

A Matching-Adjusted Indirect Comparison (MAIC) of Centanafadine versus Methylphenidate Hydrochloride in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD): Short-Term Safety and Efficacy Outcomes

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**Comparaison indirecte ajustée par appariement (MAIC)
entre centanafadine et le chlorhydrate de méthylphénidate chez les
adultes atteints d'un trouble déficitaire de l'attention avec ou sans
hyperactivité (TDAH) : Résultats en matière d'innocuité et
d'efficacité à court terme**

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Abstract

Objectives: To compare the short-term safety and efficacy of centanafadine, an investigational treatment, versus long-acting controlled-release methylphenidate hydrochloride (methylphenidate, *Foquest*®) among adult patients with attention-deficit/hyperactivity disorder (ADHD), using matching-adjusted indirect comparison (MAIC).

Methods: This anchored MAIC used pooled individual patient data (IPD) from two centanafadine trials (NCT03605680, NCT03605836) and published aggregate data from one methylphenidate trial (NCT02139124). Using propensity scores, IPD from the centanafadine trials were reweighted to match the aggregate baseline characteristics of the methylphenidate trial. Safety and efficacy outcomes were compared at Week 4. Safety outcomes were the rates of adverse events reported by ≥5% of patients in any treatment group in either trial with an incidence twice that of the placebo. The efficacy outcome was the mean change from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS)/ADHD Rating Scale-5 (ADHD-RS-5) score at Week 4.

Results: After matching, no significant differences in baseline characteristics were observed across trials. Relative to methylphenidate, centanafadine exhibited a better safety profile, with a significantly lower risk of insomnia (risk difference in percentage points: -9.46 points) and initial insomnia (-4.68 points). There was no significant difference in efficacy across treatments as measured by the mean change from baseline in AISRS/ADHD-RS-5 score.

Conclusions: In this MAIC, centanafadine was associated with a lower risk of insomnia and comparable (i.e., nondifferent) efficacy compared to methylphenidate at Week 4. Information on the comparative safety and efficacy of ADHD treatments in the adult population will help inform personalized treatment decisions given the range of treatment options with varying attributes.

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Abrégé

Objectifs: Comparer l'innocuité et l'efficacité à court terme de la centanafadine, un traitement expérimental, par rapport au chlorhydrate de méthylphénidate à libération contrôlée à action prolongée (méthylphénidate, Foquest®) chez des patients adultes atteints d'un trouble déficitaire de l'attention avec ou sans hyperactivité (TDAH), à l'aide de la comparaison indirecte ajustée par appariement (MAIC).

Méthodes: Cette MAIC ancrée a utilisé les données des patients regroupées provenant de deux essais cliniques sur la centanafadine (NCT03605680, NCT03605836) et des données agrégées publiées provenant d'un essai clinique sur le méthylphénidate (NCT02139124). En utilisant les scores de propension, les données des patients provenant des essais cliniques sur la centanafadine ont été repondérées pour correspondre aux caractéristiques de référence agrégées de l'essai sur le méthylphénidate. Les résultats en matière d'innocuité et d'efficacité ont été comparés à la semaine 4. Les résultats en matière d'innocuité étaient la proportion d'événements indésirables signalés par au moins 5% des patients de n'importe quel groupe de traitement dans l'un ou l'autre des essais cliniques, avec une incidence deux fois plus élevée que dans le groupe placebo. Le résultat en matière d'efficacité était la variation moyenne par rapport à la valeur de référence du score sur l'échelle d'évaluation des symptômes du TDAH chez les adultes (AISRS)/échelle d'évaluation du TDAH-5 (ADHD-RS-5) à la semaine 4.

Résultats: Après l'appariement, aucune différence significative dans les caractéristiques de référence n'a été observée entre les populations des essais cliniques. Par rapport au méthylphénidate, la centanafadine présentait un meilleur profil d'innocuité, avec un risque beaucoup plus faible d'insomnie (différence de risque en points de pourcentage : -9,46 points) et d'insomnie initiale (-4,68 points). Il n'y avait pas de différence significative d'efficacité entre les traitements, mesurée par la variation moyenne du score sur les échelles ASRS et DSM-5-TR par rapport au début de l'étude.

Conclusions: Dans cette MAIC, la centanafadine était associée à un risque plus faible d'insomnie et à une efficacité comparable (c.-à-d. non différente) par rapport au méthylphénidate à la semaine 4. Les renseignements sur l'innocuité et l'efficacité comparatives des traitements du TDAH chez l'adulte permettront de prendre des décisions de traitement personnalisées, compte tenu de la gamme d'options de traitement aux caractéristiques variées.

