A Matching-Adjusted Indirect Comparison of Centanafadine vs Lisdexamfetamine, Methylphenidate, and Atomoxetine in Adults with Attention-Deficit/Hyperactivity Disorder: Long-Term Safety and Effectiveness Outcomes

Jeff Schein[1], Martin Cloutier[2], Marjolaine Gauthier-Loiselle[2], Maryaline Catillon[3], Chunyi Xu[3], Alice Qu[3], Francesca Lee[2], Ann Childress[4]

[1]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; [2]Analysis Group, Inc., Montréal, QC, Canada; [3]Analysis Group, Inc., New York, NY, USA; [4]Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, USA

CO184

Poster presented at ISPOR 2024

May 5–8, 2024; Atlanta, GA, USA

Background

- Centanafadine, a norepinephrine-dopamine-serotonin triple-reuptake inhibitor, is an investigational therapy for attention-deficit hyperactivity disorder (ADHD)[1]
- In a Phase 3 open-label clinical trial, adults with ADHD treated with centanafadine showed significant reductions in ADHD symptoms at Week 52 and centanafadine appeared to be well-tolerated[1]
- Head-to-head trials comparing the long-term safety and effectiveness of treatment options for adults with ADHD are lacking

Objective

To compare long-term safety and effectiveness outcomes of centanafadine vs lisdexamfetamine dimesylate, methylphenidate, and atomoxetine hydrochloride, respectively, in adults with ADHD using matching-adjusted indirect comparisons (MAICs)

These MAICs will provide important insights on the relative safety and effectiveness of common treatment options to help inform treatment decisions in adults with ADHD

Methods

Study design and data sources

- An overview of the study design is provided in Figure 1

Figure 1. Study design

- These MAICs included patient-level data from one centanafadine trial (NCT03605849) among adult patients with ADHD[1]
- Along with published aggregate data from three trials:
  - Lisdexamfetamine dimesylate (NCT00337285)[2]
  - Methylphenidate (NCT00326300)[3]
  - Atomoxetine hydrochloride (NCT00190736)[4]

Figure 2. Trial characteristics

	Centanafadine (NCT03605849)	Lisdexamfetamine dimesylate (NCT00337285)	Methylphenidate (NCT00326300)	Atomoxetine hydrochloride (NCT00190736)
Sample size	662 patients Single arm 400 mg daily: n = 662	349 patients Single arm 30 mg daily: n = 61 50 mg daily: n = 113 70 mg daily: n = 175	550 patients Single arm 36 mg daily: n = 123 54 mg daily: n = 138 72 mg daily: n = 121 90 mg daily: n = 94 108 mg daily: n = 74	501 patients Parallel arms 100 mg daily: n = 250 Placebo: n = 251
Location	40 sites across the US	44 sites across the US	55 sites across the US	21 sites across the US
Treatment period	52 weeks Open label treatment	52 weeks Open label treatment	26-52 weeks Open label treatment	26 weeks Randomized treatment

mg: milligram; NCT: National Clinical Trial; US: United States

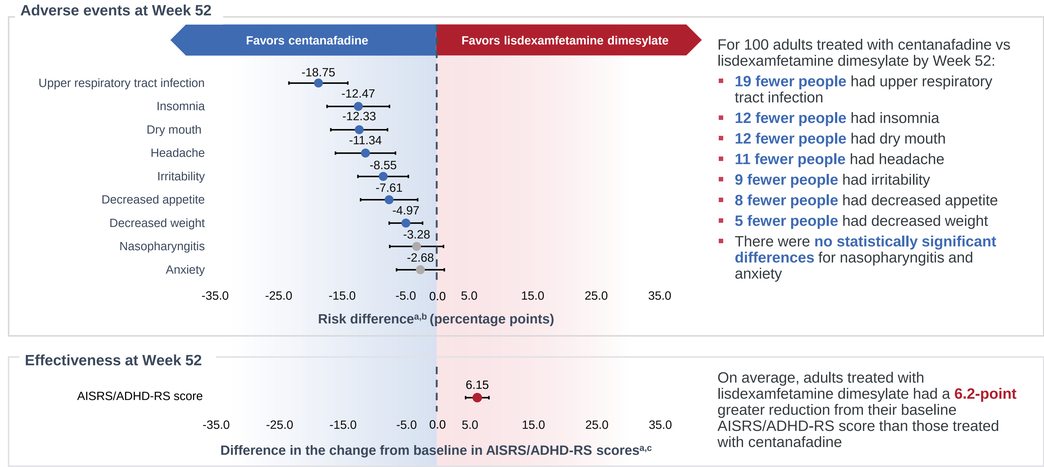
Safety and effectiveness outcomes

- Safety outcomes were defined as rates of adverse events (AEs) for which information was available in the centanafadine trial and respective comparator trials and reported by at least 5% of patients in any treatment group
- Effectiveness outcome was defined as mean change in the Adult ADHD Investigator Symptom Rating Scale (AISRS) score from baseline. The ADHD Rating Scale (ADHD-RS) was used as a proxy in the comparison with lisdexamfetamine dimesylate as AISRS was not reported and the instruments are similar (i.e., same number and types of items, and same scoring system)
- Study outcomes were assessed up to 52 weeks (26 weeks for the comparison with atomoxetine hydrochloride)

