Original Research

Solriamfetol for Attention-Deficit/Hyperactivity Disorder in Adults:

A Double-Blind Placebo-Controlled Pilot Study

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Abstract

Objective: Some individuals with attention-deficit/hyperactivity disorder (ADHD) may not tolerate or adequately respond to currently available treatments. This study examined whether solriamfetol could have a favorable pattern of effects and tolerability as a treatment for ADHD in adults.

Methods: Sixty adults with *DSM-5* ADHD participated from August 2021 through January 2023 in a remotely conducted, randomized, double-blind, placebo-controlled, 6-week dose-optimization trial of 75 mg or 150 mg of solriamfetol. Measures included the Adult ADHD Investigator Symptom Rating Scale (AISRS), which was our primary outcome measure, as well as the Clinical Global Impressions scale (CGI), vital signs, the Global Assessment of Functioning (GAF), the Behavior Rating Inventory of Executive Function-Adult Form (BRIEF-A), the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and a modified Adult ADHD Self-Report Scale (MASRS).

Results: Solriamfetol was well tolerated, with no significant effect on mean heart rate (+3.7 vs +2.2 bpm, $P=.5609$), systolic blood pressure (+2.4 vs +1.5 mm Hg, $P=.6474$), or diastolic blood pressure (+1.1 vs +1.5 mm Hg, $P=.8117$). There was no statistically significant treatment effect on occurrence of adverse events. Compared to individuals on placebo, individuals on solriamfetol treatment experienced adverse events at a rate of at least 10 percentage points higher in the categories of decreased appetite, headache, gastrointestinal, insomnia, increased energy, cardiovascular, and neurologic. Compared to individuals on placebo, by study endpoint, a greater proportion of individuals in the treatment group met the a priori–defined treatment response (CGI score indicating much or very much improved and AISRS score reduced ≥ 25%: 45% vs 6.9%, $P=.0020$); those treated with solriamfetol also had greater improvement in total AISRS scores by week 3 through week 6 ($P=.0012$; week 6 effect size = 1.09). Significantly more solriamfetol-treated adults than placebo-treated adults had 0.5–standard deviation improvement in T-score on the BRIEF-A Global Executive Composite ($P=.0173$); those treated with solriamfetol also had greater mean change in GAF score (−4.8 vs −0.3, $P=.0006$) and greater mean MASRS total score change ($P=.0047$; effect size = 1.23). Mean ESS score improved more with solriamfetol than with placebo ($P=.0056$), but this difference did not predict AISRS response ($P=.3735$). There was no significant association between solriamfetol and change in PSQI scores.

Conclusions: Solriamfetol may be a novel and effective treatment for the management of ADHD in adults. Further replication in larger trials is indicated.

Trial Registration: ClinicalTrials.gov identifier: NCT04839562

J Clin Psychiatry 2023;84(6):23m14934

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Attention-deficit/hyperactivity disorder (ADHD) is a neurobiological disorder associated with high levels of impairment in adulthood and is estimated to affect 2.5%–4.4% of adults.[1–4] Sympathomimetic agents including atomoxetine, viloxazine, guanfacine extended release (ER), and forms of methylphenidate and amphetamine salts have been approved by the US Food and Drug Administration (FDA) for ADHD. While these provide important treatment options, in some they are poorly tolerated, ineffective, or partially effective. Pharmacologically treated patients may also have residual executive function deficits.[5] For example, in a study of robust open-label dosing with lisdexamfetamine,[6] 40% of adults with ADHD were considered to have unresolved and clinically significant impairment in essential elements of executive behavior. Therefore, there is significant need for new ADHD interventions.

Solriamfetol, which the FDA has approved for treatment of excessive daytime sleepiness in patients with narcolepsy or obstructive sleep apnea,[7] is a dopamine

Clinical Points

- Some adults with attention-deficit/hyperactivity disorder (ADHD) experience inadequate benefit or intolerable response to currently available, US Food and Drug Administration–approved treatments for ADHD.
- In this pilot study, solriamfetol, a dopamine and norepinephrine reuptake inhibitor, was dose-optimized to 75 mg or 150 mg. This regimen was well tolerated and significantly improved ADHD symptoms and clinical impression of ADHD severity in adults compared with placebo.
- These results support solriamfetol as a viable treatment for ADHD in adults and merit replication in further research.

and norepinephrine reuptake inhibitor, thus sharing sympathomimetic properties present in agents that treat ADHD. In registration trials, solriamfetol was associated with significant improvement over placebo in maintenance of wakefulness test performance and self-reported sleepiness in individuals with narcolepsy and obstructive sleep apnea, with benefits identifiable at week 1. Solriamfetol was well tolerated in clinical trials, and the drug label reports the following adverse events occurring at a rate of 5% or higher and more often than with placebo in 12-week placebo-controlled trials in which subjects received between 37.5 mg and 150 mg: headache, nausea, decreased appetite, anxiety, and insomnia. In these trials, adverse events causing discontinuation in more than 1 treated patient and at a higher rate than placebo were anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).[7] If solriamfetol has a meaningful effect size for ADHD symptoms, it may be an important treatment to develop. We therefore conducted a double-blind pilot study enrolling 60 adults with ADHD. To explore clinical utility for ADHD within FDA-approved doses for sleep indications, we chose a dose-optimization protocol with a duration of 6 weeks.