Keywords

attention deficit hyperactivity disorder, matching-adjusted indirect comparison, treatment outcome, adult, drug-related side effects and adverse reactions, insomnia, drug tolerance

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity.¹ Due to impairments in executive function, including focus, motivation, and emotional regulation,² individuals with ADHD may experience academic and occupational difficulties, challenges with interpersonal relationships, increased tendency toward risky behaviors (e.g., substance abuse), and reduced quality of life.³⁻⁵ Although ADHD is commonly detected in childhood,⁶ studies have shown that a substantial proportion of adults are affected by ADHD, with an estimated prevalence ranging between 2.7% and 7.3% in Canada.⁷

Pharmacologic treatment options for adults with ADHD include stimulant and nonstimulant medications.³ The Canadian ADHD Practice Guidelines, put forth by the Canadian ADHD Resource Alliance, recommend amphetamine (e.g., lisdexamfetamine dimesylate [Vyvanse®]) and methylphenidate-based stimulants (e.g., methylphenidate hydrochloride [methylphenidate, Foquest®]) as first-line therapy,³ given their high response rate (~70%–80%) and rapid onset in alleviating symptoms of ADHD.^{8,9} Nonstimulant medications (e.g., atomoxetine [Strattera®]) may be considered in second line for patients with side effects, who experience

suboptimal responses to first-line treatments, or when misuse is of concern.^{3,8} In Canada, methylphenidate-based medications are the most commonly prescribed class of pharmacological treatment for ADHD, representing about 65% of prescriptions.⁸ Among methylphenidate-based medications, long-acting controlled-release methylphenidate hydrochloride (PRC-063, Foquest®) is one of the more recently approved medications in Canada (2017) for adults with ADHD.^{10,11} Beyond existing treatments, the landscape of ADHD treatments continues to evolve and the introduction of novel therapies offers new options to meet individual patient needs. One such treatment is centanafadine, an investigational norepinephrine, dopamine, and serotonin reuptake inhibitor.¹² Centanafadine has demonstrated its safety and efficacy in adults with ADHD in two large short-term Phase 3, double-blind, placebo-controlled randomized trials and in one Phase 3 long-term open-label trial.^{12,13}

Attention-deficit/hyperactivity disorder treatment options differ in terms of safety and efficacy profiles. Given the broad and diverse patient population taking ADHD medications, personalized treatment selection requires the consideration of individual patient needs and preferences. Finding the optimal treatment through patient/physician shared decision-making involves an informed treatment plan discussion. To facilitate and encourage this process, comprehensive

and robust information on the comparative attributes of treatments is needed.

When direct evidence from head-to-head trials is unavailable, matching-adjusted indirect comparison (MAIC) analyses may be used to indirectly compare treatment outcomes while controlling for cross-trial differences in characteristics (e.g., age, sex, race, disease severity) that may otherwise confound comparisons.¹⁴ MAICs leverage individual patient data (IPD) from one trial and published aggregate data from another trial. Prior MAICs have compared the safety and efficacy of centanafadine with other ADHD treatments, including lisdexamfetamine dimesylate, atomoxetine, and viloxazine extended-release [ER], as well as the osmotic release oral system methylphenidate (OROS-MPH; methylphenidate hydrochloride ER, Concerta®).^{15,16} However, little is known about centanafadine compared to other methylphenidate-based treatments, despite their ubiquitous use in Canada. In this context, the present study aimed to provide comparative evidence on the short-term safety and efficacy of centanafadine versus methylphenidate.

Methods

Matching-Adjusted Indirect Comparison Design and Data Sources

An anchored MAIC was conducted to compare the safety and efficacy of centanafadine and methylphenidate while adjusting for cross-trial differences. This study used pooled IPD from two centanafadine sustained-release (SR) Phase 3 trials with identical study designs (NCT03605680 and NCT03605836)¹² and published aggregate data from one methylphenidate (PRC-063, Focquest®) Phase 3 trial (NCT02139124).¹⁷ When common comparators are available across trials, as in this case (i.e., placebo arms), anchored MAICs are preferred over unanchored MAICs as they further adjust for cross-trial heterogeneity by comparing treatment effects (i.e., the difference between active and control arms) across trials.

Trials and Sample Selection

Clinical trials that were most closely comparable to the centanafadine trials in terms of population, study design, and reported outcomes were identified through a systematic search in ClinicalTrials.gov and PubMed. Potential comparator trials were identified in September 2023 based on the following prespecified criteria: (1) Condition or disease: ADHD; (2) Interventions: Focquest / PRC-063 / Adhansia XR / methylphenidate hydrochloride; (3) Recruitment status: completed; (4) Eligibility criteria: adult (≥ 18 years of age), and (5) Study phase: Phase 3 or 4. This assessment yielded one potential comparator trial for methylphenidate. Details regarding the comparator trials considered, as well as reasons for exclusion, are reported in Supplemental Table S1.

