Triple-Bead Mixed Amphetamine Salts (SPD465), a Novel, Enhanced Extended-Release Amphetamine Formulation for the Treatment of Adults With ADHD: A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study

Thomas J. Spencer, M.D.; Lenard A. Adler, M.D.; Richard H. Weisler, M.D.; and Sharon H. Youcha, M.D.

Introduction: The efficacy and safety of triple-bead mixed amphetamine salts (MAS), an oral, once-daily, enhanced extended-release amphetamine formulation designed for a duration of action up to 16 hours, were evaluated in adults with attention-deficit/hyperactivity disorder (ADHD).

Method: In this phase 3, 7-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group, dose-optimization study of 272 adults with ADHD (DSM-IV-TR criteria), subjects (aged 18 to 55 years) were randomly assigned to triple-bead MAS (starting dose 12.5 mg) or placebo. The primary outcome measure was change in ADHD Rating Scale-IV (ADHD-RS-IV). Secondary outcome measures included Clinical Global Impressions (CGI) scale, Time-Sensitive ADHD Symptom Scale (TASS) (measuring extended duration), Brown Attention-Deficit Disorder Scale (BADDS) (measuring executive function), Adult ADHD Impact Module (AIM-A) (measuring quality of life [QOL]), and ADHD-RS-IV hyperactivity-impulsivity and inattentiveness subscales. Adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory data were collected. The trial was conducted from January 2005 to June 2005.

Results: Triple-bead MAS resulted in significantly greater improvement versus placebo in mean ADHD-RS-IV total score change ($p < .0001$), CGI-Improvement ($p < .0001$), TASS total score at 13–16 hours postdose ($p = .002$), BADDS total score ($p < .0001$), all AIM-A domains ($p \leq .01$), and ADHD-RS-IV subscales ($p < .01$), demonstrating extended duration of efficacy and improvements in executive function and QOL. The most common treatment-emergent AEs included insomnia, dry mouth, decreased appetite and weight, and headache. Most treatment-emergent AEs were mild or moderate in severity.

Conclusions: Triple-bead MAS was significantly more effective than placebo in treating adult ADHD. The extended duration of action up to 16 hours and significant improvements in executive function and QOL address unique treatment needs of adults with ADHD. Treatment-emergent AEs with triple-bead MAS were consistent with amphetamine treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00150579

(J Clin Psychiatry 2008;69:1437–1448)

Received May 8, 2007; accepted June 25, 2008. From the Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston (Dr. Spencer); Department of Psychiatry, New York University School of Medicine, New York (Dr. Adler); Department of Psychiatry, Duke University Medical Center, Raleigh, N.C. and Department of Psychiatry, University of North Carolina-Chapel Hill (Dr. Weisler); and Shire Development Inc., Wayne, Pa. (Dr. Youcha).

Supported by funding from Shire Development Inc.

These data were presented at the 160th annual meeting of the American Psychiatric Association, May 23, 2007, San Diego, Calif.

Acknowledgments are listed at the end of this article.

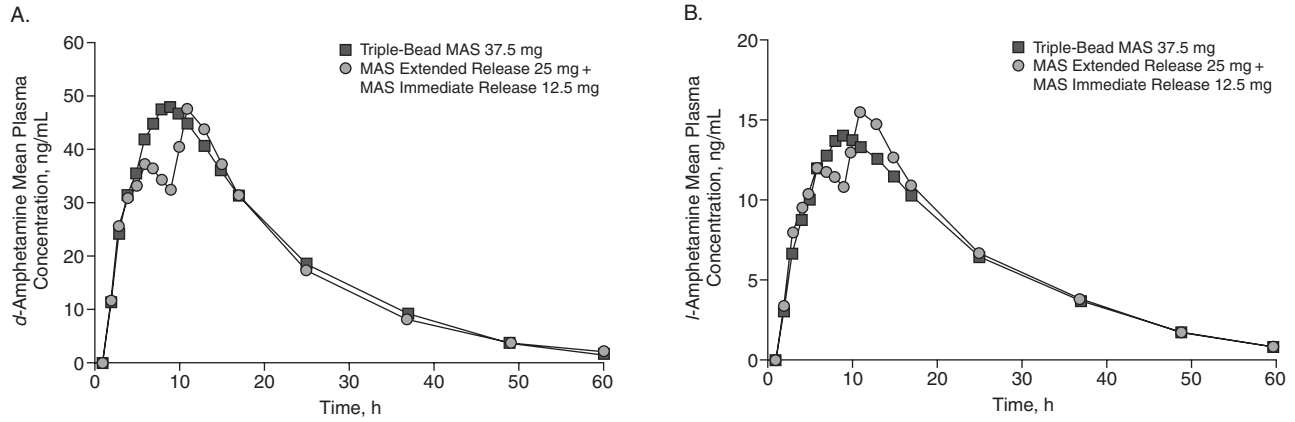
Financial disclosure is listed at the end of this article.

Corresponding author and reprints: Thomas J. Spencer, M.D., Massachusetts General Hospital, Pediatric Psychopharmacology Research Unit, 55 Fruit St., Warren 705, Boston, MA 02114 (e-mail: spencer@helix.mgh.harvard.edu).

Once considered a condition limited to childhood, attention-deficit/hyperactivity disorder (ADHD) is now recognized to be a common, chronic, neurobehavioral disorder affecting an estimated 4.4% of adults (aged 18–44 years).[1] Adults with ADHD can experience academic and occupational failures, frequent job changes, lower socioeconomic status, substance abuse or dependence, chronic conflicts with authority, decreased quality of life (QOL),[2] relationship problems, and vehicular accidents.[3–6]

Treatment of ADHD with stimulant and nonstimulant medications may significantly improve symptoms of ADHD in adults.[7] Although short-acting stimulant medications are available, multiple daily doses often are required to achieve symptom control, which can lead to treatment nonadherence.[8] Long-acting stimulants may increase medication adherence because of enhanced dosing

Figure 1. Mean *d*-Amphetamine (A) and *l*-Amphetamine (B) Plasma Concentrations Over Time With Triple-Bead MAS 37.5 mg or MAS Extended Release 25 mg + MAS Immediate Release 12.5 mg (8 hours later)[a]



[a]Reproduced with permission from Ermer et al.[11]
Abbreviation: MAS = mixed amphetamine salts.

convenience and address the persistence of ADHD impairments beyond the school day or the workday in adults.[8,9] The currently available long-acting stimulant medications are intended to provide coverage for 10 to 12 hours, which usually is sufficient for a child's functional day. Many adults, however, are particularly challenged by cognitively demanding tasks that extend into the evening,[10] and symptom coverage beyond 12 hours may be required to adequately manage family, social, and work-related activities. Therapeutic benefits may be needed in the evening, necessitating a dose-augmentation strategy, such as administering a long-acting medication in the morning followed by a short-acting formulation of the same medication later in the day.

In response to the increasing awareness of adult ADHD and the need for long-acting stimulant medications with an extended duration of action, triple-bead mixed amphetamine salts (MAS) was developed. Triple-bead MAS is an oral, once-daily, enhanced extended-release amphetamine formulation designed to provide prolonged ADHD symptom control (up to 16 hours). It contains the same 4 salts (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate USP, and amphetamine sulfate USP) in the same isomeric ratio (3:1) as MAS immediate release) and MAS extended release.