We hypothesized that, compared to placebo, solriamfetol exposure would be well tolerated and would also be associated with greater reduction of ADHD symptoms as rated on our primary outcome measure, the Adult ADHD Investigator Symptom Rating Scale (AISRS). We secondarily expected individuals on solriamfetol treatment to have a higher rate of achieving our a priori definition of clinical improvement: at least 25% reduction in ADHD symptoms and a Clinical Global Impressions scale (CGI) rating of much or very much improved. We chose a threshold of 25% reduction in AISRS score as meaningful to evaluate because prior work has shown that a change in CGI-Improvement score of at least 1 level required at least this much change in the score on a similar clinical interview scale, the ADHD Rating Scale-IV (ADHD-RS-IV).[8] Secondarily, we wished to understand the impact of solriamfetol on executive dysfunction, sleepiness, and sleep patterns in adults with ADHD and whether change in sleepiness moderated ADHD outcomes. We designed the study as a remotely conducted, virtual visit–based clinical trial to improve accessibility of participation and reduce subject burden.

METHODS

The Mass General Brigham Human Research Committee approved this study, which was conducted remotely using privacy law–compliant virtual visits. The ClinicalTrials.gov identification number of the study is NCT04839562. Informed consent was documented for all participants. Online advertisements and word of mouth ascertained participants for screening surveys and phone interviews utilizing the Adult ADHD Self-Report Scale (ASRS) v1.1 screener.[9] Participants were not paid but were offered clinical treatment for two post-study sessions. We included individuals who were at least 18 years old and younger than 65 years old. Participants enrolled and participated from August 2021 through January 2023. The principal investigator, a board-certified psychiatrist trained in neuropsychiatry and an expert administrator of the AISRS,[10] determined eligibility by a systematic virtual visit interview that included administration of the AISRS and review of current and past mental health symptoms. This systematic interview, which explored presence of symptom criteria for all major *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) mental health conditions, was supplemented by review of self-reported symptom patterns on the Adult Self-Report (ASR)[11] to increase the chance of identifying exclusionary comorbid conditions. Participants met *DSM-5*[12] criteria for ADHD and had an AISRS score of at least 20.

We excluded individuals with any of the following attributes: solriamfetol intolerance, conditions that obscured determination of an ADHD diagnosis, renal insufficiency/impairment, pregnancy, currently nursing an infant, unwillingness to use a reliable contraceptive method or methods during the trial, or cancer in the last 5 years. We excluded individuals with major unstable medical illness. We also excluded specific conditions that a sympathomimetic agent might exacerbate: current or past psychotic or bipolar disorder, current affective or anxiety disorder with more than mild symptoms, untreated hypertension (> 140/90 mm Hg), narrow-angle glaucoma, drug abuse, or drug dependence (other than to nicotine). We excluded FDA-approved ADHD treatments and catecholaminergic medications, such as duloxetine, venlafaxine, and bupropion, during the study for 5 half-lives prior to study participation, or longer if needed to assess eligibility. Less than twice-a-week use of benzodiazepines or sedative-hypnotics was allowed.

Subjects were randomized in double-blind fashion to solriamfetol 75 mg or placebo capsules and instructed to take doses in the morning. Over 6 weekly (defined as 7 ± 3 days) visits, safety and effectiveness measures were obtained. All subjects took 1 capsule in the morning between baseline and the following visit a week later. At each subsequent visit, the study investigator reviewed the following variables to determine dosing recommendations: change in blood pressure and heart rate, spontaneously reported adverse events, the amount of improvement on the AISRS rating scale, and CGI-Improvement scores. If the study agent was well tolerated, subjects were instructed to increase to 2 capsules in the morning at this first post-baseline weekly visit. At this first weekly visit, if there were adverse experiences greater than mild in severity and possibly or probably attributable to the study agent, participants were asked to remain on 1 capsule for the next week. At subsequent visits, if an individual had been held at 1 capsule in the prior week and was tolerating it well, the dose was increased to 2 capsules. Dose could also be dropped from 2 capsules to 1 capsule at any of the study visits if doing so might improve tolerability. If a subject was on 1 capsule and rated with a CGI rating of very much improved, and had nearly no ADHD symptoms on the AISRS, they were given the option of staying on 1 capsule for the next week of the study. The investigator also prioritized a goal of stable dosing for the last 4 weeks of the study, but only if a subject was tolerating the dose well. Subjects were never told to take more than 2 capsules. Data were collected from August 2021 to January 2023. Subjects were trained to operate an OMRON model 7200 automatic blood pressure cuff (OMRON Healthcare, Inc) and took readings at screening and twice at each study visit. Women with childbearing potential had urine pregnancy tests at baseline and endpoint.

