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Enclosure:

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Comparison of Caregiver Exit Survey With Efficacy Measures in the Treatment of Attention-Deficit/Hyperactivity Disorder With Centanafadine in a Pediatric Population

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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]
- 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 efficacy measures and caregiver exit survey responses from a pediatric population treated with CTN for ADHD

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 to Week 6 in Clinical Global Impression of Severity for ADHD (CGI-S) score (*key secondary endpoint*)
  - Change from baseline to Week 6 in Patient Global Impression of Severity for ADHD (PGI-S) score and Clinical Global Impression of Change for ADHD (CGI-C) (*other efficacy endpoints*)
- **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
- **ADHD Treatment Satisfaction Questionnaire (ATSQ):** A subset of items from the Exit Survey compose the ATSQ, which consists of both a Comparison Rating and Daily Impact score[3]
  - *Comparison Rating Score*: 3 items from the Exit Survey form were utilized to assess a participants' experience with the study medication compared with other medications the participant had taken: 1) Which medication worked better for your child's ADHD symptoms?, 2) Which medication lasted longer throughout the day?, and 3) Which medication do you prefer as a treatment for ADHD? A 3-point scale was applied, where 1 = "study medication," 0 = "no change," and −1 = "previous medication(s)"
  - *Daily Impact Score*: For children, 8 items from the Exit Survey were utilized to assess how the study medication affected areas of the participants' life: 1) ADHD symptoms, 2) getting along with family, 3) making new friends, 4) completing work at home, 5) completing work at school, 6) behavior at home, 7) ability to learn, and 8) feeling anxious or worried. For adolescents, there were only 7 items ("completing work at home" was excluded). A 5-point scale was applied, where −2 = "Much worse," 1 = "Somewhat worse," 0 = "No change," 1 = "Somewhat better," 2 = "Much better"
- **Analyses:** ADHD-RS-5, CGI-S, and PGI-S were analyzed using a mixed-effect model for repeated measures. CGI-C was analyzed using a Cochran-Mantel-Haenszel test
- **Other outcomes:** Safety and tolerability

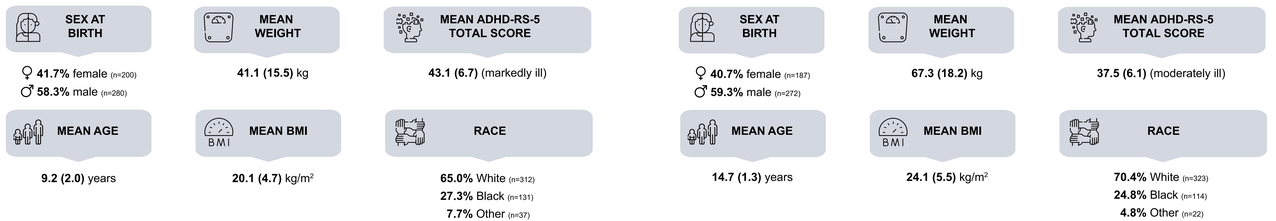
RESULTS

- 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
- At Week 6, high-dose CTN demonstrated greater differences in LS mean changes from baseline in CGI-S and PGI-S scores and in mean CGI-C score, when compared to placebo (**Figure 2**)
- Per the caregiver-reported exit survey, of those treated with high-dose CTN, 60% (*vs* 50% placebo) of children (**Figure 3A**) and 75% (*vs* 50% placebo) of adolescents (**Figure 3B**) saw improvement in ADHD symptoms
- Similarly, 56% (*vs* 45% placebo) of children and 62% (*vs* 42% placebo) of adolescents saw improvement in behavior at home and 47% (*vs* 38% placebo) of children and 47% (*vs* 27% placebo) of adolescents saw improvement in behavior at school (**Figure 3**)
- In children and adolescents, the ATSQ comparison rating and daily impact of prior ADHD treatments showed a preference for high-dose CTN (comparison rating score at Week 6 mean [standard deviation {SD}]: adolescents high-dose CTN, 0.4 [0.6] *vs* placebo, 0.2 [0.6] and children high-dose CTN, 0.3 [0.6] *vs* placebo, 0.1 [0.5]; daily impact rating score at Week 6 mean [SD]: adolescents high-dose CTN, 0.8 [0.7] *vs* placebo, 0.5 [0.6] and children high-dose CTN, 0.6 [0.7] *vs* placebo, 0.4 [0.7])