The characteristics of the trials included in this analysis are summarized in Table 1. Selected studies included Phase 3,

randomized, double-blind, placebo-controlled, parallel-group trials, respectively, evaluating the safety and efficacy of centanafadine and methylphenidate among adult patients with ADHD. The centanafadine trials included a 6-week double-blind treatment period. A total of 906 adult patients were randomized in a 1:1:1 ratio to one of three groups to receive twice-daily centanafadine SR (200 or 400 mg/day), or a matching placebo; 714 (78.8%) patients completed the trials. The methylphenidate trial consisted of a 4-week double-blind treatment period, with 375 adults randomized in a 1:1:1:1:1 ratio to one of five groups to receive the once-daily ER formulation of methylphenidate (25, 45, 70, or 100 mg/day) or a matching placebo. Of the 375 patients, 333 (88.8%) completed the trial.

Based on each trial's respective eligibility criteria (Table 1), patients included in the MAIC analysis met the following criteria: (1) were aged ≥ 18 years; (2) had a confirmed diagnosis of ADHD as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (3) had moderate to severe ADHD at baseline; (4) had no comorbid psychiatric diagnoses, and (5) were not currently taking prohibited medication. Despite the centanafadine trial being restricted to adults aged 18–55 years, it was not possible to exclude from the analysis patients from the methylphenidate trial aged >55 years as only aggregate data were available for methylphenidate. Similarly, patients in the centanafadine trial were required to have an Adult ADHD Investigator Symptom Rating Scale (AISRS) score ≥ 28 at baseline. It was not possible to exclude from the analysis patients in the methylphenidate trial with ADHD Rating Scale (ADHD-RS) scores <28 as only aggregate data were available for methylphenidate. Both age and baseline AISRS/ADHD-RS-5 scores were included as matching variables to balance cohorts on these characteristics.

Each of the trials included in this MAIC had two analytical populations, an efficacy population and a safety population, which were, respectively, used for the safety and efficacy analyses.

Safety and Efficacy Outcome Measures

Safety and efficacy outcomes for centanafadine versus methylphenidate were compared at Week 4. Analyses were matched on age, sex, race, body mass index (BMI), ADHD combined subtype, and AISRS/ADHD-RS-5 score at baseline. The safety outcomes were the rates of adverse events (AEs) reported by $\geq 5\%$ of patients in any treatment group, in either trial, with an incidence rate at least double that of placebo. The efficacy outcome was the mean change from baseline in AISRS/ADHD-RS-5 score.

Statistical Analyses

Baseline characteristics were described and compared to identify differences between trial populations based on available published comparator trial information and IPD from

Table 1. Characteristics of Clinical Trials Included in the Analyses.

Trial characteristics	Centanafadine trials (NCT03605680 and NCT03605836)	Methylphenidate trial (NCT02139124)
Sample size	906 patients • 301 received 200 mg daily • 303 received 400 mg daily • 302 received placebo	375 patients • 77 received 25 mg daily • 73 received 45 mg daily • 73 received 70 mg daily • 74 received 100 mg daily • 78 received placebo
Trial date	• Start date: January 2019 • Primary completion date: April 2020 • Publication year: 2022	• Start date: April 2014 • Primary completion date: October 2014 • Publication year: 2021
Location	• 91 sites across the US	• 34 sites across the US and Canada
Treatment period	• 1 week (placebo) • 6 weeks (randomized treatment period)	• 1 week (washout) • 4 weeks (double-blind evaluation)
Key inclusion and exclusion criteria	• Aged 18–55 years • Confirmed diagnosis of ADHD per the DSM-5 criteria • Moderate to severe ADHD at baseline (AISRS score ≥ 28 and CGI-S score of ≥ 4) • No comorbid psychiatric diagnoses • Not currently taking prohibited medication including psychotropic medications	• Aged ≥ 18 years • Diagnosis of ADHD per the DSM-5 criteria; diagnoses were confirmed using the Conners' Adult ADHD Diagnostic Interview for DSM-IV • ADHD-RS-5 score ≥ 24 at post-washout baseline • IQ ≥ 80 on the Kaufman Brief Intelligence Test-2 • No comorbid psychiatric diagnoses that required treatment • No history or risk of cardiovascular disease • Not currently taking other psychotropic drugs, medications known to interact with methylphenidate or herbal remedies • No clinically significant laboratory abnormalities or current suicide risk

Note: ADHD = attention-deficit/hyperactivity disorder; AISRS = Adult ADHD Investigator Symptom Rating Scale; ADHD-RS-5 = ADHD Rating Scale-5; AE = adverse event; CGI-S = Clinical Global Impressions Scale – Severity; DSM = Diagnostic and Statistical Manual of Mental Disorders; IQ = intelligence quotient.

the centanafadine trials. Descriptive statistics comprised frequencies and proportions for categorical variables and means and standard deviations for continuous variables.