Weekly assessments included our primary outcome, the AISRS[10]; Global Assessment of Functioning (GAF)[13]; CGI for ADHD[14]; and spontaneous adverse experience reports. Subjects completed the following baseline and endpoint self-ratings: the 18-item ASRS[9] with item order modified (MASRS) to alternate between inattentive and impulsive-hyperactive items, the Behavior Rating Inventory of Executive Function–Adult Form (BRIEF-A),[15] the Pittsburgh Sleep Quality Index (PSQI),[16] and the Epworth Sleepiness Scale (ESS).[17] The ASRS has been validated as having high internal consistency and high concurrent validity with a rater-administered ADHD symptom interview, the ADHD-RS, which is similar to the AISRS. In this validation, the item order of the ASRS used an alternating pattern of inattentive and impulsive hyperactive items,[18] so we deployed this format; we highlight this small difference by using the label *MASRS*. Pill counts were conducted visually by staff at weeks 2, 4, and 6 and upon return of pill bottles.

Statistical Analysis

AISRS total score data at each study visit were analyzed by a linear mixed-effects regression model comparing mean scores, with fixed effects for treatment group, study visit number (as a 7-level categorical variable), and a group-by-visit number interaction as well as a random patient effect. Maximum likelihood estimation obtained unbiased estimates of the weekly missing data differences. Differences between groups were similarly modeled with a 2-level fixed effect between study visits 0 and 6 for the following: AISRS total and subscale scores, GAF score, MASRS total score, BRIEF-A index and subscale T-scores, PSQI total and subscale scores, ESS score, and cardiovascular measures. Fisher exact test was used to evaluate the following: proportions of patients with ≥ 25% and ≥ 50% improvement on the AISRS; week 6 AISRS total scores ≤ 18 and ≤ 12; CGI "much improved" or "very much improved" week 6 ratings; either of these latter CGI ratings at week 6 with ≥ 25% improved AISRS scores; adverse event (AE) patterns including in any category, moderate or severe AE in a category, and repeated AEs in a category; and a 0.5–standard deviation reduction in BRIEF-A index/subscale scores and the rate of improvement in BRIEF-A index/subscale scores. Proportions of poor sleep quality (PSQI total score > 5) and excessive daytime sleepiness (ESS score ≥ 11) were evaluated at baseline and endpoint. Effect size for AISRS, MASRS, and BRIEF-A scores was estimated as the difference between the treatment groups in the mean change between baseline and week 6, divided by the standard deviation of the baseline scores.[19] Patients were counted in each AE category for which they ever reported an AE and included in the severity category corresponding to the highest severity reported. Cardiovascular analyses were based on a mean of the 2 weekly vital sign measurements and included all early drop participant data.

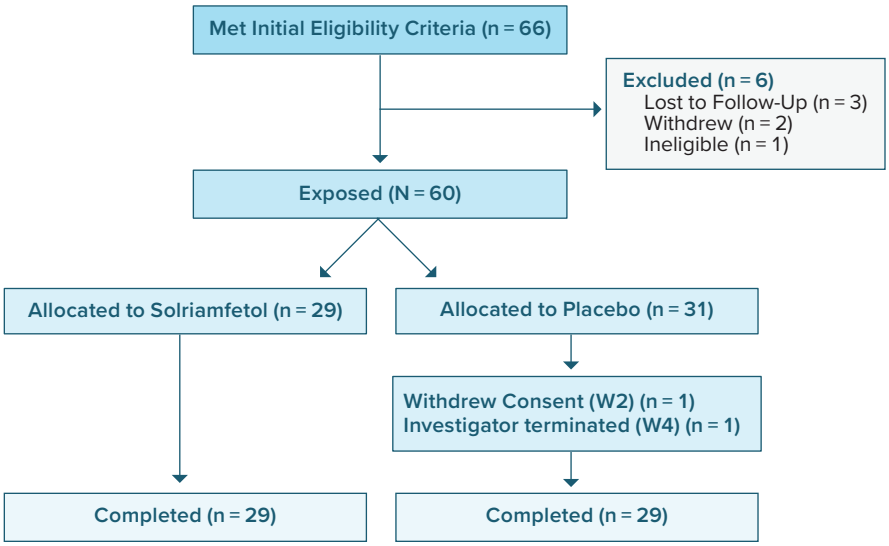
Analysis was performed using SAS v9.4.[20] The 2-sided significance level was .05 for all analyses, without adjustment for multiple comparisons given the preliminary nature of this pilot study.

