A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of AR19, a Manipulation-Resistant Formulation of Amphetamine Sulfate, in Adults With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: To assess the efficacy and safety of AR19 in the treatment of attention-deficit/hyperactivity disorder (ADHD) diagnosed by *DSM-5* criteria in adults from 18 through 55 years of age. AR19 is a pellets-in-capsule, immediate-release amphetamine sulfate investigational formulation with physical and chemical barriers designed to resist manipulation to deter snorting, smoking, and intravenous injection.

Methods: This randomized, double-blind, placebo-controlled, fixed-dose, forced titration, multicenter trial investigated the safety and efficacy of AR19 from September 2018 to April 2019. Study participants were randomized and titrated to 20 mg or 40 mg AR19 daily or placebo. Study medication was dosed once in the morning and again 4 to 6 hours later for a period of 5 weeks. The primary efficacy measure was the total score on the Adult ADHD Investigator Symptom Rating Scale (AISRS).

Results: Participants (N = 320) were randomized and received at least 1 dose of study medication. Demographics and baseline characteristics were similar across treatment groups. The least squares mean treatment differences versus placebo (97.5% CI) were −7.2 (−11.3 to −3.1) for the AR19 20-mg group and −7.3 (−11.4 to −3.2) for the AR19 40-mg group (each $P < .001$). The most common treatment-emergent adverse events occurring in participants in the AR19 treatment groups were insomnia, dry mouth, decreased appetite, palpitations, headache, and tachycardia and are consistent with the known safety profile of amphetamine sulfate.

Conclusions: AR19 demonstrated efficacy on all endpoints and was generally well tolerated, supporting the efficacy and safety of AR19 20 mg and 40 mg in adults with ADHD.

Trial Registration: ClinicalTrials.gov Identifier: NCT03659929

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Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurobehavioral disorder that often persists into adulthood. Meta-analyses estimate the prevalence of ADHD to be 5.9%–7.1% in youth[1] and 2.5% in adults.[2] Stimulant medications, including various amphetamine and methylphenidate formulations, are commonly prescribed to ameliorate the associated symptoms of ADHD—inattention, hyperactivity, and/or impulsivity—at any age.[3,4]

Amphetamine is the most prescribed type of stimulant medication in the United States,[5] and the use of immediate-release (IR) formulations remains common, especially in adults. In 2019, approximately 1 in 5 stimulant prescriptions filled for patients ≤ 19 years of age and > 50% of stimulant prescriptions filled for patients 20–39 years of age were IR formulations.[6]

The high prevalence of IR stimulant prescriptions has implications for the non-medical use (NMU) and diversion of ADHD medications. A systematic review of prescription stimulant NMU[7] found that the most common source of prescription stimulants for those who misuse them was family and friends, and 4%–35% report NMU of their own prescription. Among those who misuse prescription stimulants, the most frequently reported route of administration is oral (52%–95%).[7] In college samples, those reporting NMU of prescription stimulants also report snorting at least some of the time (7%–48%).[7] Rates of smoking or injecting stimulants were 1%–6% and 1%–11%, respectively.[7,8] The non-oral use of prescription stimulants is also associated with more frequent and severe adverse medical outcomes, including death.[9]

The US Food and Drug Administration (FDA) recognizes the serious public health concern posed by the misuse of prescription stimulant medications. In a 2014 response letter[10] to a citizen petition, the agency noted that abuse and misuse of central nervous system stimulant drugs is a serious public health concern and voiced support for efforts by manufacturers to modify formulations to reduce the risk of abuse. In 2019, the agency posted a notice in

Clinical Points

- Prescription stimulants, although efficacious in the management of attention-deficit/hyperactivity disorder (ADHD), are also liable to misuse, abuse, dependence, and diversion; in the future, manipulation-resistant formulations of prescription stimulant medications that impede snorting, smoking, and intravenous use may be an option for patients.
- AR19, a novel, investigational, manipulation-resistant formulation of amphetamine sulfate, was found to be safe and efficacious in adults with ADHD.

the Federal Register[11] soliciting input on the potential role for abuse-deterrent formulations of prescription stimulants.