To adjust for cross-trial heterogeneity in baseline patient characteristics, a model using propensity score weighting was used to estimate the likelihood (i.e., propensity) of enrollment in the methylphenidate trial for each patient in the centanafadine trials. Propensity was estimated through logistic regression using all available baseline characteristics reported across trials (effect modifiers and prognostic factors), and included age, sex, race, BMI, ADHD combined subtype, and AISRS/ADHD-RS-5 at baseline. Patient-level data from the centanafadine trials were then reweighted to match the aggregate baseline characteristics (i.e., means and standard deviations for continuous variables, proportions for categorical variables) reported in the methylphenidate trial. Safety and efficacy outcomes were compared between trials before and after matching. For the safety analyses, the risk difference between centanafadine and methylphenidate was reported for each AE. For the efficacy analyses, the difference in change from baseline in AISRS/ADHD-RS scores between centanafadine and methylphenidate was reported. Weighted Wald tests (i.e., chi-square tests for categorical

variables and z tests for continuous variables) and confidence intervals (CIs) were reported for each outcome.

Results

Baseline Characteristics

In the safety analyses, a total of 876 patients were included from the centanafadine trials (centanafadine: $n = 586$; placebo: $n = 290$) and 375 patients from the methylphenidate trial (methylphenidate: $n = 297$; placebo: $n = 78$). In the efficacy analyses, a total of 859 patients were included from the centanafadine trials (centanafadine: $n = 574$; placebo: $n = 285$) and 375 patients from the methylphenidate trial (methylphenidate: $n = 297$; placebo: $n = 78$) (Table 2).

Before matching, there were differences in baseline characteristics across trials. In the safety population, there was a lower proportion of White patients in the centanafadine treatment arm than in the methylphenidate treatment arm. In both the safety and efficacy populations, baseline BMI (kg/m^2) was lower in the centanafadine placebo arm than in the methylphenidate placebo arm. Additionally, patients from both treatment arms and placebo arms had more severe ADHD

Table 2. Baseline Characteristics of Patients in the Centanafadine versus Methylphenidate Analyses.¹

Baseline characteristics Safety analysis population ^a	Comparator trial		Before matching			After matching		
	Methylphenidate [A] n = 297	Placebo [B] n = 78	Centanafadine trials ^c		P value	Centanafadine trials ^c		P value
			Centanafadine [C] n = 586	Placebo [D] n = 290		Centanafadine [E] n = 586	Placebo [F] n = 290	
Age (years), mean ± SD	35.7 ± 11.8	37.4 ± 12.4	35.5 ± 10.0	35.3 ± 9.6	0.84	35.7 ± 11.8	37.4 ± 12.4	—
Sex (%)								
Male	142 (47.8%)	35 (44.9%)	301 (51.4%)	153 (52.8%)	0.35	47.8%	44.9%	—
Race (%)								
White	253 (85.2%)	64 (82.1%)	464 (79.2%)	236 (81.4%)	0.04*	>0.99	82.1%	—
BMI (kg/m ²), mean ± SD	28.6 ± 6.5	29.6 ± 8.7	28.1 ± 5.3	27.5 ± 5.3	0.22	0.04*	28.6 ± 6.5	—
ADHD subtype, n (%)								
Inattentive	72 (24.2%)	22 (28.2%)	111 (18.9%)	72 (24.8%)	0.08	0.65	23.6%	0.87
Hyperactive-impulsive	3 (1.0%)	2 (2.6%)	7 (1.2%)	8 (2.8%)	>0.99	>0.99	1.7%	0.49
Combined	222 (74.7%)	54 (69.2%)	468 (79.9%)	210 (72.4%)	0.10	0.68	74.7%	—
AISRS/ADHD-RS at baseline, mean ± SD	36.3 ± 7.7	35.7 ± 8.4	38.9 ± 6.8	38.6 ± 6.9	<0.001*	0.005*	36.3 ± 7.7	—
Efficacy analysis population ^b	Methylphenidate [A] n = 297	Placebo [B] n = 78	Centanafadine [C] n = 574	Placebo [D] n = 285	[A] vs [C]	[B] vs [D]	Centanafadine [E] n = 574	Placebo [F] n = 285
Age (years), mean ± SD	35.7 ± 11.8	37.4 ± 12.4	35.6 ± 10.0	35.2 ± 9.7	0.86	0.15	35.7 ± 11.8	37.4 ± 12.4
Sex (%)								
Male	142 (47.8%)	35 (44.9%)	295 (51.4%)	148 (51.9%)	0.35	0.33	47.8%	44.9%
Race (%)								
White	253 (85.2%)	64 (82.1%)	457 (79.6%)	233 (81.8%)	0.06	>0.99	85.2%	82.1%
BMI (kg/m ²), mean ± SD	28.6 ± 6.5	29.6 ± 8.7	28.1 ± 5.2	27.5 ± 5.3	0.26	0.04*	28.6 ± 6.5	29.6 ± 8.7
ADHD subtype, n (%)								
Inattentive	72 (24.2%)	22 (28.2%)	109 (19.0%)	72 (25.3%)	0.09	0.70	23.6%	29.2%
Hyperactive-impulsive	3 (1.0%)	2 (2.6%)	7 (1.2%)	8 (2.8%)	>0.99	>0.99	1.7%	1.6%
Combined	222 (74.7%)	54 (69.2%)	458 (79.8%)	205 (71.9%)	0.11	0.75	74.7%	69.2%
AISRS/ADHD-RS at baseline, mean ± SD	36.3 ± 7.7	35.7 ± 8.4	38.9 ± 6.8	38.6 ± 6.8	<0.001*	0.005*	36.3 ± 7.7	35.7 ± 8.4