Safety

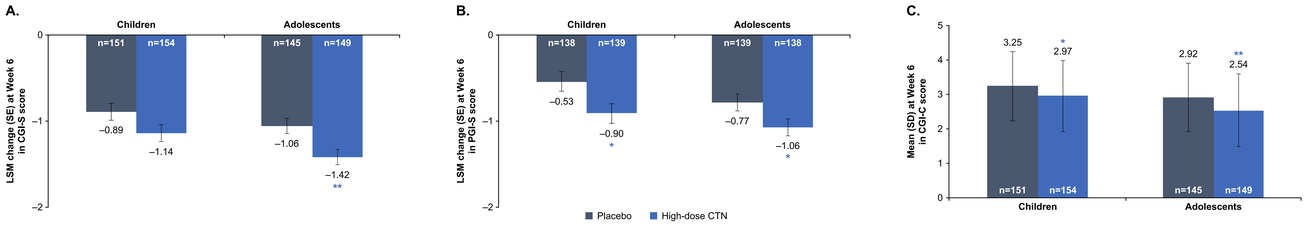
- Most treatment-emergent adverse events were mild to moderate, with the most common (≥5% in the high-dose CTN group and greater than placebo) being decreased appetite (7.6%) and rash (5.7%) for children, and decreased appetite (15.2%), nausea (9.9%), headache (6.0%), and rash (6.0%) for adolescents

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



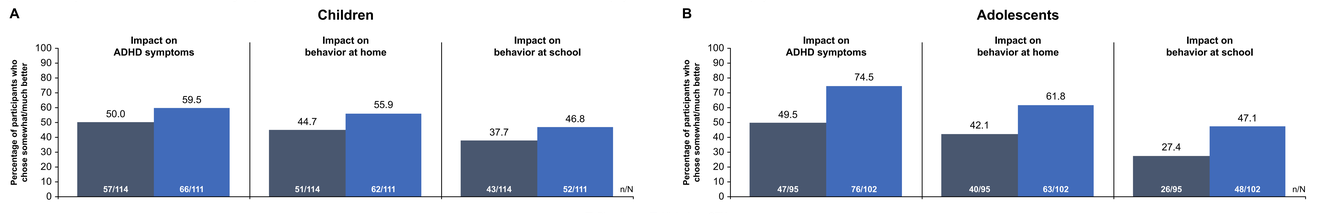
Means are presented with standard deviations. For race, the "Other" category includes participants who self-identified as Asian, American Indian / Alaskan Native, Native Hawaiian / Other Pacific Islander, or other. ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-5, ADHD Rating Scale-5; BMI, body mass index.

Figure 2. LSM change from baseline to Week 6 for CGI-S and PGI-S scores and mean CGI-C score at Week 6



*P<0.05, **P<0.01. The CGI-S and PGI-S were analyzed using a mixed-effect model for repeated measures. CGI-C was analyzed using a Cochran-Mantel-Haenszel test. CGI-C, Clinical Global Impression of Change for ADHD; CGI-S, Clinical Global Impression of Severity for ADHD; CTN, centanafadine; LSM, least squares mean; PGI-S, Patient Global Impression of Severity for ADHD; SE, standard error; SD, standard deviation.

Figure 3. Impact of CTN on ADHD symptoms and behavior at home and school 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 ADHD symptoms: ≤3.6% of any treatment arm were somewhat or much worse and the remainder were "no change" (36.9–45.6%). Impact on behavior at home: ≤4.5% of any treatment arm were somewhat or much worse and the remainder were "no change" (38.7–50.9%). Impact on behavior at school: ≤3.6% of any treatment arm were somewhat or much worse and the remainder were "no change" (43.2–49.1%). (**B**) Adolescents: Impact on ADHD symptoms: ≤3.0% of any treatment arm were somewhat or much worse and the remainder were "no change" (22.5–46.3%). Impact on behavior at home: ≤5.3% of any treatment arm were somewhat or much worse and the remainder were "no change" (32.4–50.5%). Impact on behavior at school: ≤2.0% of any treatment arm were somewhat or much worse and the remainder were "no change" (39.2–54.7%). ADHD, attention-deficit/hyperactivity disorder; CTN, centanafadine.

CONCLUSIONS

- Consistent with efficacy measures, caregiver-reported perceptions of ADHD symptom improvement and better behavior at home/school were observed at Week 6 following CTN treatment
- Once-daily extended-release high-dose CTN was efficacious with a favorable safety profile in the treatment of ADHD in children and adolescents

References

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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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