RESULTS

Of 60 participants, 1 individual on placebo dropped out of the trial at week 2 by personal preference; another individual on placebo deviated from protocol by taking a stimulant medication during the fourth week, and the investigator asked them to end study participation. Figure 1 shows the flow of participants through the study.

Four of the patients on active solriamfetol treatment were known to have dosing patterns other than 75 mg for the first week and 150 mg thereafter, while all subjects on placebo increased to 150 mg at week 1. We describe here the dosing patterns of these 4 subjects on treatment with active agent: blood pressure readings and concurrent illness delayed increase to 150 mg to

Figure 1.
Flow of Participants Through the Study



Abbreviation: W = week.

week 4; another returned to 75 mg after receiving 150 mg for 1 week because of end of day irritability by visit 2 on 150 mg; another delayed increase to 150 mg at week 2 for no attributable reason; and another subject experienced insomnia while on 150 mg between week 1 and week 2 and preferred to stay at 75 mg daily as they were experiencing meaningful benefit. In addition, evaluating pill counts suggested that 4 subjects on active treatment and 4 on placebo were likely to have missed more than few days of exposure during any study week.

Demographic and Baseline Characteristics

Table 1 presents demographic characteristics of study participants. The participants randomized to placebo, compared to those on solriamfetol, had a higher (by 15 percentage points) rate of being White/Caucasian, a higher (by 17 percentage points) rate of receiving education at the bachelor or nursing degree level, and a higher mean income (by 21 percentage points). More women than men were exposed to solriamfetol. Concomitant psychopharmacology at baseline included zolpidem, citalopram, escitalopram, gabapentin, alprazolam (1 participant each), trazodone (2 participants), escitalopram (3 participants), fluoxetine, and sertraline (5 participants each). Cardiovascular medications included tamsulosin, telmisartan (1 participant each), losartan (3 participants), and spironolactone (2 participants). Sixteen subjects on solriamfetol treatment and 11 subjects on placebo had never been on treatment with a stimulant previously. Among this stimulant-naive group, 3 individuals each in both active and placebo groups had been on treatment with a nonstimulant with potential ADHD effects in the past (either atomoxetine or bupropion).

At baseline, the ADHD CGI-Severity rating was moderate for most participants (see Table 1). There was less than a 10% difference in the percentage of individuals scoring in the impaired range on every mental health subcategory of the ASR between the active and placebo groups. At baseline, mean (SD) AISRS total scores were 25.5 (4.7) in the solriamfetol group and 24.4 (4.2) in the placebo group. At baseline, all but 1 subject met a research definition of executive function impairment, having 2 or more subscales of the BRIEF-A rated at 1.5 standard deviations from normed mean BRIEF-A scores.

Acceptability and Tolerability

There were no significant differences in changes in vital signs over the course of the study between the treatment and placebo groups. Comparing solriamfetol and placebo mean vital sign changes from baseline to week 6, we found the following: heart rate, +3.7 versus +2.2 bpm ($P = .5609$); systolic blood pressure, +2.4 versus +1.5 mm Hg ($P = .6474$); diastolic blood pressure, +1.1 versus +1.5 mm Hg ($P = .8117$). There were 3 subjects in the placebo group and 4 in the treatment group who met our definition of clinically meaningful high blood pressure readings, defined as 2 readings (> 140/90 mm Hg) in a row during any 2 consecutive visits. No subjects had abnormal heart rates (> 100 bpm) at 2 consecutive study visits.

All adverse events were analyzed regardless of likelihood of attribution to the study. All were mild or moderate in severity, except a syncope episode that occurred in a patient on placebo. We grouped adverse events into body system categories impacted. There was no statistically significant treatment effect on occurrence of events in these categories (Table 2), on occurrence of

Table 1.

Patient Characteristics at Baseline

Characteristic	Treatment Group	
	Solriamfetol	Placebo
Total enrolled, n	29	31
Age, y		
Mean	36.2	36.9
Minimum	19.0	22.0
Maximum	61.0	60.0
Gender, n (%)		
Male	10 (34.5)	17 (54.8)
Female	17 (58.6)	12 (38.7)
Other	2 (6.9)	2 (6.5)
Race, n (%)		
White/Caucasian	19 (65.5)	25 (80.6)
Black/African American	2 (6.9)	2 (6.5)
Asian	3 (10.3)	2 (6.5)
Native Hawaiian/Pacific Islander	5 (17.2)	2 (6.5)
Ethnicity, n (%)		
Hispanic or Latino	4 (13.8)	2 (6.5)
Not Hispanic or Latino	25 (86.2)	29 (93.5)
Highest education, n (%)		
High school graduate	1 (3.4)	0 (0)
Some college but no college degree	4 (13.8)	2 (6.5)
Associate degree	2 (6.9)	3 (9.7)
Bachelor or RN degree	10 (34.5)	16 (51.6)
Some graduate school but no graduate degree	2 (6.9)	2 (6.5)
Master's degree	3 (10.3)	2 (6.5)
Doctoral or law degree	7 (24.1)	6 (19.4)
Marital status, n (%)		
Married	13 (44.8)	12 (38.7)
Unmarried	16 (55.2)	19 (61.3)
Socioeconomic status[a]: estimated household annual income, mean (SD), $	98,349 (31,349)	119,593 (33,612)
CGI Severity score (baseline), n (%)		
Moderately ill	22 (75.9)	25 (80.6)
Markedly ill	7 (24.1)	6 (19.4)
GAF score (baseline)		
Mean (SD)	63.8 (1.9)	63.8 (1.5)
Minimum	60.0	61.0
Maximum	68.0	66.0