MAS immediate release is an immediate-release tablet containing mixed amphetamine salts. MAS extended release consists of 50% immediate pulse-release and 50% delayed pulse-release MAS beads within the capsule. The triple-bead MAS capsule includes 3 types of beads—33.3% immediate pulse-release, 33.3% delayed pulse-release, and 33.3% delayed extended-release beads—that together produce a dosing profile with a single, morning capsule that mimics an afternoon dose-augmentation strategy to provide coverage for evening activities. After oral administration, the first bead provides an immediate pulse-release of drug. The second bead provides a delayed pulse-release of drug and, together with the first bead, enables a double-pulsed delivery of MAS (the first 2 types of beads are the same components of the MAS extended-release formulation). The third bead, unique to this triple-bead formulation, provides an additional delayed- and extended-release dose of amphetamine during the later part of the day.

The pharmacokinetic similarity between triple-bead MAS and a dose-augmentation strategy was demonstrated in a phase 1 study showing that a single 37.5-mg morning dose of triple-bead MAS was bioequivalent to MAS extended release 25 mg supplemented 8 hours later by 12.5 mg of immediate-release MAS beads in a capsule formulation.[11] The mean plasma concentration–time profile curves for the *d*-amphetamine and *l*-amphetamine isomers had a bimodal distribution over a 16-hour period in the dose-augmentation strategy (MAS extended release + MAS immediate release 8 hours later), whereby peaks in plasma were observed between 3 hours and 5 hours, and then again between 10 hours and 11.5 hours (Figures 1A and 1B). The mean plasma concentration–time profile curves for triple-bead MAS peaked at 7.5 to 9 hours and minimized the peak-trough fluctuations over a 16-hour period that were observed with the dose-augmentation strategy. The results of this pharmacokinetic evaluation suggest that triple-bead MAS provides plasma concentrations similar to those observed with a dose-augmentation strategy through the afternoon and evening hours, but the diminution of fluctuations in plasma concentrations with a single oral dose would allow for a smoother plasma concentration–time profile.

Two phase 2, controlled, adult workplace environment studies by Wigal and colleagues[12,13] evaluated the duration

of effect and safety of triple-bead MAS in adults. In the first study,[13] mean total scores (sum of the number of math problems attempted and answered correctly) on the Permanent Product Measure of Performance (PERMP) were statistically significantly superior with triple-bead MAS 25 mg than with placebo beginning at 4 hours postdose ($p < .01$) through 16 hours postdose ($p < .0001$). In the second study,[12] PERMP total scores were significantly superior with triple-bead MAS 50 or 75 mg compared with placebo at all postdose time points from 2 hours through 16 hours ($p < .0001$). Adverse events (AEs) were generally mild to moderate in these studies and were consistent with those seen with amphetamine treatment.

The purpose of this phase 3, 7-week, randomized, double-blind, multicenter, placebo-controlled, parallel group, dose-optimization study was to evaluate the efficacy and safety of triple-bead MAS in adults with ADHD (primary objective). Secondary objectives included analyzing data on symptom control in the later part of the day and evaluating the impact on executive function and QOL after triple-bead MAS treatment.

METHOD

Subjects

Inclusion criteria. Subjects enrolled in the study (conducted from January 2005 to June 2005) were required to be men or nonpregnant/nonlactating women (women of childbearing age agreed to use acceptable methods of contraception throughout the study) between the ages of 18 and 55 years, inclusive; meet the DSM-IV-TR[14] criteria for a primary diagnosis of ADHD; have a satisfactory medical assessment with no clinically significant or relevant abnormalities; have a baseline ADHD Rating Scale-IV (ADHD-RS-IV)[15] score ≥ 24; and provide informed consent.

Exclusion criteria. Subjects were excluded if they had a body mass index < 18.5 kg/m^2; morbid obesity; comorbid psychiatric diagnosis with, in the opinion of the investigator, significant symptoms; seizure history, tic disorder, or diagnosis or family history of Tourette's syndrome; current chronic or acute illness or an unstable medical condition; mental retardation; known cardiac structural abnormality or any other cardiac condition that could affect cardiac performance; clinically significant electrocardiogram (ECG) or laboratory abnormalities at screening; used psychotropic medications that require more than a 28-day washout period; a history of controlled or uncontrolled hypertension or a resting, sitting systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg at screening; allergy, intolerance, or nonresponse to methylphenidate or amphetamines; drug dependence or substance use disorder (excluding nicotine) within 6 months before screening; a positive urine drug test result at screening or baseline; participation in another investigational trial within 30 days of screening; or pregnancy or lactation. The concomitant use of psychoactive medications that, in the opinion of the investigator, could interfere with the efficacy, safety, or tolerability of triple-bead MAS was not allowed during the study.

Study Design

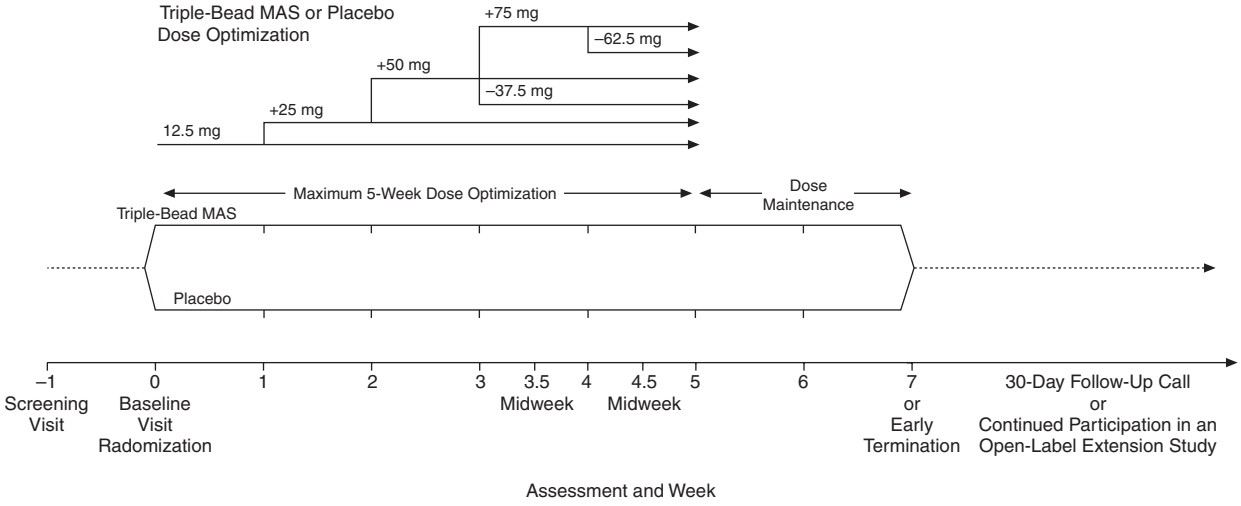
Subjects were screened over approximately 2 weeks to establish eligibility. Those currently receiving stimulant therapy underwent at least a 7-day washout period before the baseline visit; those receiving bupropion, atomoxetine, or other medications for ADHD that resulted in receptor changes in the central nervous system were required to undergo a 28-day washout period before baseline evaluation. At baseline assessment, eligible subjects with an ADHD-RS-IV score ≥ 24 were randomly assigned in a 1:1 ratio to a single morning dose of triple-bead MAS or matching placebo for a maximum 5-week, stepwise, dose-optimization phase, followed by a minimum 2-week maintenance phase (Figure 2). All subjects receiving active treatment were initiated on treatment with triple-bead MAS 12.5 mg (dosing level 1). On the basis of clinical efficacy and tolerability, the dose was adjusted weekly to dosing level 2 (25 mg), dosing level 4 (50 mg), or maximum dosing level 6 (75 mg) until an optimal dose was reached. An optimal dose was determined by the investigator on the basis of clinical improvement (at least a 30% decrease in baseline ADHD-RS-IV score) and tolerable side effects. At the discretion of the investigator, titration to a lower dose was permitted at 2 time points during the study. At the end of week 3 (visit 3), subjects could be down-titrated from 50 mg to a week 4 dose of 37.5 mg; at the end of week 4 (visit 4), subjects could be down-titrated from 75 mg to a week 5 dose of 62.5 mg. When an optimal dose level was reached (12.5 to 75 mg), the subject remained at this level until the end of the study, with weekly clinic visits scheduled for the assessment of safety and efficacy. A subject was required to return for a midweek visit if he/she had been titrated to a dose of 75 mg and/or 62.5 mg to remeasure vital signs. Subjects were eligible for participation in the open-label extension study after 4 weeks of double-blind treatment.

