Randomized Controlled Study of the Histamine H3 Inverse Agonist MK-0249 in Adult Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Background: It has been suggested that the histamine subtype 3 receptor inverse agonists such as MK-0249 might be effective in treating attention-deficit/hyperactivity disorder (ADHD). We evaluated the effects of MK-0249 in adults with ADHD.

Method: A randomized, double-blind, placebo-controlled, incomplete block, 2-period crossover study of MK-0249 5–10 mg/d and osmotic-release oral system (OROS) methylphenidate 54–72 mg/d (active comparator) was performed in 72 men and women aged ≥ 18 to ≤ 55 years who met *DSM-IV* criteria for ADHD of either inattentive or combined subtype and who had a chronic course of behavior disorder. The study was conducted from August 2007 through April 2008 at 6 US sites. Primary efficacy was assessed by the mean change from baseline in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score after 4 weeks of treatment.

Results: Change from baseline in AISRS at week 4 for MK-0249 was not different from placebo ($P = .341$), whereas a significant benefit was seen for OROS methylphenidate versus placebo ($P < .001$). Analysis of secondary end points, including the Conners Adult ADHD Rating Scales, showed results consistent with the AISRS. A similar percentage of patients reported adverse events for MK-0249 compared with placebo (73% versus 69%, respectively). However, a greater percentage of patients reported insomnia as an adverse event with MK-0249 treatment compared with placebo (32% versus 11%, respectively).

Conclusions: MK-0249 10 mg/d is not effective for the treatment of adult ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT00475735

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Attention-deficit/hyperactivity disorder (ADHD) is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity and potentially affects as many as 9.4 million adults in the United States.[1,2] Stimulants, including methylphenidate and amphetamine-based products, are the primary pharmacotherapy but are associated with approximately 30% nonresponse, as well as cardiovascular and psychiatric risks, including a perceived abuse-potential liability.[3–5]

Abnormalities of arousal, arising from hypothalamic dysfunction with alterations in noradrenergic and dopaminergic neurotransmission, are thought to be key components of ADHD.[6] Recent attention has focused on histamine as a primary neural regulator of arousal and attention.[7–11] The histamine H3 receptor subtype is mainly distributed in the central nervous system and functions as both a presynaptic autoreceptor that reduces histamine release and a heteroreceptor that regulates release of other neurotransmitters.[10,11] Histamine H3 receptor antagonists and inverse agonists increase release of brain histamine and other neurotransmitters.[10,11] The H3 receptor antagonists have been shown to promote arousal in various species, without the psychomotor activation seen with stimulants.[12] In an animal model of ADHD (spontaneously hypertensive rats), H3 antagonists facilitated the acquisition of an inhibitory learning task, as did methylphenidate.[13] These data suggest a potential role for H3 receptor antagonists or inverse agonists in treating ADHD.

MK-0249 is a potent H3 receptor inverse agonist with a $t_{1/2}$ (elimination half-life) of approximately 14 hours and a T_{max} (time to reach peak concentration) of approximately 4 hours. Steady-state is achieved within approximately 6 days. The chemical structure of MK-0249 and the chemical and biological characteristics of the class of compounds to which it belongs have been previously reported.[14,15] MK-0249 has been shown to have alertness-promoting effects following single-dose administration in human experimental medicine models.[16,17] The aim of this pilot study was to explore whether a 10-mg daily dose of MK-0249 given for 4 weeks might be effective in adults with ADHD. The selection of 10 mg/d as the dose for evaluation was based on positron emission tomography (PET) receptor occupancy data and tolerability in phase 1 studies and is addressed further in the Discussion.

METHOD

Participants

The trial (Merck Protocol 018) was conducted from August 2007 through April 2008 at 6 US sites. Patients meeting *DSM-IV* criteria for ADHD of either inattentive or combined subtype[18] and having a chronic course of behavior disorder (initiated by age 7 years), as assessed via structured interview using the Adult ADHD Clinician Diagnostic Scale, version 1.2,[19] were enrolled. The main inclusion criteria were age of 18–55 years, a total symptom severity score on the Conners Adult ADHD Rating Scales-Observer Screening Version (CAARS-O:SV)[20] of ≥ 24, and a score of ≥ 4 (moderately ill) on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[21] The main exclusion criteria were history of other psychiatric disorders (including sleep disorders

Clinical Points

- Histamine is involved in the regulation of attention, and it has been hypothesized that modulation of histamine function might be a new treatment for attention-deficit/hyperactivity disorder (ADHD).
- This hypothesis was not supported in a clinical trial in adults with ADHD using an experimental drug that modulated histamine function.
- Future work to examine other nonstimulants with varied mechanisms of action is necessary in ADHD.

and substance abuse) or neurologic disorders and history of poor or no response to a prior course of methylphenidate or other stimulant for ADHD.