[a]Median income was estimated based on the median annual household of the zip code that the participant listed.
Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning.

Table 2.

Comparison of Rates of Adverse Events (Regardless of Severity) Between Groups

Adverse Effect	Solriamfetol (n = 29), n (%)	Placebo (n = 31), n (%)	*P* Value
Cold/infection/allergy	13 (45)	17 (55)	.6058
Increased appetite	0 (0)	1 (3)	1.0000
Decreased appetite	5 (17)	2 (6)	.2472
Headache	14 (48)	9 (29)	.1844
Nausea/vomiting/diarrhea (gastrointestinal)	7 (24)	2 (6)	.0756
Insomnia	9 (31)	5 (16)	.2271
Sedation	3 (10)	1 (3)	.3455
Increased energy	4 (14)	1 (3)	.1877
Cardiovascular	5 (17)	1 (3)	.0977
Tense/jittery	1 (3)	0 (0)	.4833
Agitated/irritable	3 (10)	2 (6)	.6658
Anxious/worried	0 (0)	1 (3)	1.0000
Mucosal dryness	3 (10)	4 (13)	1.0000
Dizzy/lightheaded	1 (3)	0 (0)	.4833
Neurologic	4 (14)	1 (3)	.1877
Musculoskeletal	7 (24)	7 (23)	1.0000
Genitourinary	3 (10)	2 (6)	.6658
Dermatologic	1 (3)	4 (13)	.3547
Other	1 (3)	3 (10)	.6128

repeated (occurring at 2 or more visits in a single subject) events in these categories (*P* values ranged from .1068 to 1.0000), or on occurrence of events categorized as having moderate or worse severity (*P* values ranged from .2294 to 1.0000). The following categories were represented among treatment participants at a rate of at least 10 percentage points higher than among placebo participants: decreased appetite, headache, gastrointestinal, insomnia, increased energy, cardiovascular, and neurologic. The only category of event to occur in participants on placebo at a rate at least 10 percentage points higher than in patients than on treatment was dermatologic. Review of patterns of repeated categorized adverse events showed that rate of decreased appetite was the most differentiating, occurring in 3 individuals on solriamfetol treatment and none on placebo. Adverse events led to dose adjustment or interruption in 10 subjects on active treatment and 4 on placebo and led to discontinuation (at week 6) in 1 subject, who had skin itching while on active solriamfetol treatment.

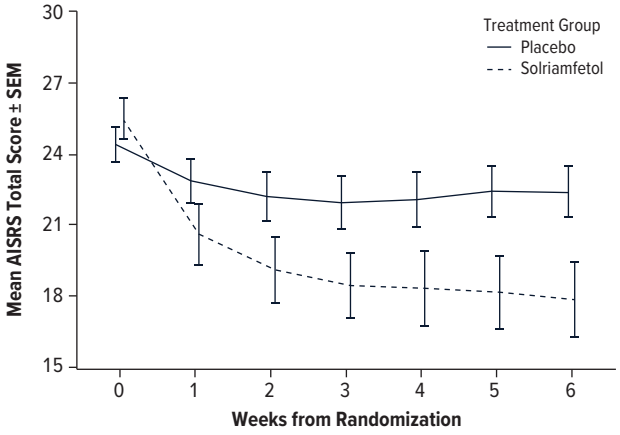
The remote virtual visit–based clinical trial format was also very well tolerated by participants. The time burden for the participants, who lived in geographically diverse areas of Massachusetts, was less than if the study had required travel to in-person visits. There were no adverse experiences that occurred that were attributed directly to the remote nature of the study.

Efficacy Measure Outcomes

Mean improvement in total AISRS ratings was significantly greater for individuals on solriamfetol treatment than for those on placebo from week 3, for which the difference in means was −3.4 (95% CI, −6.7 to −0.1; *P* = .0439), through the end of the study at week 6. By week 6, the difference in mean AISRS score was −4.3 (95% CI, −7.7 to −1.0; *P* = .0106). The mean total improvement in AISRS score by the week 6 study visit was −7.6 for active study drug participants, and −2.1 for individuals on placebo (*P* = .0012; effect size = 1.09) (Figure 2). Similar patterns were evident for the AISRS inattentive subscale (mean improvement greater for treatment than for placebo by 4.0 points; *P* = .001; effect size = 1.59) and AISRS impulsive-hyperactive subscale (improvement greater for treatment than for placebo by 1.4 points; *P* = .024; effect size = 0.34).