Herein we report the results of a randomized controlled trial of AR19, a manipulation-resistant formulation of a 1:1 racemic mixture of *d*- and *l*-amphetamine sulfate. Enhancements to the currently marketed IR formulation of racemic amphetamine sulfate (Evekeo; Arbor Pharmaceuticals, LLC)[12] are intended to achieve a level of resistance against NMU when the formulation is manipulated and administered by unintended routes such as intranasal (IN) or intravenous (IV). Although the FDA has not decided on what terminology will be used to describe medications like AR19, we use the term *manipulation resistant* because, as others have noted, *abuse deterrent* can be misleading since manipulation-resistant medications cannot deter oral abuse.

AR19 capsules are filled with dozens of hard, non-brittle pellets (~1.2 mm in diameter) that are difficult to handle for physical manipulation and are resistant to particle size reduction (crushing) required for insufflation. AR19 is also formulated with chemical barriers to slow IN absorption, to resist volatilization for smoking, and to create a gel in small volumes of aqueous solvents that impedes IV injection. These physical and chemical barriers make it difficult to transform AR19 into a material that can be used for non-oral routes. The abuse potential of AR19 has been explored in a controlled trial of recreational stimulant users, showing AR19 plasma amphetamine concentrations and exposures were lower after intranasal AR19 versus conventional amphetamine sulfate. AR19 had significantly lower abuse potential compared with conventional amphetamine sulfate, and participants were not statistically more willing to take AR19 again versus placebo.[13]

Results of a bioavailability study[14] in fasted subjects verified that oral AR19 is bioequivalent to Evekeo, a medication shown to be efficacious in children aged 6 to 12 years in a laboratory school study.[15] The 20-mg dose-concentration/time curves overlapped for AR19 and the reference drug: mean ± SD values for T_{max} (h) were 2.84 ± 1.05 and 2.52 ± 0.75, and AUC_{inf} values (h × ng/mL) were 461 ± 112 and 460 ± 94.4 for AR19 and Evekeo, respectively. The current study tested the safety and efficacy of AR19, the novel manipulation-resistant formulation of Evekeo, in adults with ADHD.

METHODS

Participants

This trial enrolled adult outpatients, aged 18–55 years inclusive, with a primary diagnosis of ADHD based on *DSM-5* criteria and confirmed by the Conners' Adult ADHD Diagnostic Interview for *DSM-IV*[16] adapted for *DSM-5*. Participants were also required to have an Adult ADHD Investigator Symptom Rating Scale (AISRS)[17] total score of ≥ 26 and a Clinical Global Impressions–Severity of Illness scale (CGI-S)[18] score of ≥ 4 at baseline.

Reasons for exclusion included active medical condition or clinically significant abnormality on physical examination, laboratory testing, or electrocardiogram (ECG) that could interfere with study participation; primary psychiatric diagnosis other than ADHD; history of bipolar disorder, schizophrenia, or other psychotic disorder; history of seizure disorder, untreated or inadequately treated hypertension, thyroid disease, glaucoma, or Tourette's disorder; use of prohibited psychotropic medication within 28 days of the baseline visit except for ADHD medication (stimulant medications were allowed until 7 days before the baseline visit); investigational drug use within the previous 60 days; history of hypersensitivity, intolerance, or poor therapeutic response to stimulant medication; history in the past 12 months of suicidal ideation or of substance abuse or dependence; or positive breath alcohol test or urine drug screen at the screening visit.

The study was conducted from September 2018 to April 2019, approved by local Institutional Review Boards, and was conducted in accordance with the protocol, Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki, and with applicable laws and regulations. Before study entry, all patients provided written informed consent, and the study was registered at ClinicalTrials.gov (Identifier: NCT03659929).

