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Enclosure:

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Impact of Centanafadine on Executive Functioning in Pediatric Patients With Attention-Deficit/Hyperactivity Disorder: Analysis of Conners 3 and Exit Survey Responses

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INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is one of the most common pediatric neurodevelopmental disorders, characterized by symptoms of inattention, hyperactivity, and impulsivity—all of which can affect overall quality of life for patients and their families[1,2]
- Individuals with ADHD can also have impairments in executive functioning or high-level cognitive processes that include inhibition, switching between tasks, working memory, planning, monitoring, and verbal and design fluency[3]
- The Conners 3–Parent Short (PS) Content Scales measure some aspects of executive functioning as well as symptoms of inattention, hyperactivity, and impulsivity[4]
- Extended-release centanafadine (CTN), a norepinephrine, dopamine, serotonin reuptake inhibitor (NDSRI), was studied in two phase 3 trials for the treatment of ADHD in children aged 6–12 years and adolescents aged 13–17 years

OBJECTIVE

- To compare the executive functioning efficacy measure with participant exit survey data in a pediatric population treated with CTN

METHODS

- **Studies:** Two phase 3, multicenter, randomized, double-blind, placebo-controlled trials conducted in the United States and Canada (children: NCT05428033; adolescents: NCT05257265)
- **Eligible participants:** Children (6–12 years) or adolescents (13–17 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 Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
- **Treatment:** Participants were randomized (1:1:1) to receive once-daily extended-release high-dose CTN, low-dose CTN, or placebo for 6 weeks without titration
- **Dosing:**
  - Adolescents: High-dose (328.8 mg) CTN, low-dose (164.4 mg) CTN, or placebo
  - Children: Weight-based, with participants divided into the following categories: <20, ≥20–<35, 35–50, or >50 kg and receiving 41.1, 82.2, 123.3, or 164.4 mg, respectively, if they were randomized to low-dose CTN, or 82.2, 164.4, 246.6, or 328.8 mg, respectively, if they were randomized to high-dose CTN. Weight categories were combined for the data analyses
- **Efficacy outcomes:**
  - Change from baseline to Week 6 in ADHD Rating Scale-5 (ADHD-RS-5) symptoms total raw score (*primary endpoint*)
  - Change from baseline in the Conners 3–PS Executive Functioning Content Scale (containing 5 individual line items: forgets to turn in work, trouble getting started, loses things, trouble organizing, and messy and disorganized) T-score at Week 6 (*key secondary endpoint*)
  - The percentage of participants with clinically meaningful change in Conners 3–PS Executive Functioning T-scores (≥13-point improvement from baseline)
    - From an anchor-based analysis using the Clinical Global Impressions of Severity (CGI-S), a ≥13-point change in Conners 3–PS Executive Functioning T-scores was used because at the population level this would correspond to a 2-point, clinically meaningful change in CGI-S score
- **Entry and Exit Surveys:** An Entry Survey (baseline) and Exit Survey (Week 6 or trial completion) consisting of questions pertaining to unmet needs, treatment history, expectations, and outcomes of interest were administered to parents/caregivers of participants
- **Analyses:**
  - Primary and key secondary efficacy outcomes were analyzed using a mixed-effect model for repeated measures
  - The meaningful change over time in Conners 3–PS Executive Functioning T-Scores was analyzed via a Cochran-Mantel-Haenszel test
  - All data reported here were collected via a parent/caregiver
- **Other outcomes:** Safety and tolerability