Figure 2.

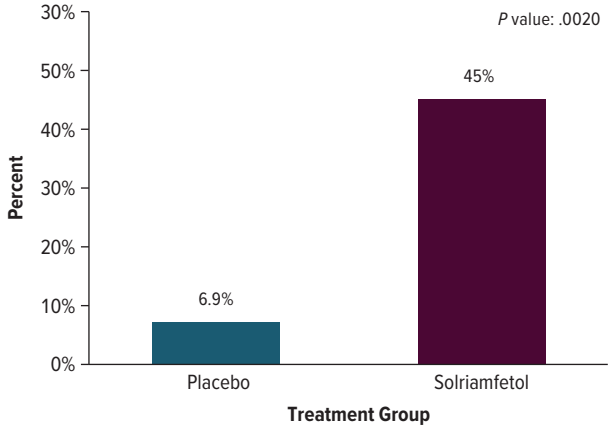
Mean AISRS Total Score by Week



Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale, SEM = standard error of the mean.

Figure 3.

CGI Score Indicating Much or Very Much Improved and 25% Improvement in AISRS Score With Solriamfetol vs Placebo



Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale, CGI = Clinical Global Impressions scale.

Total AISRS score improved 25% by week 6 in 52% of individuals on solriamfetol treatment versus 17% of individuals on placebo ($P = .0119$). Total AISRS score improved 50% by week 6 in 28% of individuals on solriamfetol treatment versus 3.4% receiving placebo ($P = .0253$). By week 6, significantly more individuals on solriamfetol treatment than on placebo met remission AISRS total score definitions of 12 (24% of participants on solriamfetol treatment and 3% of participants on placebo; $P = .0517$) or 18 (59% of participants on solriamfetol treatment and 21% on placebo; $P = .0067$ on the AISRS. By week 6, CGI ratings of much or very much improved occurred for significantly more individuals on solriamfetol treatment (45%, 13/29) than on placebo (6%, 2/31) ($P = .0020$). Breaking this down further, we note the following distributions: for active treatment: much improved = 24% (7 individuals), very much improved = 20% (6 individuals); within placebo treatment: much improved = 3% (1 individual), very much improved = 3% (1 individual). Forty-five percent of participants in the treatment group and 6.9% in the placebo group were considered responders by our a priori definition ($P = .0020$) (Figure 3).

We also evaluated outcome aligned with a slightly different post hoc improvement and response definition focused on 30% improvement to allow more direct comparison to some prior studies of adult ADHD treatments. Total AISRS score improved 30% by week 6 in 48% of individuals on solriamfetol treatment versus 14% of individuals on placebo ($P = .0096$). Response, based on this amount of improvement with CGI ratings of much or very much improved occurred in 41% of individuals on solriamfetol treatment and 6.9% of those on placebo ($P = .0046$). Mean GAF scores improved significantly more in the treatment group (−4.8 points; 95% CI, 3.1 to 6.6 vs −0.3 points; 95% CI, −1.4 to 2.1; $P = .0006$).

We evaluated self-report of executive functioning capacities using the BRIEF-A. Significantly more individuals on active treatment (69%) than placebo (34%) had a 0.5–standard deviation improvement in T-score on the BRIEF-A Global Executive Composite (GEC) ($P = .0173$), Metacognition Index (66% vs 34%, $P = .0348$), Shift subscale (69% vs 34%, $P = .0173$), and Initiate subscale (62% vs 31%, $P = .0343$). Solriamfetol was associated with significantly more change than placebo between baseline and week 6 for the following BRIEF-A subscales: Global Executive Composite, Behavioral Regulation Index, Metacognition Index, Shift subscale, Emotional Control subscale, Initiate subscale, Working Memory subscale, Plan/Organize subscale, and the Task Monitor subscale, with moderate to high effect sizes for each. The Inhibit, Self-Monitor, and Organization of Materials subscales showed no significant change relative to placebo.

Between baseline and week 6, the treatment group had a significantly greater reduction in the subject-reported mean MASRS total scores (treatment group mean = −11.1; 95% CI, −14.6 to −7.7; placebo group mean = −3.9; 95% CI, −7.4 to −0.5; $P = .0047$; effect size = 1.23), MASRS inattentive scores (treatment group mean = −5.9; 95% CI, −7.7 to −4.0; placebo group mean = −1.7; 95% CI, −1.7 to −3.5; $P = .0022$; effect size = 1.30), and MASRS hyperactivity (treatment group mean = −5.2; 95% CI, −7.1 to −3.4; placebo group mean = −2.4; 95% CI, −4.3 to −0.6; $P = .0366$; effect size = 0.55).