Results

Centanafadine had a better safety profile, but lower effectiveness compared to lisdexamfetamine dimesylate

Figure 3. Comparative safety and effectiveness of centanafadine vs. lisdexamfetamine dimesylate at 52 weeks



For 100 adults treated with centanafadine vs lisdexamfetamine dimesylate by Week 52:

- **19 fewer people** had upper respiratory tract infection
- **12 fewer people** had insomnia
- **12 fewer people** had dry mouth
- **11 fewer people** had headache
- **9 fewer people** had irritability
- **8 fewer people** had decreased appetite
- **5 fewer people** had decreased weight
- There were **no statistically significant differences** for nasopharyngitis and anxiety

On average, adults treated with lisdexamfetamine dimesylate had a **6.2-point** greater reduction from their baseline AISRS/ADHD-RS score than those treated with centanafadine

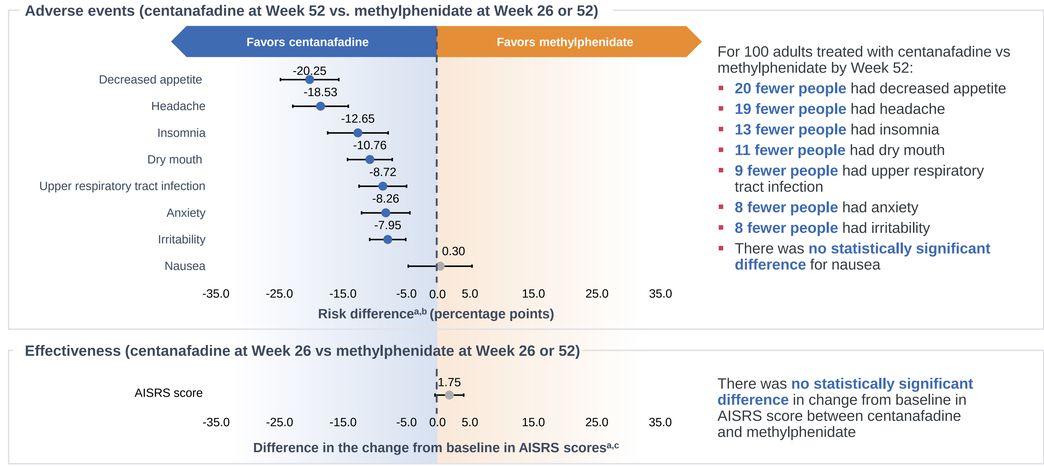
[a]Analyses were matched on age, sex, race, ethnicity, height, weight, baseline AISRS/ADHD-RS, and baseline Clinical global impression – Severity (CGI-S).

[b]Comparisons were calculated in the safety population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine were included in the safety population. For lisdexamfetamine dimesylate, all subjects who received ≥ 1 dose of lisdexamfetamine dimesylate were included in the safety population.

[c]Comparisons were calculated in the effectiveness population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine and had a baseline and ≥ 1 post-baseline AISRS total score were included in the effectiveness population. For lisdexamfetamine dimesylate, all subjects included in the intention-to-treat population, (i.e., those who were treated and had both baseline and ≥ 1 post-baseline ADHD-RS total score) were included in the effectiveness population.

Centanafadine had a better safety profile and comparable effectiveness compared to methylphenidate

Figure 4. Comparative safety and effectiveness of centanafadine vs. methylphenidate at final observation



For 100 adults treated with centanafadine vs methylphenidate by Week 52:

- **20 fewer people** had decreased appetite
- **19 fewer people** had headache
- **13 fewer people** had insomnia
- **11 fewer people** had dry mouth
- **9 fewer people** had upper respiratory tract infection
- **8 fewer people** had anxiety
- **8 fewer people** had irritability
- There was **no statistically significant difference** for nausea

There was **no statistically significant difference** in change from baseline in AISRS score between centanafadine and methylphenidate

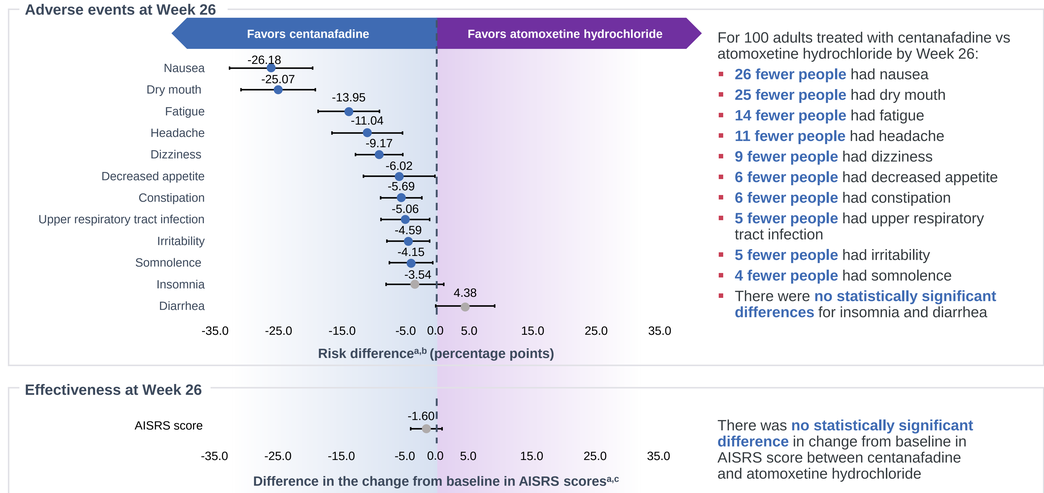
[a]Analyses were matched on age, sex, baseline AISRS, and baseline CGI-S.