Study Design and Treatment

This randomized, double-blind, placebo-controlled, parallel, fixed-dose trial of AR19 in adults 18 through 55 years of age with ADHD was conducted at 31 sites in the United States. A 30-day screening period and baseline evaluation was followed by a 5-week double-blind treatment phase and a post-withdrawal follow-up phone call. During the screening period, psychiatric, medical, and laboratory screening tests were completed, and any current medication for ADHD was discontinued (a 28-day washout for non-stimulant medication and a 7-day washout for stimulant medication). Participants continuing to meet all study inclusion and exclusion criteria at baseline were randomized to 20 or 40 mg AR19 daily or placebo in a 1:1:1 ratio. AR19 or placebo was then started, with AR19 initiated at 10 mg/d and titrated in weekly intervals in 10-mg increments to 20 or 40 mg/d, depending on randomization. Participants received study drug twice daily, once in the morning and again 4 to 6 hours later, for 5 weeks. Safety and clinical response assessments were performed at each weekly visit or more frequently if clinically indicated.

Figure 1. Participant Disposition

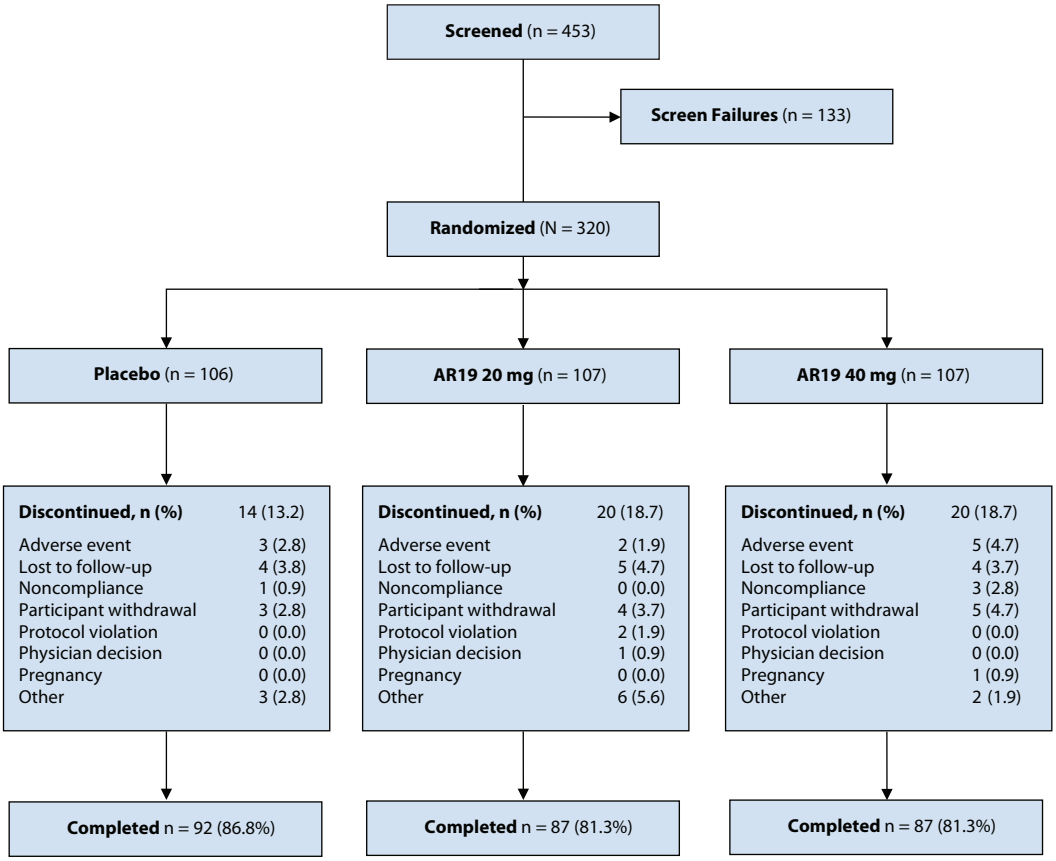


Table 1. Demographics and Baseline Characteristics[a]