A total of 39 sites in the United States participated in the study. Randomization was accomplished using a centralized, interactive, voice response system. All subjects provided informed consent to participate prior to any study-related procedures. Institutional review board approval was obtained either through a central governing body (33 sites) or through a local institutional review board (6 sites).

Assessments

The primary outcome measure was the clinician-administered ADHD-RS-IV, which consists of 18 items designed to reflect current ADHD symptomatology.[15] Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms). While this scale

Figure 2. Study Design Flowchart for the 7-Week, Double-Blind, Randomized Controlled Study of the Efficacy and Safety of Triple-Bead MAS



Abbreviation: MAS = mixed amphetamine salts.

was developed and standardized for use in children, the ADHD-RS-IV also has been shown to correlate with drug effects in adults with ADHD,[16–20] and with appropriate training—including the use of prompts, which enable information about ADHD symptoms in adults to be obtained in a semistructured format using an extensive list of examples[3]—it can be used by clinicians to assess the impact of ADHD in adults.[3]

Secondary outcome measures included the baseline value obtained from the Clinical Global Impressions-Severity of Illness (CGI-S) scale, followed by weekly analyses using the CGI-Improvement (CGI-I) scale, the Time-Sensitive ADHD Symptom Scale (TASS), the Brown Attention-Deficit Disorder Scale (BADDS), the Adult ADHD Impact Module (AIM-A), and the ADHD-RS-IV hyperactivity-impulsivity and inattentiveness subscales.

The CGI-S evaluates baseline severity on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). The CGI-I scale provides a global evaluation of improvement from baseline in ADHD symptoms over time; it is a 7-point scale that assesses subject improvement on a range from 1 (very much improved) to 7 (very much worse). Both measures have an optional rating of 0 to denote a lack of assessment.[21]

The TASS is a self-report scale designed to assess ADHD symptom severity in a password-protected electronic diary (eDiary) format. It was designed to focus on real-time reports of symptom severity and was used in this study to evaluate the extended duration of action of triple-bead MAS. The TASS[22] was derived from the previously validated Adult ADHD Self-Report Scale (version 1.1)[1] and the ADHD-RS-IV.[15,22] The scale consists of the 18 items indexed by the ADHD-RS-IV, and it is scored on a 4-point scale from 0 (not at all) to 3 (severe); it also includes a *not applicable* response option that enables the responder to indicate when a particular task or symptom had not been experienced. A total score and scores for the hyperactivity-impulsivity and inattentiveness subscales can be reported for the TASS.

The BADDS for adults is a validated, normed, self-report scale administered by the clinician (clinician-recorded subject responses) that is composed of 40 items grouped in 5 clusters of conceptually related symptoms of ADHD: (1) organizing and activating to work, (2) sustaining attention and concentration, (3) sustaining energy and effort, (4) managing affective interference, and (5) utilizing working memory and accessing recall.[23] Of the available methods used to evaluate executive functions in patients with ADHD, the BADDS was chosen for this study because it assesses a broad range of executive functions.[23–28] The BADDS has been used previously to evaluate executive functions in children and adults receiving pharmacotherapy for ADHD.[29,30]

The AIM-A is a self-report instrument validated in adults[31] that builds on previous work in children[32] and consists of 4 global QOL questions, 5 economic-impact questions, and 5 multi-item scales that evaluate ADHD-specific impact on 6 QOL domains (living with ADHD, general well-being, performance and daily functioning, relationships and communication, bothersomeness and concern, and daily interference).

Schedule of Assessments

At baseline, all efficacy and QOL assessments were performed, except that the CGI-S was measured at base-

line (instead of the CGI-I). The ADHD-RS-IV and CGI-I assessments were performed at each weekly visit. The TASS was completed twice daily via password-protected eDiary at 5 (± 2) hours (early) and at 13 to 16 hours (late) postdose; however, baseline TASS was completed on paper. The BADDS and AIM-A were completed at the final study visit. Physical examinations and clinical laboratory evaluations (clinical chemistry, hematology, serum pregnancy test, and routine urinalysis with urine drug screen) were performed at the screening and final visits. Electrocardiogram and drug compliance were assessed at all weekly visits, and vital signs (blood pressure and pulse rate) were evaluated at all study visits. Using nonleading questions to assess their current state of health, subjects were queried for AEs at all visits; AEs also were gathered from spontaneous participant reports during study visits and at follow-up. The possible impact of triple-bead MAS on sleep was assessed at baseline and at all visits through endpoint using the Pittsburgh Sleep Quality Index (PSQI),[33] a self-rated questionnaire that assesses sleep quality and disturbances.

Statistical Analysis

The primary efficacy measurement was defined as the change from baseline to endpoint in the ADHD-RS-IV total score in the intention-to-treat (ITT) population. To minimize the effects of variance between the measured ADHD-RS-IV scores after dose optimization, the endpoint score for each subject was defined as the mean of the available values from weeks 5, 6, and 7. Alternately, if all of the data from visits 5, 6, and 7 were missing, the endpoint score was the last postrandomization treatment assessment for which an ADHD-RS-IV total score was obtained. If more than 3 items had missing or invalid data, the ADHD-RS-IV total score was set to *missing*. If data for fewer than 3 of the items were missing or invalid, the values for the missing items were imputed using the rounded mean of the nonmissing items. The null hypothesis stated that there were no differences between subjects receiving active treatment and those receiving placebo. A 1-way analysis of covariance (ANCOVA) model was used with baseline ADHD-RS-IV as the covariate, with a type I error rate for rejecting the null hypothesis set at an α level of .05.

The CGI-I score was dichotomized into 2 categories—*improved* (including measures of *very much improved* and *much improved*) or *not improved* (including all other categories)—and was analyzed using a χ^2 test. Endpoint was defined as the last nonmissing postbaseline value.

