached with the same priority and urgency as our physical health and recognized as chronic diseases that warrant early, equitable, and accessible intervention for patients and caregivers everywhere.

Disclosures

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