Characteristic	Placebo (n = 106)	AR19 20 mg (n = 107)	AR19 40 mg (n = 107)	Total (N = 320)	*P* Value
Age, mean (SD), y	34.2 (10.75)	35.6 (10.28)	33.5 (9.35)	34.4 (10.15)	.4479
Sex					.4124
Male	54 (50.9)	57 (53.3)	63 (58.9)	174 (54.4)	
Female	52 (49.1)	50 (46.7)	44 (41.1)	146 (45.6)	
Race					.2211
White	80 (75.5)	89 (83.2)	88 (82.2)	257 (80.3)	
Black or African American	13 (12.3)	13 (12.1)	15 (14.0)	41 (12.8)	
Asian	6 (5.7)	1 (0.9)	2 (1.9)	9 (2.8)	
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)	
American Indian or Alaskan Native	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)	
Other	6 (5.7)	4 (3.7)	1 (0.9)	11 (3.4)	
Ethnicity					.9553
Hispanic or Latino	14 (13.2)	13 (12.1)	14 (13.1)	41 (12.8)	
Not Hispanic or Latino	92 (86.8)	94 (87.9)	93 (86.9)	279 (87.2)	
ADHD type					.5257
Inattentive	14 (13.2)	19 (17.8)	20 (18.7)	53 (16.6)	
Hyperactive/impulsive	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)	
Combined	91 (85.8)	88 (82.2)	87 (81.3)	266 (83.1)	

[a]Values are shown as n (%) unless otherwise noted.
Abbreviation: ADHD = attention deficit/hyperactivity disorder.

Efficacy Assessments

The primary efficacy endpoint was the change from baseline in AISRS total score at week 5 in AR19 (20 and 40 mg/d) versus placebo. The AISRS is a validated[17] 18-item scale that corresponds directly to the 18 ADHD symptom items in the *DSM-IV-TR* and includes adult prompts for each item. Each item is scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). An AISRS assessment was completed at baseline and at each study visit. Secondary efficacy endpoints included changes from baseline in the hyperactivity/impulsivity and inattentive subscale scores of the AISRS.

The Clinical Global Impressions (CGI) scales are used to measure features associated with ADHD in terms of disease severity (CGI-S) and improvement (CGI-I).[18] The CGI-S

rates global severity from 1 to 7, for which 1 is normal and 7 is among the most extremely ill patients. The CGI-I rates global improvement on a 7-point scale for which 1 is very much improved and 7 is very much worse. The CGI-S was completed at all study visits. The CGI-I relative to baseline was completed at the end of each active treatment week (weeks 1 through 5). Key secondary endpoints included CGI-S at week 5 compared to baseline and the CGI-I at week 5.

Another key secondary endpoint was the change from baseline to week 5 in the Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A).[19] The BRIEF-A is a standardized measure designed to assess adult executive functioning and self-regulation.[19] It is composed of 75 items and 9 clinical scales that form two indexes—Behavioral Regulation and Metacognition—and these indexes form the overall summary score, the Global Executive Composite. Higher scores indicate reduced executive function.

Safety Assessments

Safety and tolerability were assessed by physical examinations, vital sign evaluations, 12-lead electrocardiograms, hematology and serum chemistry evaluations, urinalysis, and reported incidence and severity of adverse events (AEs). The investigator assessed each AE according to severity (mild, moderate, severe) and relatedness to study drug (related, possibly related, unlikely related, not related). Potential treatment-emergent suicidal ideation was monitored using the Columbia Suicide Severity Rating Scale (C-SSRS).[20]

Statistical Analysis

All analyses were performed using SAS System version 9.3 or higher. The primary efficacy analysis was performed on the full analysis set (FAS) population, defined as all participants who were randomized, received at least 1 dose of study medication, and had at least 1 post-baseline on-treatment primary efficacy assessment. The primary efficacy outcome was the change from baseline in AISRS total score at week 5 in AR19 (20 and 40 mg/d) versus placebo. Comparisons were made between each active treatment group and placebo using a Bonferroni adjustment at the .025 (.05/2) α level to adjust for our two primary outcomes. A restricted maximum likelihood (REML)–based mixed-model repeated measures (MMRM) analysis was utilized with fixed effects planned for treatment, study week, baseline AISRS total score, and treatment-by-week interaction; missing values were not imputed. Pairwise comparisons (using least squares [LS] mean contrasts) were made to compare AISRS score at week 5 for each AR19 dose level with placebo separately.