The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from the patients. The study was registered at ClinicalTrials.gov (identifier: NCT00475735).

Interventions

This was a randomized, double-blind, placebo-controlled, incomplete block, 2-period (4 weeks per period) crossover study of MK-0249 10 mg/d and an active comparator, with a 1-week placebo run-in period and a 1-week placebo washout between treatment periods. The active comparator was osmotic-release oral system (OROS) methylphenidate. The trial design is summarized in Figure 1. Eligible patients were randomized to 1 of six 2-period (4 weeks per period) sequences: MK-0249/placebo, placebo/MK-0249, MK-0249/OROS methylphenidate, OROS methylphenidate/MK-0249, placebo/OROS methylphenidate, and OROS methylphenidate/placebo.

OROS methylphenidate was provided as 18-mg tablets, and MK-0249 was provided as 5-mg tablets. Patients were instructed to take medication orally, once daily in the morning. OROS methylphenidate was titrated from 36 mg/d to 72 mg/d over the first week of each period. The starting and maximum dose of MK-0249 was 10 mg/d. The dose of either study drug could be lowered at any time due to emergence of adverse events (from 72 mg/d to 54 mg/d for OROS methylphenidate or from 10 mg/d to 5 mg/d for MK-0249). In the event of tolerability issues at the lower dose following down-dosing, the patient could discontinue the study drug during period 1 and enter the placebo washout followed by period 2. Up-dosing and down-dosing were performed in a blinded manner.

Randomization (stratified by site) was achieved using a computer-generated allocation schedule prepared by a blinded statistician at Merck. Blinded drug supplies were provided in numbered containers. All study personnel, including investigators, study site personnel, patients, and Merck staff, remained blinded to treatment allocation throughout the study. Unblinding took place after data collection was finalized and medical/scientific review had been completed. Compliance was evaluated by tablet counts at each weekly clinic visit.

Concomitant Therapy

The main medications prohibited throughout the study were methylphenidate (other than as part of study treatment) or other drugs for ADHD, clonidine, warfarin, heparin, ticlopidine, corticosteroids, psychotropic medications (eg, antidepressants, anxiolytics), potent cytochrome P450 3A4 inhibitors and inducers, and drugs with significant anticholinergic or antihistaminergic effects. Limited use of analgesics or prescription sleep medications was allowed but was prohibited the day before a clinic visit.

Efficacy Assessments

The following efficacy measurements were administered: the Adult ADHD Investigator Symptom Rating Scale (AISRS),[22] the CAARS-O:SV,[20] the CGI-S,[21] the Stroop test,[23] and the Conners' Continuous Performance Test (CPT).[24] All assessments were administered at baseline (end of placebo run-in). The AISRS and CGI-S were repeated at weekly intervals. The other assessments were performed at the end of period 1, at the end of placebo washout, and at the end of period 2. All raters were trained and certified as per established procedures and reference rater training.[25] Every effort was made to have the same rater administer the assessments throughout the trial.

