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Enclosure:

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# Emotional Dysregulation 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 symptoms of emotional dysregulation, including affective lability, emotional over-reactivity, frustration tolerance, and irritability[1-3]
- Affecting up to 70% of adults with ADHD, emotional dysregulation is a major source of impairment and is associated with poorer clinical outcomes[3]
- Despite available treatments that manage core symptoms, substantial unmet need remains in adults with ADHD, particularly for associated features such as emotional dysregulation[4-6]
- 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[7]

## Objective

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

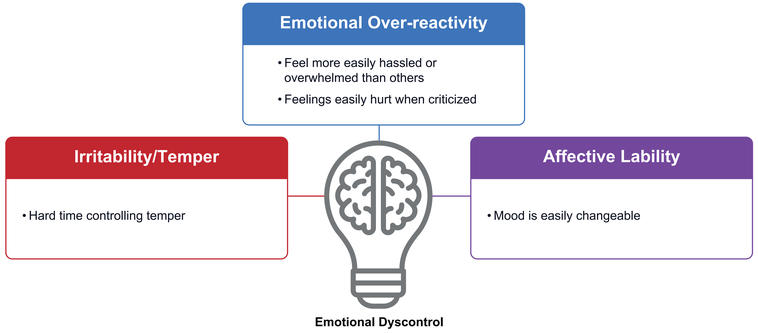
## Methods

- **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 Emotional Dyscontrol (ED) subscale scores and individual ED items at Week 6
- The Expanded ASRS is a validated, self-administered, 31-item questionnaire used to screen for and assess ADHD symptoms and symptom severity, including 4 items that assess aspects of emotional dysregulation (**Figure 1**)[8]
  - Response choices consist of 0 (never), 1 (rarely), 2 (sometimes), 3 (often), and 4 (very often)[8]
- **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

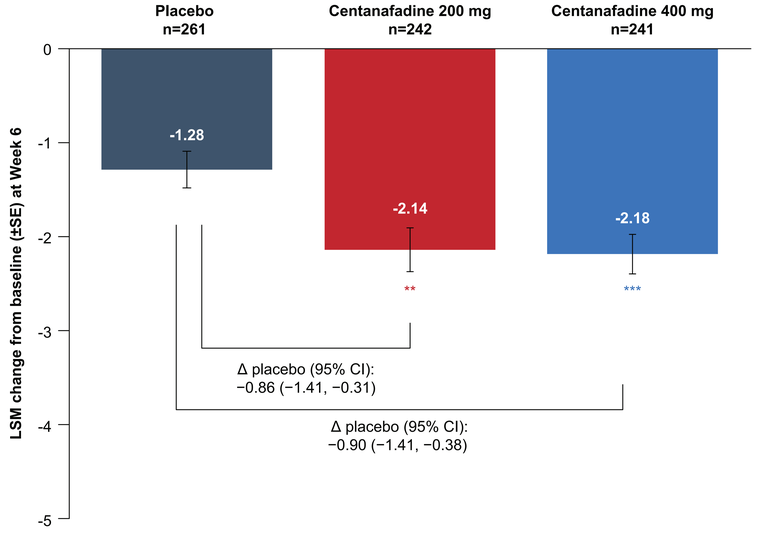
- Of the 859 treated adults in the pooled population, 744 participants with available ASRS Expanded Version data were included in these analyses (centanafadine 200 mg, n=242; 400 mg, n=241; placebo, n=261)
- At baseline, the mean ± standard deviation ASRS Expanded Version ED subscale score was 9.3 ± 3.6, consistent with notable burden of symptoms
- At Week 6, adults treated with centanafadine reported improvements from baseline in the ASRS Expanded Version ED subscale compared with placebo, reflecting reductions in the frequency of specific patient-reported emotional dysregulation dimensions assessed by the scale (**Figure 2**)
- Effect sizes for the ED subscale were 0.27 for centanafadine 200 mg and 0.31 for 400 mg
- Consistent with the subscale-level findings, improvements from baseline versus placebo were observed across individual ASRS Expanded Version ED items at Week 6, including those related to affective lability, emotional over-reactivity, and irritability/temper (**Figure 3**)
- In the pooled analysis, centanafadine was also associated with improvements from baseline at Week 6 in ASRS 18-item total score and the Inattention and Hyperactivity/Impulsivity subscale scores (all $P<0.001$), with effect sizes ranging from 0.30 to 0.45 across core symptom domains

**Figure 1. Aspects of Emotional Dysregulation captured by the ASRS Expanded Version ED subscale**



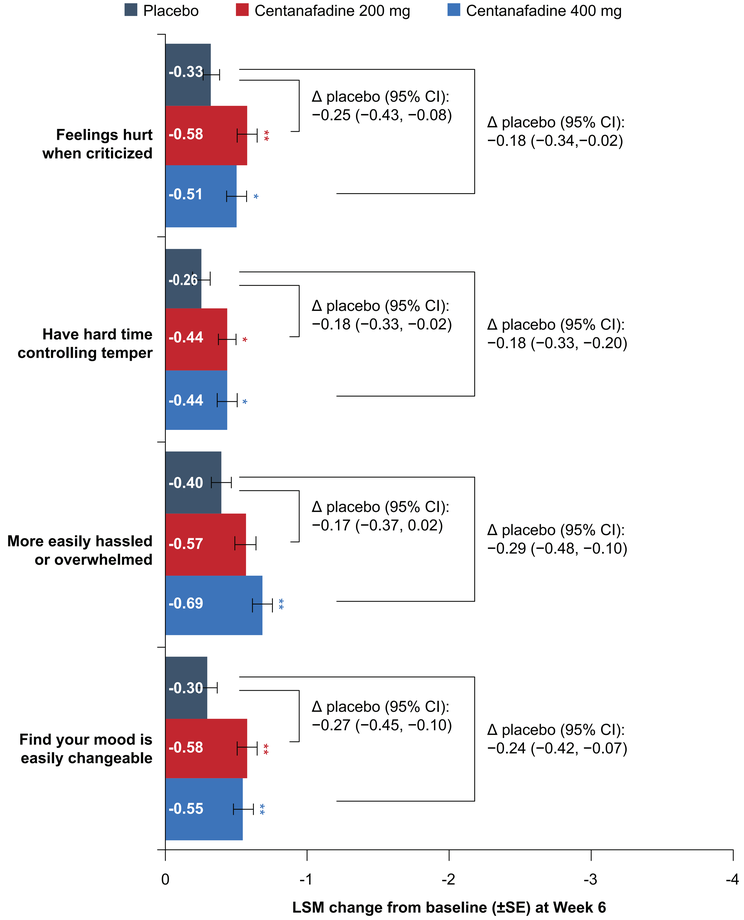

ASRS, adult ADHD Self-Report Scale; ED, Emotional Dyscontrol.

**Figure 2. Change from baseline in the ASRS Expanded Version ED subscale score at Week 6**




**$P<0.01$, ***$P<0.001$ versus placebo.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; ED, Emotional Dyscontrol; LSM, least squares mean; SE, standard error.

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




*$P<0.05$, **$P<0.01$ versus placebo.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; ED, Emotional Dyscontrol; LSM, least squares mean; SE, standard error.

## Conclusions

- In this post hoc analysis, centanafadine was associated with improvements in patient-reported emotional dysregulation in adults with ADHD, as assessed by the ASRS Expanded Version
- Improvements were observed across ED items capturing externally expressed, behavioral dimensions of emotional dysregulation, including affective lability, emotional over-reactivity, and irritability/temper, with improvements of similar magnitude to those observed for core ADHD symptom domains
- 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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