Note: ADHD = attention-deficit/hyperactivity disorder; AISRS/ADHD-RS = Adult ADHD Investigator Symptom Rating Scale/ADHD Rating Scale; BMI = body mass index.

*Significant at the 5% level.

^aFor centanafadine, all randomized subjects who received ≥ 1 dose of centanafadine or placebo during the double-blind treatment period were included in the safety analysis. For methylphenidate, all randomized subjects who received ≥ 1 dose of methylphenidate or placebo were included in the safety analysis.

^bFor centanafadine, all randomized subjects who received ≥ 1 dose of centanafadine or placebo and had a baseline and ≥ 1 post-randomization AISRS assessment in the double-blind treatment period were included in the efficacy analysis. For methylphenidate, all randomized subjects who received ≥ 1 dose of methylphenidate or placebo and had an ADHD-RS-5 assessment during the 2-week stable dose period were included in the efficacy analysis.

^cAnalyses were matched on age, sex, race, BMI, ADHD combined subtype, and AISRS/ADHD-RS-5 at baseline. The AISRS/ADHD-RS-5 instruments contain the same number of questions (18 items), review the same symptoms, and are scored in the same way; these two instruments were considered interchangeable. Higher scores indicate more severe ADHD symptoms.

at baseline in the centanafadine trials relative to those in the methylphenidate trial. After matching, there were no significant differences in baseline characteristics across trials in either population.

Safety and Efficacy

After matching, compared to methylphenidate at Week 4, centanafadine was associated with a significantly lower risk of insomnia (risk difference [in percentage points]: -9.46 points; CI: -15.60 , -3.33 ; $P=0.003$) and initial insomnia (-4.68 points; CI: -8.38 , -0.99 ; $P=0.01$) (Figure 1). Meanwhile, there were no statistically significant differences in the risk of dry mouth (-6.96 points; CI: -19.55 , 5.63 ; $P=0.28$), decreased appetite (-2.87 points; CI: -9.00 , 3.26 ; $P=0.36$), and nausea (-1.12 points; CI: -8.13 , 5.88 ; $P=0.75$).

In the efficacy analysis, the difference in change of AISRS/ADHD-RS score from baseline between centanafadine and methylphenidate was not significant (1.59 points, CI: -3.55 , 6.72 ; $P=0.55$; Figure 1). The arm-by-arm safety and efficacy outcomes before and after matching are presented in Figure 2.

Discussion

Using anchored MAIC to adjust for cross-trial heterogeneity in patient populations, this study compared short-term treatment outcomes of centanafadine, an investigational treatment for ADHD, and methylphenidate, a common treatment option for ADHD in Canada. The findings suggest that centanafadine may have a better safety profile and similar (i.e., nondifferent) efficacy compared to methylphenidate. In particular, there was a significantly lower risk of insomnia and initial insomnia with centanafadine versus methylphenidate (Figure 1). Specifically, for every 100 adults receiving treatment for ADHD, nine fewer adults would experience insomnia, and five fewer adults would experience initial insomnia by Week 4 if treated with centanafadine versus methylphenidate (Supplemental Figure S1).

These results are consistent with a recent MAIC comparing centanafadine to OROS-MPH, another methylphenidate-based treatment. In that study, centanafadine exhibited a better safety profile than OROS-MPH, with a significantly lower incidence of dry mouth, decreased appetite, initial insomnia, anxiety, palpitations, and feeling jittery.¹⁶ Similarly, other recent MAICs comparing centanafadine with lisdexamfetamine dimesylate, atomoxetine, and viloxazine ER found significantly lower incidence of lack of appetite, dry mouth, insomnia, anxiety, nausea, feeling jittery, and diarrhea with centanafadine.¹⁵

The lower rates of insomnia and initial insomnia observed with centanafadine in this study and in prior MAICs may have noteworthy implications for adults with ADHD. Indeed, insomnia has been shown to have a substantial effect on a patient's daily life.¹⁸ A systematic review found