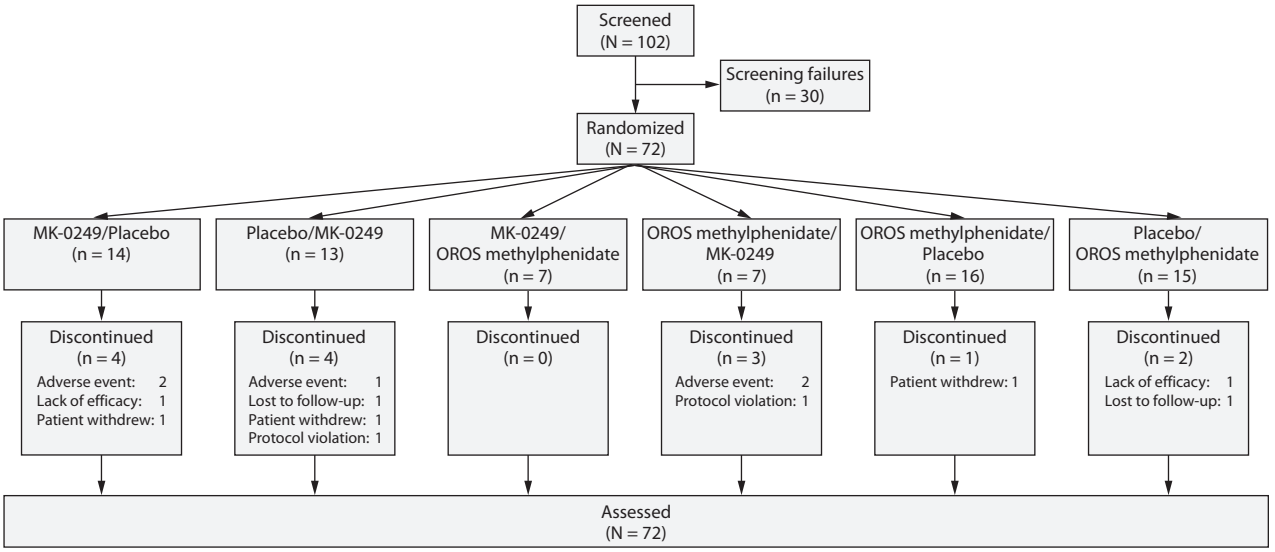
Safety Assessments

Tolerability and safety were assessed via spontaneous adverse event reports and by physical and laboratory examinations, electrocardiograms, and vital sign measurements performed prestudy and at subsequent clinic visits.

Statistical Analysis

The primary efficacy analysis compared MK-0249 versus placebo with respect to the mean change from baseline (ie, from the end of the placebo run-in) in the AISRS total score after 4 weeks of treatment. The population for efficacy analyses was the full-analysis-set population and included data as observed. All patients who were randomized, received at least 1 dose of study medication, and had at least 1 efficacy assessment were analyzed in the treatment group to which they were randomized. Secondary analyzed measures were percentage of responders on the AISRS (those who achieved ≥ 30% improvement from baseline on total score), mean change from baseline in the AISRS inattentive subscale score, mean change from baseline in the AISRS hyperactive/impulsive subscale score, and mean change from baseline in the CAARS-O:SV total ADHD symptom score. Exploratory measures that were analyzed were mean change from baseline in Stroop color-word score, Stroop color score, CPT commissions score, CPT response-style score, and CPT hit reaction time block change score. The CGI-S was also prespecified for analysis

Figure 1. Study Flow Diagram[a]



[a]The study had a 2-period crossover design. The diagram shows overall patient disposition by treatment sequence; the first named treatment was administered in treatment period 1 and the second named treatment was administered in treatment period 2. *Discontinued* means that the patient discontinued study treatment during 1 or both of the treatment periods. Patients could discontinue treatment during treatment period 1 and enter treatment period 2. For patients who discontinued from more than 1 treatment period, the reason for the latest discontinuation is shown. Hence, the number of discontinuations due to adverse events shown here does not correspond to the data shown by treatment group in Table 3. The maximum daily dose of MK-0249 was 10 mg (down-dosing to 5 mg was allowed for tolerability issues). The maximum daily dose of OROS methylphenidate was 72 mg (down-dosing to 54 mg was allowed for tolerability issues).
Abbreviation: OROS = osmotic-release oral system.

but was not analyzed since the study was negative for the primary hypothesis.

A mixed-effects model was used to analyze the continuous efficacy variables. The analysis estimated the mean response at each of the following time points: week −1 (baseline), weeks 1–4 (period 1), week 5 (placebo washout), and weeks 6–9 (period 2). A constrained longitudinal data analysis was used that imposes equal baselines across treatment groups; the analysis included terms for tobacco use, prior stimulant use, site, and sequence × time as covariates. An unstructured covariance was used for the within-subject correlation. For the categorical variable of AISRS responders, a generalized estimation equation model was used with the term sequence × time. No multiplicity adjustments were used for the primary hypothesis.