Secondary efficacy variables were analyzed using the same MMRM method. For the CGI-S and CGI-I assessments, Cochran-Mantel-Haenszel (CMH) row mean score tests were used. Analysis of responder rates (defined as ≥30% reduction in AISRS total score from baseline to week 5) was also performed.

Table 2. Primary Efficacy Endpoint: AISRS Total Score and Subscale Scores[a]

Treatment	LS Mean Change From Baseline (SE)	LS Mean Treatment Difference vs Placebo (97.5% CI)	*P* Value
AISRS Total Score			
Week 1			
Placebo	−7.8 (1.08)		
AR19 20 mg	−13.1 (1.07)	−5.3 (−8.7 to −1.8)	<.001
AR19 40 mg	−13.0 (1.06)	−5.2 (−8.7 to −1.8)	<.001
Week 2			
Placebo	−9.8 (1.16)		
AR19 20 mg	−15.7 (1.15)	−5.9 (−9.6 to −2.2)	<.001
AR19 40 mg	−16.4 (1.16)	−6.6 (−10.3 to −2.9)	<.001
Week 3			
Placebo	−11.2 (1.19)		
AR19 20 mg	−17.6 (1.19)	−6.4 (−10.2 to −2.6)	<.001
AR19 40 mg	−17.3 (1.19)	−6.1 (−9.9 to −2.3)	<.001
Week 4			
Placebo	−11.6 (1.20)		
AR19 20 mg	−17.8 (1.20)	−6.2 (−10.0 to −2.4)	<.001
AR19 40 mg	−18.1 (1.20)	−6.5 (−10.3 to −2.6)	<.001
Week 5 (primary endpoint)			
Placebo	−11.2 (1.29)		
AR19 20 mg	−18.4 (1.29)	−7.2 (−11.3 to −3.1)	<.001
AR19 40 mg	−18.5 (1.30)	−7.3 (−11.4 to −3.2)	<.001
AISRS Subscale Score at Week 5			
Hyperactivity/impulsivity			
Placebo	−5.3 (0.62)		
AR19 20 mg	−8.4 (0.62)	−3.1 (−5.1 to −1.1)	<.001
AR19 40 mg	−8.2 (0.62)	−2.9 (−4.9 to −1.0)	<.001
Inattentive			
Placebo	−6.0 (0.75)		
AR19 20 mg	−10.1 (0.75)	−4.1 (−6.4 to −1.7)	<.001
AR19 40 mg	−10.3 (0.75)	−4.3 (−6.7 to −2.0)	<.001

[a]Statistics calculated using a restricted maximum likelihood mixed model repeated measures analysis with fixed effects for treatment, week, treatment-by-week interaction, and baseline AISRS total score.
Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale; LS = least squares.

The safety population was defined as all participants who were randomized and received at least one dose of study medication. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 21.0 and were summarized descriptively by treatment on the safety population. An AE was considered treatment emergent if it started or worsened at the time or after the first dose of study medication was administered.

RESULTS

Participants

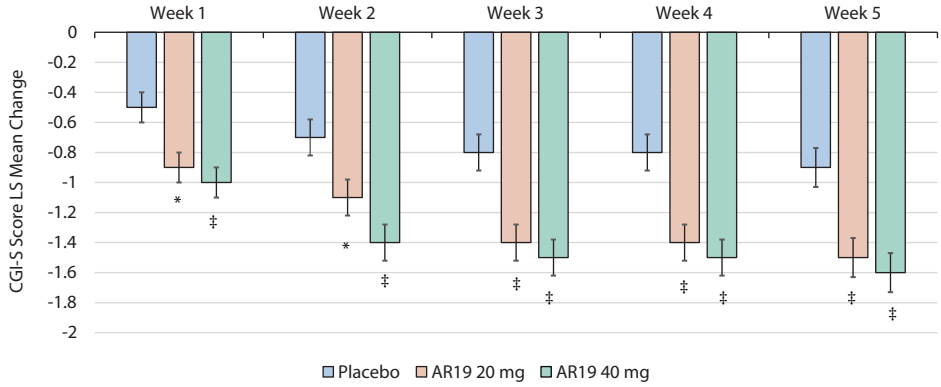
A total of 320 participants were randomized to double-blind treatment (Figure 1) and received at least 1 dose of study medication (safety population). Of those, 314 participants (98.1%) had at least 1 post-baseline on-treatment primary efficacy assessment (the FAS population). Baseline demographic and clinical characteristics were similar across all 3 treatment groups (Table 1).