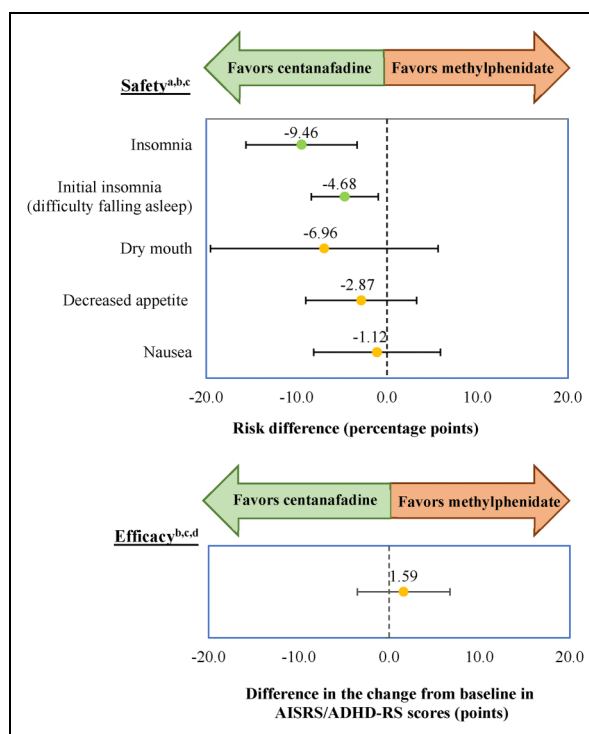


Figure 1. Comparisons of safety and efficacy between centanafadine and methylphenidate at Week 4.

Note. ADHD = attention-deficit/hyperactivity disorder; AISRS/ADHD-RS = Adult ADHD Investigator Symptom Rating Scale/ADHD Rating Scale; BMI = body mass index.

^aAdverse events for which information was available in both trials, and which were reported by $\geq 5\%$ of patients in any treatment group with an incidence twice that of placebo at Week 4.

^bAnalyses were matched on age, sex, race, BMI, ADHD combined subtype, and AISRS/ADHD-RS-5 at baseline.

^cData from the centanafadine trials were pooled across intervention arms.

^dEfficacy was compared at Week 4. The primary efficacy outcome instrument used in the methylphenidate trial was the ADHD-RS-5. Since this instrument contains the same number of questions (18 items), reviews the same symptoms, and is scored in the same way as the AISRS, these two instruments were considered interchangeable. Higher scores indicate more severe ADHD symptoms.

that insomnia was associated with reduced work performance, physical and mental health, social functioning, and quality of life.¹⁸ Similarly, a recent survey of more than 500 adult patients with ADHD reported insomnia in nearly half of patients receiving ADHD treatment. Insomnia negatively affected the overall well-being of these patients, who commonly reported difficulties with daily activities, interpersonal relationships, obtaining and/or maintaining a job, and their concentration and productivity in the workplace.¹⁹ The burden of insomnia highlights the importance of informed decision-making in treatment selection. A medication less likely to cause insomnia may help alleviate the patient's treatment burden. The current MAIC focuses on