The TASS, BADDS, and AIM-A assessments were evaluated using the same ANCOVA model employed in the analysis of the ADHD-RS-IV data. For the TASS, endpoint was defined and analyzed similarly to that for the ADHD-RS-IV. The results from all available 5 (± 2) hours' postdose and 13 to 16 hours' postdose assessments obtained during weeks 5, 6, and 7 were averaged to yield mean values for the early and late time points, respectively. If week 5, 6, and 7 data were missing, the last week with nonmissing postbaseline assessments was used as the endpoint for the early and late postdose time points. For BADDS and AIM-A, the endpoint was defined as the last scheduled postbaseline study visit with a nonmissing value (either week 7 or early termination).

The efficacy measurements (except for CGI-I) also were summarized and presented in descriptive statistics for endpoint and each scheduled assessment by treatment group in the ITT population. The proportion of subjects with improvement (*very much improved* and *much improved*) and summaries of the original 7-point scales in CGI-I are presented for endpoint and each study week by randomized treatment group. Safety was assessed through evaluation of treatment-emergent AEs, vital signs, ECGs, clinical laboratory values, and physical examinations. Treatment-emergent AEs were coded using criteria from the *Medical Dictionary for Regulatory Activities*, version 7.1 (Northrop Grumman MedDRA, Chantilly, Virginia; available at http://www.meddramsso.com/MSSOWeb/index.htm). Frequency of treatment-emergent AEs was calculated for each body system and was recorded as the number and percentage of subjects reporting the event. Descriptive statistics (number of observations, mean, standard deviation [SD], and minimum, median, and maximum values) were provided for vital signs, ECG parameters, and clinical laboratory test values.

RESULTS

Randomization and Outcome

A total of 280 subjects who were recruited for participation completed all screening procedures and were deemed eligible to begin washout or return for the baseline assessment. Of these 280 subjects, 274 were randomly assigned (137 in each group). Two subjects randomly assigned to the placebo group were excluded from the safety analysis because they never took a dose; hence, the randomized safety population comprised 272 subjects (137 in the triple-bead MAS group and 135 in the placebo group). One subject who had received triple-bead MAS and 3 who had received placebo discontinued the study before the first assessment; thus, the ITT population comprised 268 subjects (136 in the triple-bead MAS group and 132 in the placebo group). The study was completed by 170 subjects, with a higher percentage completing the study in the triple-bead MAS group (68.6%) than in the placebo group (55.5%). There were more placebo-treated subjects (22.2%) than triple-bead MAS–treated subjects (7.3%) who discontinued early due to lack of efficacy. Of the subjects who discontinued early, 41.2% entered the open-label extension study. Table 1 provides an overview of the reasons for study discontinuation.

Table 1. Disposition of Subjects in the Randomized Controlled Trial of Triple-Bead MAS, N (%)[a]

Variable	Placebo (N = 137)	Triple-Bead MAS (N = 137)	Total (N = 280)
Population			
Enrolled population	137 (100.0)	137 (100.0)	280 (100.0)[b]
Randomized safety population	135 (98.5)	137 (100.0)	272 (97.1)
ITT population	132 (96.4)	136 (99.3)	268 (95.7)
Completion of study	76 (55.5)	94 (68.6)	170 (60.7)
Early termination	61 (44.5)	43 (31.4)	110 (39.3)[b]
Entrance to open-label study	103 (75.2)	99 (72.3)	202 (72.1)
Primary reason for discontinuation			
Adverse event	6 (4.4)	17 (12.4)	23 (8.2)
Lack of efficacy[c]	30 (22.2)	10 (7.3)	40 (14.7)
Protocol violation	4 (2.9)	4 (2.9)	12 (4.3)[d]
Noncompliance	4 (2.9)	2 (1.5)	6 (2.1)
Withdrawn consent	9 (6.6)	5 (3.6)	14 (5.0)
Pregnancy	1 (0.7)	0	1 (0.4)
Lost to follow-up	2 (1.5)	4 (2.9)	6 (2.1)
Other[c]	5 (3.7)	1 (0.7)	6 (2.2)[e]

[a]Percentages are based on the number of subjects in the enrolled population in each group.
[b]Six subjects terminated before randomization.
[c]Based on randomized safety population.
[d]Four subjects terminated before randomization.
[e]Two subjects terminated before randomization.
Abbreviations: ITT = intention-to-treat, MAS = mixed amphetamine salts.

Dose Optimization

After triple-bead MAS dose optimization in the ITT population, 16 subjects received triple-bead MAS 12.5 mg; 16 subjects, 25 mg; 6 subjects, 37.5 mg; 21 subjects, 50 mg; 6 subjects, 62.5 mg; and 32 subjects, 75 mg during weeks 5 through 7.

Study Population

Demographic information is shown in Table 2. Most of the subjects were white (84.9%), with 50% men and 50% women. At the time of study baseline, the mean age of study subjects was 36.5 years and most subjects had combined ADHD subtype (70.6%). On the basis of retrospective self-report, the mean age at time of ADHD symptom onset was 5.5 years, and the mean time since adult ADHD diagnosis was 5.5 years. Confirming other research suggesting a greater preponderance of girls than boys with the inattentive ADHD subtype,[34] nearly two thirds of the subjects in this study diagnosed with the inattentive subtype were women. Approximately one fourth of subjects had received previous therapy for ADHD within 30 days of the study, most frequently MAS extended release (15.1%).

Efficacy Analysis

The triple-bead MAS–treated population showed significantly greater improvement in mean ADHD-RS-IV total score from baseline to endpoint when compared with the placebo group. At endpoint, the mean (SD) change in score from baseline was –14.3 (12.1) in the triple-bead MAS group and –6.3 (11.2) in the placebo group (least squares [LS] means of –14.4 and –6.3, respectively). The difference in LS mean changes from baseline between the triple-bead MAS and placebo treatment groups was –8.1 (95% confidence interval [CI] = –10.8 to –5.4, $p < .0001$). Significant differences between the triple-bead MAS and placebo groups were observed beginning at week 1 at the time of the first study ratings and were sustained throughout the entire 7-week treatment period (Figure 3). Compared with baseline, ADHD-RS-IV hyperactivity-impulsivity and inattentiveness subscale scores were significantly more improved in the active treatment group versus the placebo group throughout the treatment period ($p < .01$).

Figure 4 shows the CGI-I dichotomized scores over the entire study period. Clinicians rated a greater number of triple-bead MAS–treated subjects (51.5%) as improved at study endpoint, compared with 21.2% of placebo-group subjects ($p < .0001$). As with the primary efficacy analysis, significant differences in CGI-I ratings were apparent beginning at the first measurement (week 1) and continuing throughout the 7-week treatment period.

Significant improvement in the TASS total scores (ITT population) were observed at both the 5 (± 2) hours' (early) (LS means for triple-bead MAS vs. placebo were –16.6 vs. –11.7, respectively; LS mean difference, –4.98; $p = .0003$) and 13 to 16 hours' (late) (LS means for triple-bead MAS vs. placebo were –16.6 vs. –12.4, respectively; LS mean difference, –4.26; $p = .002$) time points. These results demonstrate the extended duration of efficacy of triple-bead MAS for up to 16 hours postdose.