Safety and tolerability were assessed by adverse events within 14 days after the last dose of treatment (or after discontinuation), laboratory values, vital signs, physical/neurologic examination, and electrocardiograms. The primary population for all safety analyses was the all-patients-as-treated population, which included all patients who received at least 1 dose of study medication according to the treatment they received (in practice, identical to the population used for the efficacy analysis).

Adherence to Treatment

The percentage adherence for a patient was calculated as follows: [no. of days exposed to therapy]/[no. of days from first day on therapy to last visit day for completers *or* no. of days from first day on therapy to last day on therapy for patients who discontinued] × 100.

Sample Size

Expected improvements in AISRS were estimated on the basis of a prior study of bupropion.[26] A total of 60 patients were planned to be randomized: MK-0249/placebo (n = 12), placebo/MK-0249 (n = 12), MK-0249/OROS methylphenidate (n = 6), OROS methylphenidate/MK-0249 (n = 6), placebo/OROS methylphenidate (n = 12), and OROS methylphenidate/placebo (n = 12). The planned sample size provided 97% power to detect a true difference of 8 points between MK-0249 and placebo with respect to mean change from baseline in AISRS total score at week 4 (2-sided test, 5% level of significance), based on a mean-square error of 60.5 points and assuming a correlation of 0 for the change-from-baseline values between periods.

RESULTS

Patient Accounting and Demographics

The trial profile by treatment sequence group is shown in Figure 1. Of the 72 randomized patients, 59 completed period 1, 63 entered period 2, and 58 completed period 2. A total of 14 patients discontinued the study, with the main reason being an adverse event (see Tolerability and Safety section below). The numbers of patients who took treatment were 37 for MK-0249, 44 for OROS methylphenidate, and 54 for placebo.

Table 1. Baseline Characteristics of Patients by Treatment Group[a]

Characteristic	MK-0249 (n = 37)	OROS Methylphenidate (n = 44)	Placebo (n = 54)
Demographic			
Male sex, n (%)	21 (56.8)	28 (63.6)	35 (64.8)
Age, mean (SD), y	38.7 (10.1)	38.6 (11.4)	38.3 (11.4)
White race, n (%)	30 (81.1)	33 (75.0)	45 (83.3)
Tobacco use, n (%)	5 (13.5)	6 (13.6)	8 (14.8)
Prior stimulant use, n (%)	1 (2.7)	2 (4.5)	1 (1.9)
Common secondary diagnoses[b]			
Drug hypersensitivity, n (%)	4 (10.8)	9 (20.5)	10 (18.5)
Headache, n (%)	5 (13.5)	3 (6.8)	7 (13.0)
Common concomitant treatment[b]			
Ibuprofen, n (%)	7 (18.9)	8 (18.2)	11 (20.4)

[a]Because of the crossover nature of the study design, in this table an individual patient is counted up to 2 times, once for each therapy received in treatment periods 1 and 2. For example, a patient randomized to and treated in each period of the treatment sequence MK-0249/placebo is counted once in the MK-0249 group and once in the placebo group. The totals of the treatment groups do not add up to the number randomized (72 × 2 = 144) because not all patients entered both treatment periods.
[b]Greater than 10% in any treatment group.
Abbreviation: OROS = osmotic-release oral system.

Of the 72 randomized ADHD patients, 10 (13.9%) were of the inattentive subtype and 62 (86.1%) were of the combined subtype. Baseline characteristics of the patients by treatment group are summarized in Table 1. Overall, the treatment groups were similar with regard to age and race. A higher percentage of men participated in the study, but the sex distribution was similar across treatment groups. Baseline AISRS scores were similar across treatment groups.

Mean percentage adherence was 96.7% for MK-0249, 97.6% for OROS methylphenidate, and 96.3% for placebo. The mean number of adherent days on therapy was 23.7 days for MK-0249, 26.0 days for OROS methylphenidate, and 26.1 days for placebo. The pharmacokinetic results showed that the mean maximum concentration (C_{max}) after approximately 28 days of dosing of MK-0249 was 33.4 nmol/L (standard deviation [SD] = 15.5 nmol/L), which is comparable to findings from phase 1 studies for the 10-mg/d dose (Merck & Co, Inc; unpublished data on file; 2008), confirming that patients were adherent to the medication regimen.