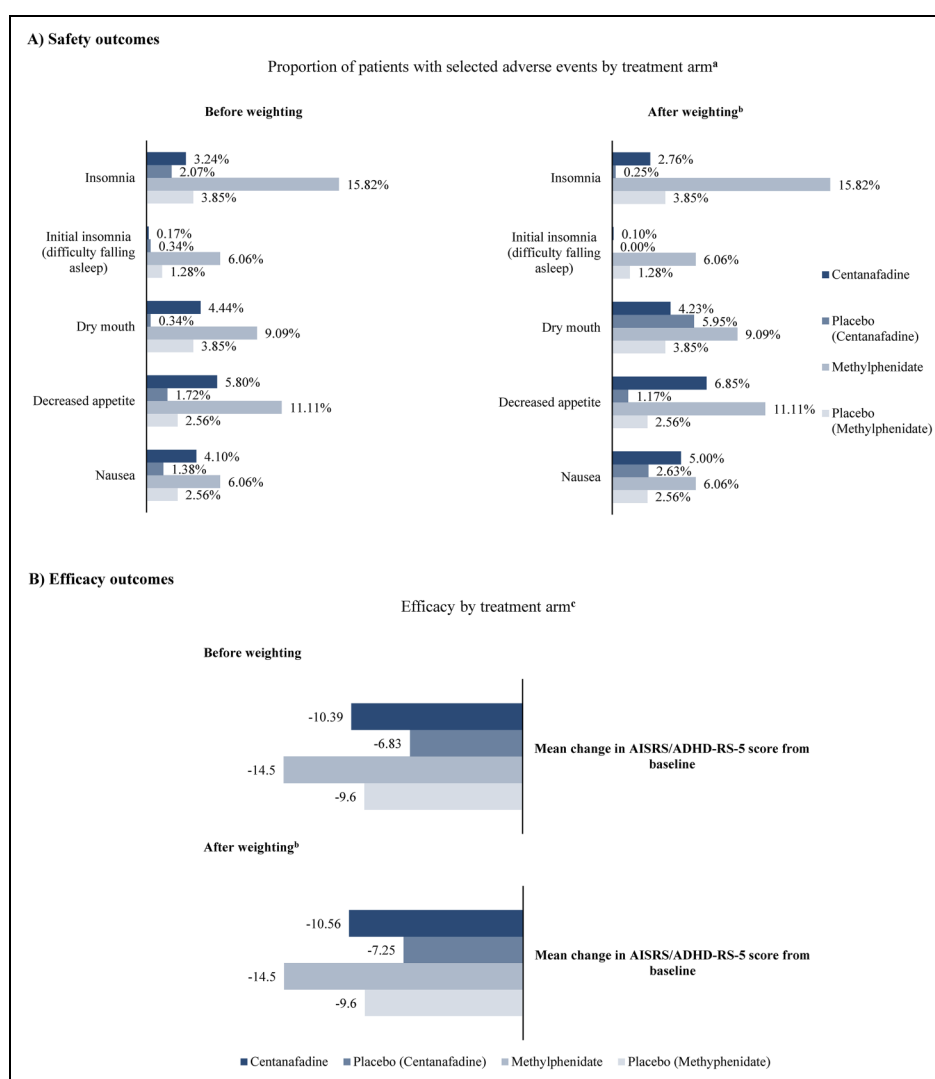


Figure 2. Arm-by-arm outcomes before and after matching: centanafadine versus methylphenidate at Week 4. A) Safety outcomes B) Efficacy outcomes.

Note. ADHD = attention-deficit/hyperactivity disorder; AISRS/ADHD-RS-5 = Adult ADHD Investigator Symptom Rating Scale/ADHD Rating Scale-5; BMI = body mass index.

^aThe proportion of adverse events was calculated at Week 4 in the safety analysis population. For centanafadine, all randomized subjects who received ≥ 1 dose of centanafadine or placebo during the double-blind treatment period were included in the safety analysis. For methylphenidate, all randomized subjects who received ≥ 1 dose of methylphenidate or placebo were included in the safety analysis.

^bAnalyses were matched on age, sex, race, BMI, ADHD combined subtype, and AISRS/ADHD-RS-5 at baseline. The AISRS/ADHD-RS-5 instruments contain the same number of questions (18 items), review the same symptoms, and are scored in the same way; these two instruments were considered interchangeable. Higher scores indicate more severe ADHD symptoms.

^cThe efficacy outcome was calculated at Week 4 in the efficacy analysis population. For centanafadine, all randomized subjects who received ≥ 1 dose of centanafadine or placebo and had a baseline and ≥ 1 post-randomization AISRS/ADHD-RS assessment in the double-blind treatment period were included in the efficacy analysis. For methylphenidate, all randomized subjects who received ≥ 1 dose of methylphenidate or placebo and had an ADHD-RS-5 assessment during the 2-week stable dose period were included in the efficacy analysis.

short-term outcomes, and future research should investigate differences in outcomes between centanafadine and methylphenidate in the long term.

With respect to efficacy, stimulant medications, such as methylphenidate, may be favored in short-term clinical trials as they typically have a more rapid onset of action

and reach their maximum therapeutic effect faster than medications with an alternate mechanism of action.⁹ In this study, the efficacy between centanafadine and methylphenidate was nondifferent at Week 4. Although the efficacy outcome of centanafadine was available in the IPD up to Week 6, efficacy could only be compared at Week 4 due to the length

of the comparator trial. It is worth noting that additional efficacy gains were observed with centanafadine from Week 4 to Week 6.¹² Future research is warranted to assess the comparative efficacy of centanafadine to methylphenidate in the longer term as long-term trials and real-world data emerge. Nevertheless, considering the absence of significant differences in efficacy observed between the two treatments in this study, centanafadine may be an option for adults with ADHD with concerns about insomnia.

Selecting a treatment for ADHD that best addresses the patient's needs, preferences, and lifestyle can be challenging for physicians and patients alike. Highlighting this difficulty, two Canadian studies using discrete choice experiments identified a disconnect between patient and physician preferences for ADHD treatment attributes.^{20,21} Among physicians, efficacy had a greater relative importance than all safety attributes considered in the study and was the single most important attribute when making treatment decisions.²¹ Conversely, patients considered safety, especially insomnia, to have greater relative importance than efficacy.²⁰ In addition, patients were willing to trade off efficacy for a lower risk of treatment-related AEs.²⁰ Specifically, the willingness-to-trade-off was high for insomnia, particularly among currently untreated but previously treated patients.²⁰ Taken together, these studies denote the importance of taking into consideration AEs when selecting a treatment, particularly as the experience of undesired AEs may lead to reduced treatment adherence. Indeed, a systematic review examining ADHD medication usage found AEs were the most commonly cited reason for discontinuation, followed by ineffectiveness and suboptimal response.²² Furthermore, a previous study investigating ADHD treatment-related symptoms reported that the vast majority of patients taking ADHD medication experienced at least one symptom associated with ADHD/treatment-related adverse side effects in the previous month, with patients experiencing nearly six symptoms on average.¹⁹ Therefore, treatment options with a better safety profile may lead to greater treatment satisfaction, adherence, and outcomes. Studies such as this one, which provides robust information on the comparative safety and efficacy of treatment options, may help reduce the disconnect between patients and physicians in treating ADHD by facilitating shared medical decision-making and optimizing individualized treatment choices.