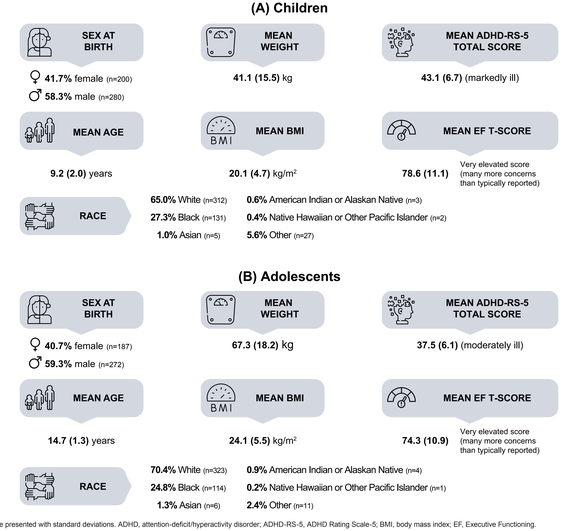
RESULTS

- Overall, 76.5% (367/480) of children (mean age 9.2 years, 58.3% male; **Figure 1A**) and 80.8% (371/459) of adolescents (mean age 14.7 years, 59.3% male; **Figure 1B**) completed their respective studies
- In children, the mean change (standard error [SE]) from baseline in ADHD-RS-5 symptoms total raw score at Week 6 was −16.3 (1.2) for high-dose CTN and −13.5 (1.2) for low-dose CTN versus −10.8 (1.2) for placebo (P=0.0008 and P=0.1023, respectively). Benefit was seen as early as Week 1 for high-dose CTN (P=0.0009)
- In adolescents, the mean change (SE) from baseline in ADHD-RS-5 symptoms total raw score at Week 6 was −18.5 (0.9) for high-dose CTN and −15.5 (0.9) for low-dose CTN versus −14.2 (0.9) for placebo (P=0.0006 and P=0.3016, respectively). Benefit was seen as early as Week 1 for high-dose CTN (P=0.001)
- In both studies, low-dose CTN did not meet the primary endpoint; thus, low-dose CTN has been excluded from this presentation of secondary and/or exploratory endpoints and subsequent presented P-values were not controlled for multiplicity
- In participants treated with high-dose CTN, a greater improvement than placebo in the mean change from baseline at Week 6 in Conner 3–PS Executive Functioning T-score was observed for both children (mean change [SE]: CTN, −11.3 [1.1]; placebo, −6.8 [1.1], P=0.0026; **Figure 2A**) and adolescents (CTN, −13.0 [1.0]; placebo, −8.1 [1.0], P=0.0003; **Figure 2B**)
- In participants treated with high-dose CTN, a greater number of children (40% *vs* 26%; P=0.0163) and adolescents (48% *vs* 26%; P=0.0002) had a clinically meaningful change from baseline (≥13-point reduction) in Conners 3–PS Executive Function T-scores versus placebo (**Figure 3**)
- Per the caregiver-reported exit survey, of those treated with high-dose CTN, 52% (*vs* 38% placebo) of children (**Figure 4A**) and 69% (vs 45% placebo) of adolescents (**Figure 4B**) saw improvement in completing tasks at home
- Similarly, 51% (*vs* 38% placebo) of children (**Figure 4A**) and 64% (vs 44% placebo) of adolescents (**Figure 4B**) saw improvement in completing work at school
- Likewise, 51% (*vs* 37% placebo) of children (**Figure 4A**) and 59% (*vs* 42% placebo) of adolescents (**Figure 4B**) saw improvement in their ability to learn

Safety

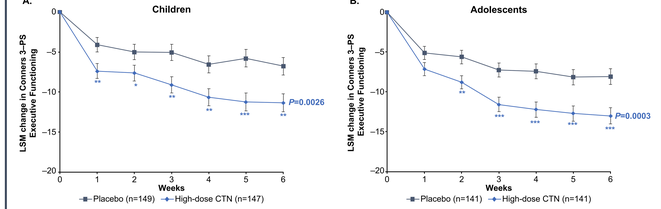
- Most treatment-emergent adverse events were mild to moderate, with the most common (≥5% in the high-dose CTN group and greater than placebo) being decreased appetite (7.6%) and rash (5.7%) for children, and decreased appetite (15.2%), nausea (9.9%), headache (6.0%), and rash (6.0%) for adolescents

Figure 1. Baseline demographics and clinical characteristics of all randomized children (N=480) (A) and adolescents (N=459) (B)



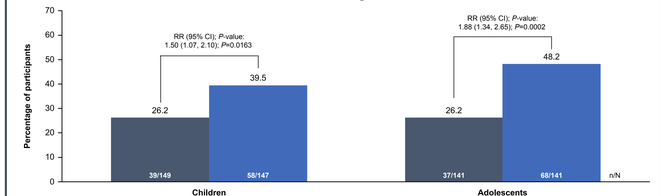
Means are presented with standard deviations. ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-5, ADHD Rating Scale-5; BMI, body mass index; EF, Executive Functioning.

Figure 2. Change from baseline in Conners 3–PS Executive Functioning Content Scale T-score in children (A) and adolescents (B)



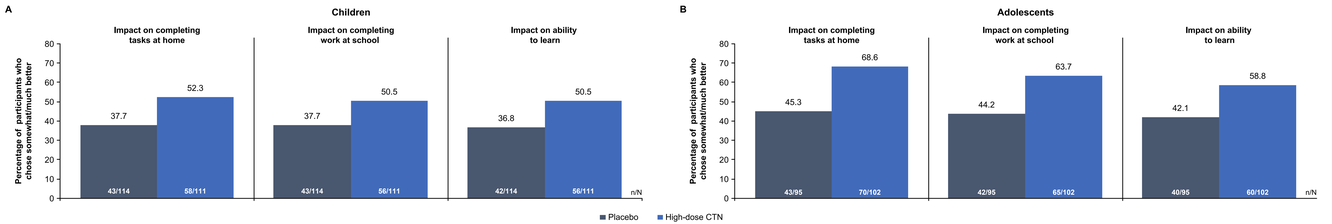
*P<0.05, **P<0.01, ***P<0.001. Mean change is derived from a mixed-effect model for repeated measures. Error bars are standard error of the means. Conners 3–PS, Conners 3–Parent Short; CTN, centanafadine; LSM, least squares mean.

Figure 3. Proportion of participants meeting clinically meaningful within-patient change thresholds for Conners 3-PS Executive Functioning Content Scale



Evaluated using the Cochran–Mantel–Haenszel general association test, controlling for trial site, in the last observation carried forward analysis. CI, confidence interval; Conners 3–PS, Conners 3–Parent Short; CTN, centanafadine; RR, relative risk.

Figure 4. Impact of CTN on completing tasks at home, completing work at school, and ability to learn in children (A) and adolescents (B)



Survey Question: How did the study medication affect each of the following areas of your child's life? (Please select one response for each row.) Reponses included: much worse, somewhat worse, no change, somewhat better, much better. Values reflect those who selected either "somewhat better" or "much better." (**A**) Children: Impact on completing tasks at home: ≤4.4% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (45.0–57.0%). Impact on completing work at school: ≤3.5% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (40.5–51.8%). Impact on ability to learn: ≤3.6% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (45.9–57.0%). (**B**) Adolescents: Impact on completing tasks at home: ≤4.2% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (31.4–48.4%). Impact on completing work at school: ≤2.1% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (28.4–42.1%). Impact on ability to learn: ≤2.0% of any treatment arm were "somewhat" or "much worse" and the remainder were "no change" (32.4–50.5%). CTN, centanafadine.

CONCLUSIONS

- Consistent with clinically meaningful change in executive function, caregiver-reported perceptions of completing tasks at home and school showed improvement in children and adolescents with ADHD treated with high-dose CTN
- Once-daily extended-release high-dose CTN was efficacious with a favorable safety profile in the treatment of ADHD in children and adolescents

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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.

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