Efficacy

Efficacy results are summarized in Table 2. Analysis of the primary efficacy end point of change from baseline in AISRS score at week 4 showed that MK-0249 10 mg/d was not statistically significantly different from placebo, whereas OROS methylphenidate was statistically significantly better than placebo. The results by week on the primary efficacy end point are shown in Figure 2. Only the OROS methylphenidate group separated from placebo, beginning at week 1.

There was some evidence of carryover effects in the study, in that observed AISRS scores at the start of period 2 (after a 1-week washout) were lower in all treatment groups compared to the baseline score at the beginning of period 1. For example, patients who received MK-0249 in period 1 started with a baseline value of 34.7 on the AISRS, whereas, at the start of period 2 (after the 1-week washout), their mean value on the AISRS was 27.5. An analysis of data from period 1 only suggested that the conclusions regarding the efficacy of MK-0249 were not altered, since period 1 results paralleled the overall results. The differences in change from baseline least-squares means for period 1 only were as follows: MK-0249 versus placebo: −2.9 (95% CI, −9.0 to 3.2; $P = .344$); OROS methylphenidate versus placebo: −8.8 (95% CI, −15.0 to −2.8; $P = .005$).

The number and percentage of responders on the AISRS (≥ 30% improvement in total score at week 4) were 8 of 29 (27.6%) for MK-0249, 22 of 39 (56.4%) for OROS methylphenidate, and 12 of 48 (25.0%) for placebo. The difference between MK-0249 and placebo was not significant ($P = .455$), whereas the difference between OROS methylphenidate and placebo was significant ($P = .003$). Similarly, analysis of the secondary end points of AISRS inattentive subscale score, AISRS hyperactive/impulsive subscale score, and CAARS-O:SV score showed results consistent with the AISRS primary end point (see Table 2).

Analysis of exploratory CPT and Stroop end points showed no significant effects of either treatment versus placebo, other than an isolated significant difference for MK-0249 over placebo on CPT response style (see Table 2).

Tolerability and Safety

MK-0249 was generally well tolerated. Clinical adverse events are summarized in Table 3; there were no serious adverse events. Nine patients discontinued due to clinical adverse events: 5 in the MK-0249 group, 3 in the OROS methylphenidate group, and 2 in the placebo group (1 patient discontinued due to separate adverse events that occurred in both treatment periods). Adverse events resulting in discontinuation in the MK-0249 group were insomnia (n = 3), decreased libido plus erectile dysfunction (n = 1), and chest discomfort (n = 1). Adverse events resulting in discontinuation in the OROS methylphenidate group were irritability plus feeling jittery (n = 1); nervousness plus insomnia (n = 1); and dry mouth, mydriasis, anxiety, tachycardia, and urinary hesitation (n = 1).

The percentage of patients with adverse events was similar among the treatment groups. The percentage of patients with drug-related adverse events in the MK-0249 group was higher than in the placebo group, but lower than in the OROS methylphenidate group. The most common adverse event that showed an increase for MK-0249 versus placebo was insomnia, which was mostly mild to moderate in intensity. The most common adverse events that showed an increase for OROS methylphenidate versus placebo were dry mouth and anxiety.

There were no other clinically relevant changes in laboratory values, vital signs, physical or neurologic examinations, or electrocardiograms in any treatment group.

Table 2. Summary of Efficacy: LS Mean Scores at Baseline and Week 4, Change From Baseline, and Difference Versus Placebo for Continuous Efficacy Variables[a]