Evaluating change in the PSQI overall or subscale scores from baseline to week 6, there was no significant difference between participants in the treatment

groups. Mean sleepiness scores on the ESS improved significantly more for the treatment group (−2.4 points; $P = .0056$). We ran an analysis on change from baseline in AISRS total score within the ESS subgroups of normal daytime sleepiness and excessive daytime sleepiness and found that AISRS improvement was not moderated by changes in ESS ratings of sleepiness ($P = .3735$).

We also evaluated shifts from good sleep to bad (defined as PSQI score > 5) sleep and vice versa between baseline and end of study to assign study participants to improved, unchanged, or worsened sleep quality trends. Overall, 24.1% in the active group and 20.7% in the placebo group showed improved sleep, and 6.9% in the active group and 10.3% in the placebo group showed worsened sleep. A total of 69% of both active and placebo groups remained in the same sleep category.

DISCUSSION

To our knowledge, this report is the first on the effects of solriamfetol in adults with ADHD and the first remotely conducted clinical psychopharmacology trial in adults with ADHD. Solriamfetol was well tolerated and was associated with significantly greater improvement than placebo with robust effect sizes based on both clinician and participant measures of ADHD as well as participant self-report of executive function.

The effect size of solriamfetol for ADHD symptom improvement in adults was like that of stimulant medications in prior studies that also calculated effect sizes for symptom improvement. There was notably a low placebo response in this study, which could contribute to the larger effect size estimates. While there is no mean clinically important difference (MCID) established for the AISRS grounded in data from an identical controlled 6-week study, analysis based on a 6-month exposure to atomoxetine suggests that the AISRS change level which discriminated individuals with a 1-point difference in ADHD CGI severity from those with no change in ADHD CGI severity was −10.1.[10] Inspecting response patterns, we found that 10 of the subjects receiving active treatment in our study had greater than a 10-point improvement, while only 1 subject on placebo had this much improvement. In the atomoxetine study that estimated MCID, a 1-point change in CGI severity correlated with at least 30% improvement on the AISRS rating scale. Because we found that 48% of individuals on solriamfetol had this much improvement in AISRS ratings, we believe that future research is needed to clarify how MCID for the AISRS may be best estimated in studies like the pilot one we present. For example, we note that AISRS baseline scores were much higher in the atomoxetine study used to estimate this MCID: 38.5 in the active group and 39.2 in the placebo group. This means the populations may not be comparable in the amount of AISRS change that was possible. Some clinical trials have explored effects of lisdexamfetamine and atomoxetine on executive function, and the estimated effect size of solriamfetol on BRIEF-A measures was on par with or stronger than those findings.[5]

Adverse effects that occurred at a higher rate in the treatment group than the placebo group were typical of FDA guidance for solriamfetol and for sympathomimetic agents used for ADHD, and we found no evidence of stronger cardiovascular effects in the treatment group than in the placebo group. This combination of efficacy and tolerability, as well as the Schedule IV status of solriamfetol, positions it as potentially preferable for subsets of patients. However, because we allowed participants to be on some other forms of medication, we cannot discern whether adverse effects may have been influenced by presence of these other agents. We note that 5 participants were taking medications at baseline that could have sedative effects. However, our sensitivity to solriamfetol-specific sleepiness and sleep quality effects was probably only marginally reduced because only 1 of these individuals, who took trazodone, was in the active treatment group.

Some characteristics of our study that could have influenced our results are worth noting. More women were blindly randomized to solriamfetol than men, and we are not aware of prior research that would predict how this could have impacted our findings. Because nearly all subjects on active solriamfetol increased to 150 mg, it is possible that higher doses could have produced even stronger effects for some participants, though the safety of this approach is important to evaluate because the package insert for solriamfetol indicates that the agent increases heart rate and blood pressure in a dose-dependent fashion.[7] We utilized home blood pressure monitoring in our study, and while this is a validated method to evaluate blood pressure, and uniform application of home measures in the active and placebo groups allows treatment effects to be evaluated, home monitoring may have sensitivity to hypertension and cardiovascular outcomes different from in-office or ambulatory blood pressure monitoring.[21]

Sleep disorders are highly comorbid with ADHD, and treatments that improve sleepiness may contribute to improved daytime function.[22] While prior research has evaluated the impact of stimulant treatment on sleep quality in adults with ADHD, showing that there is no clear effect over that of placebo,[23] this study was, to our knowledge, the first clinical trial of an ADHD treatment to evaluate change in a validated measure of sleepiness. We found that improvement in wakefulness did not moderate change in ADHD symptom burden with solriamfetol, suggesting that the robust improvement in ADHD symptoms was not due to wakefulness alone.