Efficacy

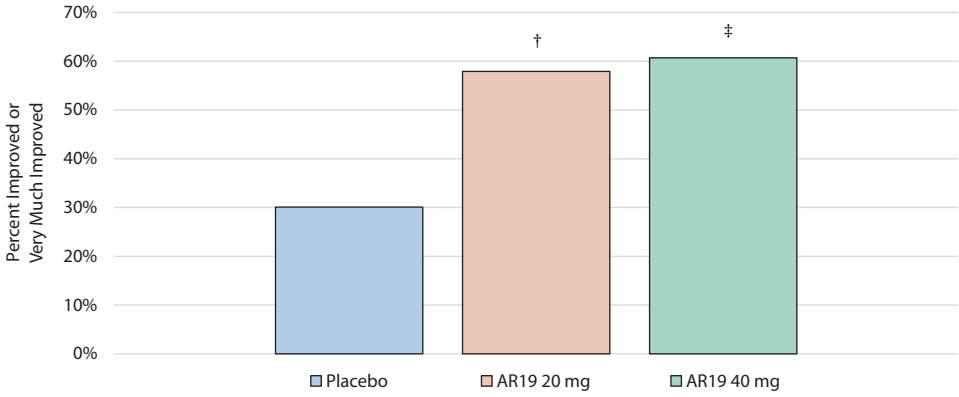
The LS mean change from baseline in score on the AISRS at week 5 was −18.4 for the AR19 20-mg group, −18.5 for the

Figure 2. Key Secondary Endpoints

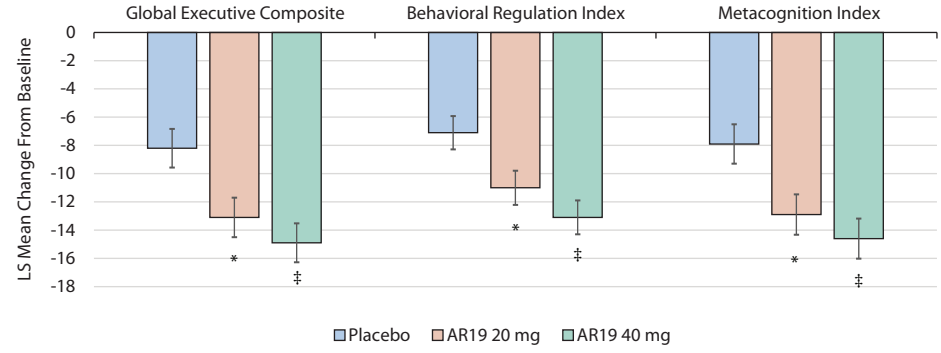
A. CGI-S scores, LS mean change from baseline by treatment week[a]



B. CGI-I, percent of participants improved at week 5[b]



C. BRIEF-A scores, LS mean change from baseline at week 5[c]



[a]LS mean change from baseline in CGI-S scores presented by treatment week. Statistics calculated using a restricted maximum likelihood mixed-model repeated measures analysis with fixed effects for treatment, week, and treatment-by-week interaction.
[b]Percent of participants rated as improved or very much improved (scores of 1 or 2) at week 5 in the CGI-I. Descriptive *P* values were calculated using a CMH row mean scores test.
[c]LS mean change from baseline in BRIEF-A scores at week 5. Statistics calculated using a restricted maximum likelihood mixed-model repeated measures analysis with fixed effects for treatment, week, treatment-by-week interaction, and baseline BRIEF-A score.
Abbreviations: BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version, CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, CMH = Cochran-Mantel-Haenszel, LS = least squares.
*$P \leq .05$, †$P \leq .01$, ‡$P \leq .001$.