Subjects treated with triple-bead MAS showed significantly greater improvement from baseline to endpoint in mean (SD) BADDS total scores than subjects taking placebo (–22.3 [25.7] vs. –7.1 [20.6]; LS means of –22.6 and –6.8, respectively; $p < .0001$). Statistically significant greater improvement was evident in all 5

Table 2. Demographic Characteristics of Subjects in the Randomized Controlled Trial of Triple-Bead MAS[a]

Variable	Placebo (N = 135)	Triple-Bead MAS (N = 137)	Total (N = 272)
Age, y			
Mean (SD)	37.0 (10.3)	36.1 (10.1)	36.5 (10.2)
Median	38.0	37.0	38.0
Range	18–55	18–55	18–55
Age group, N (%)			
18–25 y	24 (17.8)	26 (19.0)	50 (18.4)
26–35 y	29 (21.5)	36 (26.3)	65 (23.9)
36–45 y	48 (35.6)	50 (36.5)	98 (36.0)
46–55 y	34 (25.2)	25 (18.2)	59 (21.7)
Sex, N (%)			
Male	67 (49.6)	69 (50.4)	136 (50.0)
Female	68 (50.4)	68 (49.6)	136 (50.0)
Race, N (%)			
White	113 (83.7)	118 (86.1)	231 (84.9)
Black	12 (8.9)	9 (6.6)	21 (7.7)
Asian	3 (2.2)	4 (2.9)	7 (2.6)
Other	7 (5.2)	6 (4.4)	13 (4.8)
Weight at screening, lb[b]			
Mean (SD)	177.8 (41.1)	180.4 (43.6)	179.1 (42.3)
Median	176.0	173.0	175.0
Range	96–306	102–333	96–333
ADHD subtype, N (%)			
Inattentive	34 (25.2)	38 (27.7)	72 (26.5)
Hyperactive-impulsive	4 (3.0)	4 (2.9)	8 (2.9)
Combined	97 (71.9)	95 (69.3)	192 (70.6)
Duration since ADHD diagnosis, y			
Mean (SD)	5.3 (9.3)	5.7 (9.8)	5.5 (9.5)
Median	1.0	1.1	1.1
Range	0–46	0–44	0–46
Previous ADHD medications, N (%)			
Any	33 (24.4)	33 (24.1)	66 (24.3)
MAS immediate release	2 (1.5)	7 (5.1)	9 (3.3)
MAS extended release	24 (17.8)	17 (12.4)	41 (15.1)
Atomoxetine	3 (2.2)	0	3 (1.1)
Bupropion	3 (2.2)	2 (1.5)	5 (1.8)
Dextroamphetamine	1 (0.7)	1 (0.7)	2 (0.7)
Methylphenidate	3 (2.2)	8 (5.8)	11 (4.0)
CGI-S score at baseline, N (%)			
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	2 (1.5)	2 (0.7)
Moderately ill	53 (39.3)	57 (41.6)	110 (40.4)
Markedly ill	72 (53.3)	62 (45.3)	134 (49.3)
Severely ill	9 (6.7)	15 (10.9)	24 (8.8)
Among the most extremely ill	1 (0.7)	1 (0.7)	2 (0.7)

[a]Results are based on the number of subjects in the randomized safety population in each group.
[b]For this variable, data were available for only 136 subjects in the triple-bead MAS group.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale, MAS = mixed amphetamine salts.

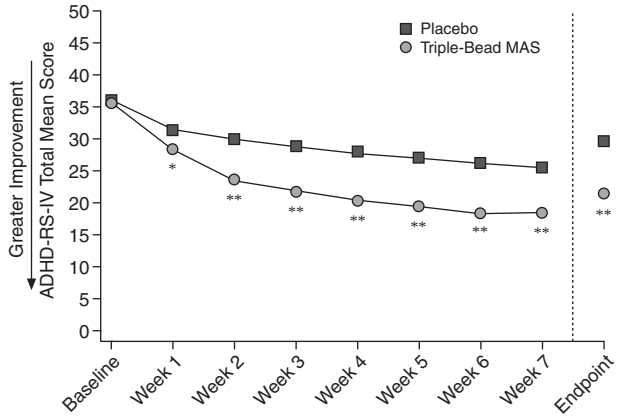
BADDS cluster scores among those treated with triple-bead MAS compared with those who received placebo (Figure 5).

Global QOL, as assessed by the AIM-A, suggested a positive effect of triple-bead MAS over placebo, with triple-bead MAS showing statistically significant improvements from baseline to endpoint compared with placebo. Significant improvement with triple-bead MAS was observed in each of the 6 AIM-A domains (living with ADHD, general well-being, performance and daily functioning, relationships and communication, bothersomeness and concern, and daily interference) (Figure 6).

Safety Analysis

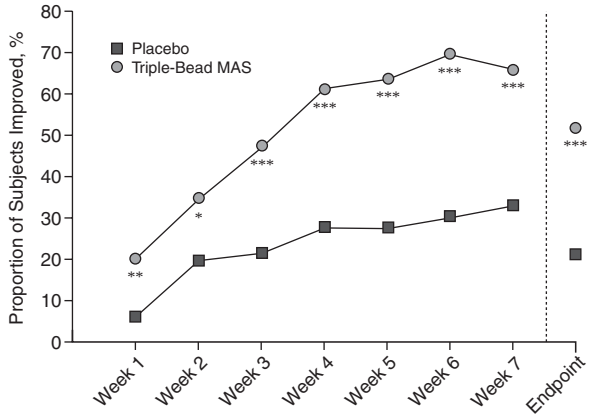
Overall, 89.1% of subjects receiving triple-bead MAS and 63.7% of those receiving placebo reported at least 1 treatment-emergent AE. The most common treatment-emergent AE associated with triple-bead MAS was insomnia (29.2%). Most insomnia events were mild to moderate in severity (93.5%), did not require pharmacologic intervention (4.3% required intervention), resolved while on treatment with study drug (73.9%), did not result in discontinuation (2.2% resulted in discontinuation), and decreased in frequency over time. Other commonly reported treatment-emergent AEs included dry mouth (22.6%), decreased appetite (19.7%), headache (18.2%),

Figure 3. Mean ADHD-RS-IV Total Scores by Week and at Endpoint (ITT Population)[a,b]



[a]Weekly values displayed in figure are mean values based on observed cases each week.
[b]p Values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate.
*p < .01 vs. placebo.
**p < .0001 vs. placebo.
Abbreviations: ADHD-RS-IV = ADHD Rating Scale-IV, ITT = intention-to-treat, MAS = mixed amphetamine salts.

Figure 4. Percentage of Subjects With Improvement[a] in CGI-I Scores by Week and at Endpoint (ITT Population)[b,c]



[a]Improvement = scores of very much improved and much improved.
[b]Weekly values displayed in figure are based on observed cases each week.
[c]p Values are based on a χ^2 statistic comparing the 2 groups on the proportion of subjects with improvement.
*p < .01 vs. placebo.
**p < .001 vs. placebo.
***p < .0001 vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, ITT = intention-to-treat, MAS = mixed amphetamine salts.