Future research replicating our findings could confirm whether solriamfetol is a well-tolerated and effective treatment for ADHD in adults, clarify optimal dosing regimens, and offer more clarity about how effects compare to those of other drugs. Our study also demonstrated the

feasibility, utility, and efficacy of an all-remote clinical trial, although comparison to an in-person study would be necessary to understand specifically how participant characteristics or outcomes would be different.

Article Information

Published Online: October 9, 2023. https://doi.org/10.4088/JCP.23m14934

Submitted: May 8, 2023; accepted August 10, 2023.

To Cite: Surman CBH, Walsh DM, Horick N, et al. Solriamfetol for attention-deficit/hyperactivity disorder in adults: a double-blind placebo-controlled pilot study. *J Clin Psychiatry.* 2023;84(6):23m14934.

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Relevant Financial Relationships: In the past 2 years, **Dr Surman** has been a consultant to Kayuna, Ironshore, Neurocentria, Otsuka, and Supernus; has conducted clinical research at Massachusetts General Hospital supported by Shire/Takeda, Neurocentria, and Jazz/Axsome; and has received royalties for publications with Berkeley/Penguin and from Humana/Springer. The other authors have no financial or other relationships relevant to the subject of this article.

Funding/Support: This research was an investigator-initiated trial supported by Jazz Pharmaceuticals and Axsome Therapeutics. Materials for this study were provided by Jazz Pharmaceuticals and Axsome Therapeutics.

Role of the Funders/Sponsors: The sponsors provided financial support and study drug for the study. The sponsors were not involved in the conception, design, operation, analysis, or reporting of the study.

Acknowledgments: We would like to acknowledge the staff of the Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD for their support of our project.

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References

1. Simon V, Czobor P, Bálint S, et al. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry.* 2009;194(3):204–211.
2. Fayyad J, Sampson NA, Hwang I, et al; WHO World Mental Health Survey Collaborators. The descriptive epidemiology of *DSM-IV* adult ADHD in the World Health Organization World Mental Health Surveys. *Atten Defic Hyperact Disord.* 2017;9(1):47–65.
3. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry.* 2007;164(6):942–948.
4. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry.* 2006;163(4):716–723.
5. Surman CBH, Walsh DM. Do ADHD treatments improve executive behavior beyond core ADHD symptoms in adults? evidence from systematic analysis of clinical trials. *J Clin Pharmacol.* 2023;63(6):640–653.
6. Brown TE, Landgraf JM. Improvements in executive function correlate with enhanced performance and functioning and health-related quality of life: evidence from 2 large, double-blind, randomized, placebo-controlled trials in ADHD. *Postgrad Med.* 2010;122(5):42–51.
7. Sunosi (solriamfetol) [package insert]. New York: NAT, Inc; June 2022.
8. Goodman DW, Faraone SV, Adler LA, et al. Interpreting ADHD rating scale scores: linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. *Prim Psychiatry.* 2010;17:44–52.
9. Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol Med.* 2005;35(2):245–256.
10. Spencer TJ, Adler LA, Meihua Qiao, et al. Validation of the adult ADHD investigator symptom rating scale (AISRS). *J Atten Disord.* 2010;14(1):57–68.
11. Achenbach TM, & Rescorla, L.A. *Manual for ASEBA Adult Forms & Profiles.* 2003.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* American Psychiatric Association; 2013.
13. Aas IH. Guidelines for rating Global Assessment of Functioning (GAF). *Ann Gen Psychiatry.* 2011;10(1):2.
14. Busner J, Targum SD. The Clinical Global Impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont).* 2007;4(7):28–37.
15. Roth RM, Lance CE, Isquith PK, et al. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function-Adult version in healthy adults and application to attention-deficit/hyperactivity disorder. *Arch Clin Neuropsychol.* 2013;28(5):425–434.
16. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
17. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540–545.
18. Adler LA, Spencer T, Faraone SV, et al. Validity of pilot Adult ADHD Self- Report Scale (ASRS) to Rate Adult ADHD symptoms. *Ann Clin Psychiatry.* 2006;18(3):145–148.
19. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods.* 2002;7(1):105–125.
20. Statistical Analysis Software [computer program]. Users' Guide Statistics Version 9.4. SAS Institute Inc; 2013.
21. Cepeda M, Pham P, Shimbo D. Status of ambulatory blood pressure monitoring and home blood pressure monitoring for the diagnosis and management of hypertension in the US: an up-to-date review. *Hypertens Res.* 2023;46(3):620–629.
22. Surman CBH, Walsh DM. Managing sleep in adults with ADHD: from science to pragmatic approaches. *Brain Sci.* 2021;11(10):1361.
23. Weiss MD, Surman C, Khullar A, et al. Effect of a multi-layer, extended-release methylphenidate formulation (PRC-063) on sleep in adults with ADHD: a randomized, double-blind, forced-dose, placebo-controlled trial followed by a 6-month open-label extension. *CNS Drugs.* 2021;35(6):667–679.