AR19 40 mg group, and −11.2 for the placebo group (Table 2). These data resulted in a LS mean treatment difference (AR19–placebo) of −7.2 and −7.3 for the AR19 20 and 40 mg treatment groups, respectively ($P < .001$). At each study visit beginning with week 1, the treatment difference for the AR19 20 mg and 40 mg groups demonstrated improvement over the placebo group ($P < .001$). Secondary endpoints also included change scores at week 5 for the AISRS subscales, which demonstrated similar statistically significant differences ($P < .001$) between the placebo and active treatment groups for both subscales (Table 2). The Cohen *d* effect sizes for AR19 versus placebo were 0.53 and 0.56 for the 20 mg and 40 mg dose groups, respectively. No clear dose-dependent difference was observed between the two

Table 3. Frequently Occurring Treatment-Emergent Adverse Events (TEAEs) Reported by ≥ 5% in any Treatment Group (Safety Population)

TEAE[a]	Placebo (n = 106), n (%)	AR19 20 mg (n = 107), n (%)	AR19 40 mg (n = 107), n (%)
Insomnia	4 (3.8)	9 (8.4)	10 (9.3)
Dry mouth	4 (3.8)	6 (5.6)	12 (11.2)
Headache	13 (12.3)	14 (13.1)	12 (11.2)
Nasopharyngitis	6 (5.7)	5 (4.7)	3 (2.8)
Decreased appetite	5 (4.7)	11 (10.3)	14 (13.1)
Palpitations	2 (1.9)	2 (1.9)	7 (6.5)
Tachycardia	0 (0.0)	6 (5.6)	4 (3.7)
Any TEAE rated as "severe"	5 (4.7)	5 (4.7)	3 (2.8)

[a]Preferred terms are shown.
Abbreviation: TEAE = treatment-emergent adverse event.

dose levels when they were assessed for AISRS total score change or for either of the AISRS subscale scores at week 5.

Responder rates (≥ 30% reduction in AISRS total score) were 75.5% and 74.3%, respectively for the AR19 20 mg and 40 mg groups, compared with 52.4% of participants in the placebo group ($P \leq .001$).

Figure 2 summarizes key secondary efficacy endpoints. For change in CGI-S scores, a statistically significant treatment difference between the 20 mg and 40 mg treatment arms and the placebo arm is apparent at each study visit beginning at week 1 ($P < .05$) with continued improvements through week 5 ($P < .001$; Figure 2A). At week 5, both AR19 treatment groups demonstrated comparable levels of improvement in CGI-I scores over the placebo group ($P \leq .01$; Figure 2B). Both active treatment groups demonstrated statistically significant differences from placebo on the BRIEF-A Global Executive Composite (GEC), the Behavioral Regulation Index (BRI), and the Metacognition Index (MI, Figure 2C). The magnitude of change from baseline was numerically larger in the AR19 40 mg group when compared with the AR19 20 mg group, but not statistically significant ($P > .20$ for the GEC, BRI, and MI).

Safety

Treatment-emergent AEs occurring in at least 5% of participants in any treatment group were considered frequently occurring and are summarized in Table 3. The majority of events in all treatment groups were mild or moderate in severity. No serious adverse events or deaths were reported during the study. Ten participants in the study reported at total of 23 TEAEs that resulted in study drug discontinuation—3 in the placebo group, 2 in the AR19 20 mg group, and 5 in the AR19 40 mg group. The most common adverse events leading to discontinuation and occurring in ≥ 2 patients were palpitations (1 with placebo, 3 with AR19 40 mg), insomnia (2 with AR19 40 mg), decreased appetite (1 with placebo, 1 with AR19 40 mg), feeling abnormal (1 with placebo, 1 with AR19 20 mg), and hyperhidrosis (1 with AR19 20 mg, 1 with AR19 40 mg).

Suicidal Ideation. On the C-SSRS, no participants in any treatment group reported suicidal ideation with severity ≥ 2 or self-injurious behavior at any study visit.

Weight. The mean change in weight from baseline to week 5 was +0.34, −1.03, and −1.66 kg in placebo, AR19 20 mg, and AR19 40 mg participants, respectively. At week 5, potentially significant changes in weight of a ≥ 5% increase were experienced in 3 (3.3%) and 2 (2.3%) placebo and AR19 20 mg participants, respectively. Changes of ≥ 5% decrease in weight were experienced in 1 placebo participant (1.1%) and 14 AR19 participants (5 [5.7%] and 9 [10.3%] of AR19 20 mg and AR19 40 mg participants, respectively).