Overall, the findings of this study are consistent with previous MAICs and suggest that centanafadine may be a treatment option of interest for patients and physicians seeking a medication with a favorable safety profile, particularly with respect to insomnia.

Limitations

The findings of this study should be considered within the context of some limitations. First, matching was only possible for the baseline characteristics available across trials;

therefore, additional unobserved differences in baseline characteristics, such as comorbidities, concomitant medications, and prior ADHD treatment history may exist. Despite overall consistent inclusion and exclusion criteria across trials, some cross-trial differences related to study design or specific definitions could not be accounted for (e.g., minimum IQ [intelligence quotient] requirements). Regarding inclusion criteria, in instances when the methylphenidate trial was more inclusive than the centanafadine trial, patients from the methylphenidate trial could not be excluded because patient-level data were only available for centanafadine. Specifically, the methylphenidate trial included patients aged 18 years and older, while the centanafadine trial included patients 18 to 55 years of age. Similarly, the methylphenidate trial included patients with a baseline ADHD-RS-5 score ≥ 24 , while the centanafadine trial included patients with a baseline AISRS score ≥ 28 . To mitigate the effect of these differences in population overlap, age and AISRS/ADHD-RS-5 scores at baseline were included as matching variables. Pertaining to efficacy, although both trials used similar instruments, notably, ADHD-RS (for the methylphenidate trial) and AISRS (for centanafadine trials), variations in wording and interpretation could have resulted in differences in measurements. With regard to safety, reasons for treatment discontinuation were not available. Lastly, given that reweighting approaches used patient-level data available for one trial (i.e., centanafadine) to match aggregated characteristics reported by a published trial (i.e., methylphenidate), the studied sample of this analysis is more representative of the population included in the methylphenidate trial. Thus, the generalizability of these findings to a broader or different population may be limited.

Other differences in trial design are noteworthy. The centanafadine trial began with a 1-week single-blind placebo run-in phase, whereby patients with an Adult ADHD Self-report Symptom Checklist score improvement $\geq 30\%$ post-versus pre-run-in phase were not eligible to participate in the trial. This practice was meant to limit the placebo effect, such as to increase the sensitivity to detect a treatment effect, should one exist. Overall, 24.1% of patients who entered the single-blind run-in phase were not included in the double-blind treatment periods. At Week 6, patients receiving placebo reported a 17.7% improvement in AISRS total score in study 1 (NCT03605680) and 21.4% improvement in study 2 (NCT03605836). As noted in Adler (2022), while direct comparison of placebo arms across studies of different medications is not possible without adjustments, other randomized control trials without run-in periods report placebo response rates in similar ranges. No run-in phase was conducted in the methylphenidate trial; a placebo response rate of 27.5% improvement from baseline was reported. Authors from the methylphenidate publication note the high response rate may be an unintended effect of therapeutic interactions with study staff. In addition, the conclusions of this study were based on the dosages used in the clinical trials, which

may influence the observed outcomes. Moreover, safety outcomes in the methylphenidate trials were reported only in aggregate, without differentiation by dosage. As a result, subgroup analyses by dosage could not be conducted. Furthermore, it is acknowledged that the distribution of dosages in real-world settings may differ from those used in the trials, which could potentially impact the generalizability of the findings. In the absence of head-to-head trials, the MAIC approach allows for comparative safety and efficacy results, while controlling for as much trial heterogeneity as possible.

Conclusions

In this comparative analysis among adult patients with ADHD, centanafadine was associated with a significantly lower incidence for insomnia and initial insomnia than methylphenidate at Week 4 while having similar efficacy. These results suggest that centanafadine may be a promising pharmacotherapeutic option for adults with ADHD who have concerns pertaining to insomnia. Future studies comparing long-term safety and efficacy outcomes of centanafadine to methylphenidate are warranted as long-term trial and real-world data become available.

Disclosures

Data Access

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms agreed upon their receipt. Data for the centanafadine trial were provided by the trial sponsor, Otsuka Pharmaceutical Development & Commercialization, Inc. Data for the comparator trials were publicly available on the ClinicalTrials.gov website and the respective trial publications cited in this manuscript.

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Supplemental Material

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