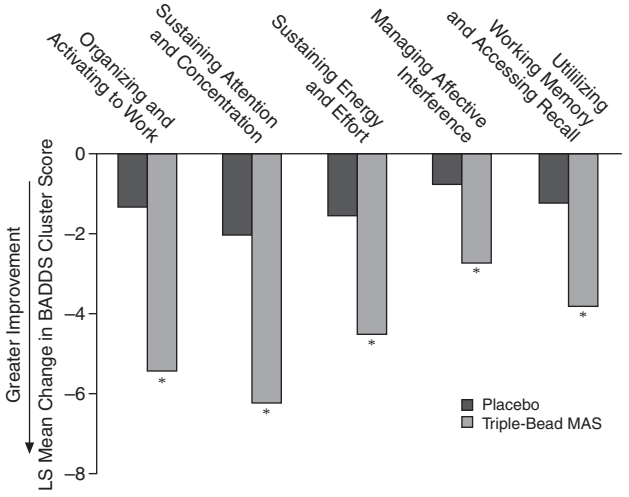
and weight decreased (13.1%). All of these events were reported with greater frequency in the active treatment group compared with the placebo group (Table 3). With the exception of insomnia, the selected treatment-emergent AEs in both groups occurred more frequently in the subjects who were stimulant naive. Most treatment-emergent AEs reported in the study were mild or moderate in severity, and their incidence decreased with continued treatment. A total of 13 subjects (11 receiving active treatment and 2 receiving placebo) reported 17 severe treatment-emergent AEs, most commonly insomnia (reported by 3 subjects receiving active treatment). One placebo subject experienced nausea and a second experienced a limb injury.

One serious AE, described as a possible transient ischemic attack, was reported in the study. On the seventh day of taking triple-bead MAS 12.5 mg, a 36-year-old man experienced difficulty speaking, with no other neurologic signs or symptoms and unremarkable vital signs. The subject reported having experienced similar symptoms after taking an over-the-counter weight loss preparation that has been known to contain ephedra or ephedrine before entering the study. The subject was hospitalized, a complete neurologic workup was performed, and the discharge diagnosis by the consulting neurologist was Tourette's syndrome with vocal tic. The investigator disagreed and felt that a possible transient ischemic attack could not be ruled out. The event resolved on the day it occurred; the subject was discharged from the hospital the next day and reported no further episodes. The subject was discontinued from the study.

Twenty-three subjects (8.5%) discontinued due to treatment-emergent AEs, 17 (12.4%) from the triple-bead MAS group (most commonly due to elevated blood pressure, palpitations, insomnia, or irritability) and 6 (4.4%) from the placebo group (most commonly due to elevated blood pressure). No deaths were reported in the study.

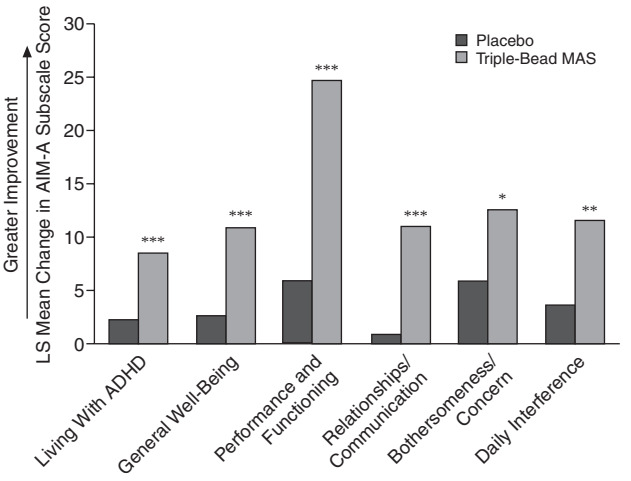
Changes in mean values from baseline to endpoint for vital signs are shown in Table 4. A mean increase in pulse rate of 4.7 bpm was observed with triple-bead MAS (compared with a mean increase of 0.4 bpm with placebo). Three subjects taking triple-bead MAS had a pulse rate > 110 bpm at any visit during the study. A mean increase in systolic blood pressure of 1.3 mm Hg was observed with triple-bead MAS (compared with a mean increase of 0.2 mm Hg with placebo), and a mean increase in diastolic blood pressure of 1.8 mm Hg was observed with triple-bead MAS (compared with a mean increase of 1.1 mm Hg with placebo). Elevated blood pressure led to study discontinuation in 2 placebo-treated and 4 triple-bead MAS–treated subjects. All were mild to moderate in severity, with the highest blood pressure readings in these 4 triple-bead MAS–treated subjects: 130/80, 132/90, 138/110, and 145/88 mm Hg. Table 4 also shows the number of subjects with outlier systolic and/or diastolic blood pressures observed on ≥ 2 consecutive visits at any time during the study. A mean

Figure 5. Brown Attention-Deficit Disorder Scale (BADDS) Cluster Scores at Endpoint (least squares mean change from baseline in the ITT population)[a]



[a]p Values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate.
*p ≤ .0001 vs. placebo.
Abbreviations: ITT = intention-to-treat, LS = least squares, MAS = mixed amphetamine salts.

Figure 6. Adult ADHD Impact Module Multi-Item Subscales at Endpoint (least squares mean change from baseline in the ITT population)[a]



[a]p Values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect, and baseline value as a covariate.
*p = .01.
**p = .003.
***p < .0001.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AIM-A = Adult ADHD Impact Module, ITT = intention-to-treat, LS = least squares, MAS = mixed amphetamine salts.

decrease in weight of 4.7 lb was observed in subjects receiving triple-bead MAS, compared with a mean increase in weight of 1.2 lb in the placebo group (compared with mean weight values at screening for subjects in both groups shown in Table 2). These changes in vital sign values and weight were small in magnitude and consistent with amphetamine treatment.

Mean changes in ECG parameters (Table 5) during the study were small in magnitude and were similar in the 2 groups. No subjects had any evidence of QT-interval prolongation resulting in a corrected QT interval > 500 ms or an increase in corrected QT interval ≥ 60 ms from baseline to endpoint by either the Bazett or Fridericia method. Overall, minor changes from baseline were observed in hematology, clinical chemistry, and urinalysis, with 11 abnormal hematology values (placebo, 8; triple-bead MAS, 3) and 20 abnormal chemistry values (placebo, 11; triple-bead MAS, 9) reported. Physician investigation revealed no trends for any treatment in any laboratory variable.

Despite reports of insomnia in the triple-bead MAS and placebo groups during the study, and 3 discontinuations among triple-bead MAS–treated subjects attributed to insomnia, PSQI results revealed no notable differences in overall sleep quality between the treatment groups at any weekly time point. Mean (SD) changes from baseline to week 7 in PSQI total score were –1.9 (2.9) for triple-bead MAS and –1.7 (2.8) for placebo, with a reduced score reflecting improved sleep quality.

DISCUSSION

In this study of adults with ADHD, triple-bead MAS was shown to be an effective treatment with treatment-emergent AEs that were predominantly mild to moderate in severity. The positive effect of triple-bead MAS on ADHD-RS-IV total scores was observed at each weekly time point throughout the 7-week study period. This effect was supported by significantly greater improvements in measures completed by the subjects and clinicians, including the CGI-I scores, TASS, BADDS executive function scores, and ADHD-RS-IV subscale scores. The BADDS questionnaire has been used to measure 1 (behavioral) construct of executive function.[29,30] However, the relationship between the BADDS and objective tests of cognitive function is unknown. Global QOL, as measured by the AIM-A, improved significantly from baseline with triple-bead MAS compared with placebo, and statistically significant improvements also were observed in all 6 ADHD-specific domains.