[b]Comparisons were calculated in the safety population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine during the treatment period were included in the safety population. For methylphenidate, all subjects who received ≥ 1 dose of methylphenidate during the treatment period were included in the safety population.

[c]Comparisons were calculated in the effectiveness population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine and had a baseline and ≥ 1 post-baseline AISRS total score were included in the effectiveness population. For methylphenidate, effectiveness population was not clearly defined, but it was assumed all subjects who received ≥ 1 dose of methylphenidate and had ≥ 1 post-randomized AISRS assessment were included in the effectiveness population.

Centanafadine had a better safety profile and comparable effectiveness compared to atomoxetine hydrochloride

Figure 5. Comparative safety and effectiveness of centanafadine vs. atomoxetine hydrochloride at 26 weeks



For 100 adults treated with centanafadine vs atomoxetine hydrochloride by Week 26:

- **26 fewer people** had nausea
- **25 fewer people** had dry mouth
- **14 fewer people** had fatigue
- **11 fewer people** had headache
- **9 fewer people** had dizziness
- **6 fewer people** had decreased appetite
- **6 fewer people** had constipation
- **5 fewer people** had upper respiratory tract infection
- **5 fewer people** had irritability
- **4 fewer people** had somnolence
- There were **no statistically significant differences** for insomnia and diarrhea

There was **no statistically significant difference** in change from baseline in AISRS score between centanafadine and atomoxetine hydrochloride

[a]Analyses were matched on age, sex, race, baseline AISRS, baseline AISRS hyperactive-impulsive subscale, and baseline CGI-S.

[b]Comparisons were calculated in the safety population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine during the treatment period were included in the safety population. For atomoxetine hydrochloride, all subjects who received ≥ 1 dose of atomoxetine hydrochloride during the treatment period were included in the safety population.

[c]Comparisons were calculated in the effectiveness population. For centanafadine, all subjects who received ≥ 1 dose of centanafadine and had a baseline and ≥ 1 post-baseline AISRS total score were included in the effectiveness population. For atomoxetine hydrochloride, the efficacy population was not clearly defined, but it was assumed all subjects who received ≥ 1 dose of atomoxetine hydrochloride and had ≥ 1 post-randomized AISRS assessment were included in the efficacy population.

Conclusions

Centanafadine showed a better long-term safety profile than lisdexamfetamine dimesylate, methylphenidate, and atomoxetine hydrochloride, as evidenced by significantly lower incidence of several adverse events

Effectiveness of centanafadine was significantly lower than lisdexamfetamine dimesylate and non-different from methylphenidate and atomoxetine hydrochloride

Future studies should evaluate patients' and physicians' preferences regarding the safety and efficacy of ADHD treatments

Limitations

- Matching on baseline characteristics for this study was only possible when variables were collected across trials
- It was not possible to conduct an anchored MAIC to further adjust for cross-trial heterogeneity due to the lack of a common comparator (i.e., placebo group) across comparisons; an unanchored MAIC was conducted instead
- While ADHD-RS and AISRS are similar, differences may have occurred due to variation in wording and interpretation
- The target population of this analysis is more closely representative of the populations included in the lisdexamfetamine dimesylate, methylphenidate, and atomoxetine hydrochloride trials than of the population included in the centanafadine trials. Therefore, generalizability to a broader or different population may be limited

Acknowledgments

Medical writing assistance was provided by Flora Chik, PhD, an employee of Analysis Group, Inc.

References

1. A Trial Evaluating the Long-term Safety and Tolerability of Centanafadine Sustained-release Tablets in Adults With Attention-Deficit/Hyperactivity Disorder. 2002. https://clinicaltrials.gov/study/NCT03605849
2. Weisler R, et al. *CNS Spectr* 2009; 14(10): 573-85.
3. Adler LA, et al. *J Clin Psychopharmacol* 2011; 31(1): 108-14.
4. Adler LA, et al. *J Clin Psychopharmacol* 2009; 29(1): 44-50

Disclosures

This work was supported by Otsuka Pharmaceutical Development & Commercialization, Inc. JS is an employee of Otsuka Pharmaceutical Development & Commercialization Inc. MC, MGL, MC, CX, AQ, and FL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Otsuka Pharmaceutical Development & Commercialization, Inc. AC is an employee of the Center for Psychiatry and Behavioral Medicine.