Vital signs and ECG. Mean change in pulse rate at week 5 was −0.9, +6.0, and +7.1 bpm in the placebo, AR19 20 mg, and AR19 40 mg groups, respectively. Mean change from baseline systolic blood pressure at week 5 was +0.5, +1.1, and +2.3 mm Hg in the placebo, AR19 20 mg, and AR19 40 mg groups, respectively. Mean change from baseline diastolic blood pressure at week 5 was −0.3, +2.0, and +2.3 mm Hg in the placebo, AR19 20 mg, and AR19 40 mg groups, respectively. On ECG, minimal mean changes were observed at week 5 in corrected QT interval by Fredericia (QTcF) of −0.9, +0.5, and - 0.1 msec, respectively for the placebo, AR19 20 mg and AR19 40 mg groups.

Laboratory. No AEs were reported for chemistry or hematology changes. One event of urobilinogen urine was reported in 1 participant from the AR19 40 mg group at week 5. The event was of moderate severity, was considered possibly related to the study drug, and resolved after 8 days.

DISCUSSION

We report here the first placebo-controlled efficacy trial of a manipulation-resistant stimulant medication. In this 5-week study of AR19 in adult patients with ADHD, the AISRS total score change from baseline (the primary efficacy outcome measure) relative to placebo was significant beginning at week 1 for both the 20 mg and 40 mg dose groups and maintained significance relative to placebo in each group at each weekly visit to the end of the study. No clinically meaningful difference in efficacy outcomes was observed between the AR19 20 mg and 40 mg dose groups, which may be due to a possible plateauing effect at the respective doses. Compared with placebo, AR19 led to significantly greater responder rates (≥ 30% reduction in AISRS total score), improved global ADHD symptom severity on the CGI-S, a greater proportion of participants improved on the CGI-I, and greater improvement in BRIEF-A scores.

The most frequent adverse events reported for AR19 in this study were insomnia, dry mouth, decreased appetite, palpitations, headache, and tachycardia, all consistent with amphetamine treatment.[21] Most AEs were mild or moderate in severity. Monitoring of vital signs and laboratory parameters did not identify any clinically significant safety concerns for AR19. Small increases were noted in mean heart rate and in mean systolic and diastolic blood pressure for the AR19 dose groups. There was no notable effect on QTc or other ECG parameters. AE rates were not systematically greater in the 40 mg compared with the 20 mg group.

Given that prescription stimulants are prescribed to a substantial minority of adults with ADHD,[5] the manipulation-resistant properties of AR19 make it an important addition to the treatment options for ADHD. Diversion and NMU of prescription stimulants are an increasingly common problem. Although the most frequently reported route of administration for NMU is oral, manipulating prescription stimulants for snorting, smoking, and injection is well-documented, especially in college-based studies.[7] The NMU of prescription stimulants via non-oral routes is associated with significant morbidity and mortality. The odds of death are 13 times greater among intranasal users and 22 times greater among intravenous users compared with non-intentional oral NMU.[9] The availability of manipulation-resistant formulations of stimulants, like AR19, would provide a public health benefit by reducing the risk of harm to individuals who may experiment with the non-oral use of these drugs.

The limitations of this study include the short (ie, 5-week) treatment period. Moreover, although the forced-dose titration design is useful for evoking adverse events, it does not conform to typical clinical practice, in which doses are optimized. It is not known if a wider increase in therapeutic effect would be seen between AR19 dosage groups with a longer duration trial and individual titration. The generalization of our results is limited by our exclusion criteria, which excluded some cases of psychiatric comorbidity that would typically be treated in clinical practice.

In conclusion, this placebo-controlled trial found twice-daily dosing with AR19, a novel, immediate-release, manipulation-resistant amphetamine formulation, to be an efficacious treatment of ADHD in adults. AR19, which was well-tolerated for most patients, adds an important therapeutic choice for the treatment of ADHD.

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