Duration of ADHD Symptom Control

Adler and Chua[10] assert that, despite the similar core symptomatology between childhood and adult ADHD, the adult day is comparatively longer and requires the navigation of more cognitively demanding tasks. They conclude that "the unique, whole-life needs of the adult population

Table 3. Common Treatment-Emergent Adverse Events (reported in ≥ 5% of triple-bead MAS subjects in the randomized safety population), %[a]

System Organ Class (MedDRA) Preferred Term	Placebo (N = 135)	Triple-Bead MAS (N = 137)
Gastrointestinal disorder	15.6	38.7
Dry mouth	5.2	22.6
Nausea	4.4	7.3
Infections and infestations	16.3	21.2
Upper respiratory tract infection	7.4	8.0
Metabolic and nutrition disorders	4.4	25.5
Anorexia	1.5	5.1
Decreased appetite	1.5	19.7
Weight decreased	0.7	13.1
Musculoskeletal and connective tissue disorders	10.4	19.0
Back pain	2.2	5.8
Myalgia	2.2	5.1
Nervous system disorders	24.4	30.7
Dizziness	5.9	5.8
Headache	14.1	18.2
Psychiatric disorders	17.8	43.1
Anxiety	3.0	6.6
Insomnia[b]	8.9	29.2
Irritability	3.7	9.5

[a]Percentages are based on the number of subjects in the randomized safety population in each group.
[b]Includes the preferred terms *insomnia*, *initial insomnia*, *middle insomnia*, *early morning awakening*, and *terminal insomnia*. Subjects with multiple types of insomnia were counted once.
Abbreviations: MAS = mixed amphetamine salts, MedDRA = *Medical Dictionary for Regulatory Activities*.

Table 4. Vital Signs of Subjects in the Randomized Controlled Trial of Triple-Bead MAS[a]

Parameter	Placebo (N = 133)	Triple-Bead MAS (N = 136)
Pulse rate: mean (SD) change from baseline to endpoint, bpm	0.4 (10.5)	4.7 (11.1)
Systolic blood pressure: mean (SD) change from baseline to endpoint, mm Hg	0.2 (9.4)	1.3 (9.3)
Diastolic blood pressure: mean (SD) change from baseline to endpoint, mm Hg	1.1 (6.4)	1.8 (6.7)
Subjects with 2 or more consecutive postdose outlier blood pressure measurements over entire study, N (%)[b]		
Systolic blood pressure		
≥ 140 mm Hg	0	2 (1.5)
≥ 150 mm Hg	0	0
Diastolic blood pressure		
≥ 90 mm Hg	3 (2.4)	6 (4.6)
≥ 95 mm Hg	1 (0.8)	2 (1.5)

[a]Results are based on the number of subjects in the randomized safety population in each group.
[b]N = 126 for the placebo group and N = 130 for the triple-bead MAS group.
Abbreviation: MAS = mixed amphetamine salts.

require medications with a longer duration of action" than those needed to control ADHD in children.[10] In this dose-optimization study, the significant improvements in TASS scores in subjects taking triple-bead MAS during both the early and late assessments provide support for the ability of triple-bead MAS to control ADHD symptoms for up to 16 hours. These data support phase 2 study data demonstrating the extended duration of efficacy of triple-bead MAS up to 16 hours without the need for repeat dosing.[12,13]

Safety/Tolerability

Treatment-emergent AEs reported in this study were predominantly mild or moderate in severity and reflect the types of AEs commonly associated with currently marketed amphetamine products.[35] Only 12% of subjects discontinued triple-bead MAS due to treatment-emergent AEs. Vital sign changes associated with active treatment were notable for small increases in pulse rate and blood pressure and decreases in weight, changes that are commonly seen with amphetamine treatment. Insomnia (including the preferred terms *insomnia*, *initial insomnia*, *middle insomnia*, and *early morning awakening*) was reported by 29.2% of subjects receiving triple-bead MAS. Most of these events resolved following treatment with active study drug (73.9%), were mild to moderate in severity (93.5%), did not require pharmacologic intervention (only 4.3% required intervention), and did not result in discontinuation from the study (only 2.2% resulted in discontinuation). On a more fine-grained measure of sleep,

Table 5. Mean (SD) Change From Baseline to Endpoint in Electrocardiogram Parameters (randomized safety population)[a]

Parameter	Placebo (N = 133)	Triple-Bead MAS (N = 134)
PR interval, ms[b]	1 (9.8)	–4 (10.7)
QRS, ms	–1 (6.9)	0 (6.2)
QT interval, ms	1 (21.7)	–8 (21.6)
QTc–Bazett, ms	3 (16.9)	5 (16.6)
QTc–Fridericia, ms	2 (13.8)	0 (13.5)

[a]Results are based on the number of subjects in the randomized safety population in each group.
[b]For this variable, data were available for only 133 subjects in the triple-bead MAS group.
Abbreviations: MAS = mixed amphetamine salts, QTc = QT interval corrected for heart rate.

the PSQI, the total score indicated that overall sleep quality was not impaired in triple-bead MAS–treated subjects compared with subjects who received placebo.

Subjects in this study were screened to rule out known structural cardiac abnormalities, as well as any other condition that might affect cardiac performance; an additional exclusionary criterion was controlled or uncontrolled hypertension or resting systolic blood pressure > 139 mm Hg or diastolic blood pressure > 89 mm Hg. As this study did not address treatment of subjects with underlying hypertension or those ≥ 55 years of age, generalizability to these populations is limited. Adults in this age range are at risk for asymptomatic, occult hypertension that is unrelated to ADHD or its treatment; therefore, baseline and periodic measurement of blood pressure and pulse rate may be clinically helpful in monitoring this population. In adulthood, tasks requiring organization and planning often occur beyond the traditional 10–12 hours of treatment provided by existing formulated stimulants. An effective treatment with a longer duration of action (up to 16 hours) may be beneficial in adults who require ADHD symptom control throughout the evening hours.

Study Limitations

Because the presence of psychiatric comorbidities is common among adults with ADHD, exclusion of subjects with a comorbid psychiatric diagnosis with significant symptoms may have limited the generalizability of the study findings to a broader population of adults with ADHD.

CONCLUSIONS

In this study, triple-bead MAS was significantly more effective than placebo for the treatment of ADHD in adults, as demonstrated by the primary and secondary efficacy measures. Treatment-emergent AEs were generally mild to moderate in intensity and both treatment-emergent AEs and mean vital sign changes were similar to those typically seen with currently marketed amphetamine products. Many adults with ADHD may benefit from medication coverage for both their workday and their evening hours at home. Improved executive function (e.g., organizing, prioritizing, focusing, managing frustration, and utilizing working memory) contributes to optimal parenting, healthy relationships, safer driving, and management of personal finances and domestic obligations, as well as effective planning for future goals and tasks. The extended duration of action of triple-bead MAS, up to 16 hours postdose, combined with significant improvements in executive function and QOL, may address the unique treatment needs of the adult with ADHD.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Daytrana, Ritalin, and others), mixed amphetamine salts (Adderall and others).

Acknowledgments: The authors wish to acknowledge Colleen S. Anderson, M.Ed. (study manager and clinical lead); Arthur Silverberg, Ph.D. (biostatistician); Gwendolyn E. Niebler, D.O. (manuscript review); and Beth D. Hamilton, M.S. (publications team lead) of Shire; Craig S. Ornstein, Ph.D. (manuscript review) of Advogent, which received payment from Shire for manuscript management; and Quintiles, Inc., for their contributions to this article. Dr. Ornstein has no other financial interests relating to this article and no conflict of interest. Quintiles, Inc., a contract research organization, received payment from Shire for clinical study monitoring and management.

Financial disclosure: **Dr. Spencer** has received research support from Shire, Eli Lilly, GlaxoSmithKline, Pfizer, McNeil, Cephalon, Janssen, Novartis, and the National Institute of Mental Health (NIMH) and is a member of the speakers/advisory boards for Cephalon, GlaxoSmithKline, Eli Lilly, Novartis, Pfizer, Shire, McNeil, and Janssen. **Dr. Adler** has received research support from Eli Lilly, Neurosearch, Cortex, Cephalon, Pfizer, Novartis, McNeil/J&J, Abbott, Merck, Bristol-Myers Squibb, National Institute of Drug Abuse, and Shire and is a member of the speakers/advisory boards and a consultant for Eli Lilly, Neurosearch, Cortex, Cephalon, Pfizer, Novartis, McNeil/J&J, Abbott, Merck, and Shire. **Dr. Weisler** has received research support from NIMH, Pfizer, Eli Lilly, GlaxoSmithKline, Abbott, Merck, Organon, Biovail, Shire, Sanofi-Synthelabo, AstraZeneca, Janssen, Wyeth Ayerst, Solvay, Novartis, Schwabe/Ingenix, Bristol-Myers Squibb, TAP, Synaptic, Eisai, UCB Pharma, Cephalon, Lundbeck, Forest, Pharmacia, Neurochem, Ciba-Geigy, Vela, Parke Davis, Sandoz, Upjohn, MediciNova, SmithKline Beecham, Saegis, Corcept, New River, McNeil, Burroughs Wellcome, and CoMentis; is a consultant for the Agency for Toxic Solvent Disease Registry/Centers for Disease Control, Bristol-Myers Squibb, Biovail, Eli Lilly, Wyeth Ayerst, Shire, Organon, Sanofi-Synthelabo, Forest, Solvay, Johnson & Johnson, Novartis, Otsuka America Pharma, Corcept, Abbott, Pfizer, and GlaxoSmithKline; is a member of the speakers/advisory boards for Wyeth Ayerst, Solvay, GlaxoSmithKline, Eli Lilly, AstraZeneca, Cephalon, Biovail, Abbott, Forest, Bristol-Myers Squibb, Shire, Pfizer, Organon, and Sanofi; and is a stock shareholder of Merck, Pfizer, and Bristol-Myers Squibb. **Dr. Youcha** is an employee of Shire Development, Inc., and reports no additional financial or other relationships relevant to the subject of this article.

REFERENCES

1. 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;163:716–723
2. Able SL, Johnston JA, Adler LA, et al. Functional and psychosocial impairment in adults with undiagnosed ADHD. Psychol Med 2007;37:97–107

3. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:187–201
4. Barkley RA. Driving impairments in teens and adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:233–260
5. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. J Clin Psychiatry 2006 Apr;67(4):524–540
6. Okie S. ADHD in adults. N Engl J Med 2006;354:2637–2641
7. Wilens TE. Drug therapy for adults with attention-deficit/hyperactivity disorder. Drugs 2003;63:2395–2411
8. O'Connor PJ. Improving medication adherence: challenges for physicians, payers, and policy makers. Arch Intern Med 2006;166:1802–1804
9. Biederman J, Spencer T, Wilens T. Evidence-based pharmacotherapy for attention-deficit/hyperactivity disorder. Int J Neuropsychopharmacol 2004;7:77–97
10. Adler LA, Chua HC. Management of ADHD in adults. J Clin Psychiatry 2002;63(suppl 12):29–35
11. Ermer JC, Shojaei A, Pennick M, et al. Bioavailability of triple-bead mixed amphetamine salts compared with a dose-augmentation strategy of mixed amphetamine salts extended release plus mixed amphetamine salts immediate release. Curr Med Res Opin 2007;23:1067–1075
12. Wigal T, Kollins S, Golarz H, et al. SPD465 Duration of effect: a prospective, double-blind, crossover study. Presented at the 53rd annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 26, 2006; San Diego, Calif
13. Wigal T, Childress A, Golarz H, et al. Clinical evaluation of SPD465, a novel ADHD compound. Presented at the 53rd annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 26, 2006; San Diego, Calif
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
15. DuPaul GJ, Power TJ, Anastopoulos AD, et al. ADHD Rating Scale-IV. New York, NY: The Guilford Press; 1998
16. Spencer TJ, Adler LA, McGough JJ, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007 Jun;61(12): 1380–1387
17. Spencer T, Biederman J, Wilens T, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2001;58:775–782
18. Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention-deficit/hyperactivity disorder. Am J Psychiatry 1998;155:693–695
19. Spencer T, Wilens T, Biederman J, et al. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1995;52: 434–443
20. Wilens TE, Haight BR, Horrigan JP, et al. Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. Biol Psychiatry 2005;57:793–801
21. Guy W. Clinical Global Impressions (CGI). ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
22. Adler LA, Sitt D, Faraone S, et al. Reliability and validity of the Time-Sensitive ADHD Symptom Scale (TASS) in adults. Presented at the 53rd annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 27, 2006; San Diego, Calif
23. Brown TE. Brown Attention-Deficit Hyperactivity Disorder Scales for Adolescents and Adults. Toronto, Ontario, Canada: The Psychological Corporation, Harcourt Assessment Canada; 1996
24. Brown TE. Executive functions and attention-deficit/hyperactivity disorder: implications of two conflicting views. Int J Disability Development and Education 2006;53:35–46
25. Barkley RA, Murphy KR, Fischer M. The Science of ADHD in Adults: Clinic-Referred Adults vs. Children Grown Up. New York, NY: Guilford Press; 2007
26. Biederman J, Petty C, Fried R, et al. Impact of psychometrically defined deficits of executive functioning in adults with attention-deficit/hyperactivity disorder. Am J Psychiatry 2006;163:1730–1738
27. Brown TE. Attention Deficit Disorder: The Unfocused Mind in Children and Adults. New Haven, Conn: Yale University Press; 2005
28. Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 2004;18:485–503
29. Brown TE, Quinlan DM. Assessing the effects of OROS methylphenidate on executive function in adults with ADHD. Presented at the 56th American Psychiatric Association Institute on Psychiatric Services; Oct 6–10, 2004; Atlanta, Ga
30. Brown TE, Sutton VK, Rogers AE, et al. Atomoxetine alleviates executive function impairment associated with ADHD. Presented at the 158th annual meeting of the American Psychiatric Association; May 21–26, 2005; Atlanta, Ga
31. Landgraf JM. Monitoring quality of life in adults with ADHD: reliability and validity of a new measure. J Atten Disord 2007;11:351–362
32. Landgraf JM, Rich M, Rappaport L. Measuring quality of life in children with attention-deficit/hyperactivity disorder and their families: development and evaluation of a new tool. Arch Pediatr Adolesc Med 2002;156: 384–391
33. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213
34. Biederman J, Mick E, Faraone SV, et al. Influence of gender on attention-deficit/hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry 2002;159:36–42
35. Goldman LS, Genel M, Bezman RJ, et al, for the Council on Scientific Affairs, American Medical Association. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. JAMA 1998 Apr;279(14):1100–1107