Variable	N	Baseline LS Mean (SE)	Week 4 LS Mean (SE)	Change From Baseline, LS Mean (95% CI)[b]	Difference Versus Placebo (95% CI)	*P* Value
Primary end point						
AISRS						
MK-0249	29	34.6 (2.8)	24.8 (3.4)	−9.8 (−13.5 to −6.0)	−2.1 (−6.6 to 2.3)	.341
OROS methylphenidate	39	34.6 (2.8)	19.3 (3.3)	−15.3 (−18.7 to −11.8)	−7.6 (−12.0 to −3.4)	.001
Placebo	48	34.6 (2.8)	27.0 (3.1)	−7.6 (−10.5 to −4.7)	…	…
Secondary end points						
AISRS inattentive score						
MK-0249	29	21.1 (1.2)	16.0 (1.7)	−5.2 (−7.5 to −2.8)	−0.9 (−3.6 to 1.9)	.533
OROS methylphenidate	39	21.1 (1.2)	12.5 (1.6)	−8.6 (−10.7 to −6.5)	−4.3 (−6.9 to −1.7)	.001
Placebo	48	21.1 (1.2)	16.8 (1.5)	−4.3 (−6.1 to −2.5)	…	…
AISRS hyperactive/impulsive score						
MK-0249	29	12.8 (2.0)	8.5 (2.2)	−4.3 (−6.2 to −2.4)	−0.7 (−2.8 to 1.5)	.549
OROS methylphenidate	39	12.8 (2.0)	6.5 (2.1)	−6.3 (−8.1 to −4.6)	−2.7 (−4.8 to −0.6)	.013
Placebo	48	12.8 (2.0)	9.2 (2.1)	−3.6 (−5.1 to −2.2)	…	…
CAARS-O:SV score						
MK-0249	29	32.7 (2.8)	22.9 (3.6)	−9.8 (−14.3 to −5.4)	−2.1 (−7.2 to 2.9)	.401
OROS methylphenidate	41	32.7 (2.8)	17.5 (3.3)	−15.2 (−18.9 to −11.6)	−7.6 (−12.0 to −3.1)	.001
Placebo	49	32.7 (2.8)	25.0 (3.2)	−7.7 (−10.8 to −4.6)	…	…
Exploratory end points						
CPT commissions						
MK-0249	19	17.2 (4.8)	14.7 (5.1)	−2.4 (−6.9 to 2.0)	−3.8 (−8.6 to 1.1)	.128
OROS methylphenidate	23	17.2 (4.8)	18.5 (5.0)	−1.2 (−5.3 to 3.0)	−2.5 (−7.2 to 2.2)	.298
Placebo	26	17.2 (4.8)	18.5 (5.0)	1.3 (−2.3 to 5.0)	…	…
CPT response style						
MK-0249	34	1.4 (0.7)	1.1 (0.3)	−0.3 (−1.7 to 1.2)	0.5 (0.1 to 0.9)	.016
OROS methylphenidate	44	1.4 (0.7)	0.7 (0.3)	−0.6 (−2.0 to 0.8)	0.1 (−0.3 to 0.5)	.576
Placebo	51	1.4 (0.7)	0.6 (0.3)	−0.7 (−2.1 to 0.6)	…	…
CPT hit reaction time block change						
MK-0249	19	0.838 (0.827)	0.000 (0.009)	−0.837 (−2.487 to 0.812)	−0.002 (−0.015 to 0.012)	.798
OROS methylphenidate	23	0.838 (0.827)	0.002 (0.008)	−0.836 (−2.485 to 0.814)	−0.000 (−0.013 to 0.012)	.962
Placebo	26	0.838 (0.827)	0.002 (0.008)	−0.836 (−2.485 to 0.814)	…	…
Stroop color-word score						
MK-0249	33	106.7 (4.7)	109.0 (4.7)	2.3 (−0.9 to 5.6)	−1.0 (−4.4 to 2.4)	.563
OROS methylphenidate	43	106.7 (4.7)	110.5 (4.6)	3.8 (0.7 to 6.8)	0.4 (−2.8 to 3.7)	.795
Placebo	51	106.7 (4.7)	110.0 (4.6)	3.3 (0.6 to 6.1)	…	…
Stroop color score						
MK-0249	33	111.7 (0.4)	111.3 (0.5)	−0.4 (−1.1 to 0.3)	−0.6 (−1.3 to 0.1)	.071
OROS methylphenidate	43	111.7 (0.4)	112.0 (0.4)	0.3 (−0.4 to 0.9)	0.0 (−0.6 to 0.7)	.904
Placebo	51	111.7 (0.4)	112.0 (0.4)	0.2 (−0.4 to 0.8)	…	…

[a]For AISRS, CAARS-O:SV, CPT commissions, and CPT hit reaction time block change measures, a negative change from baseline indicates improvement relative to baseline. For Stroop color-word score and Stroop color score measures, a positive change from baseline indicates improvement relative to baseline. For the CPT response style measure, a negative change from baseline indicates a change in response style to one that is less cautious about mistakenly responding to a nontarget.

[b]Results based on a constrained longitudinal data analysis that imposes equal baselines across treatment groups. The analysis included terms for tobacco use, prior stimulant use, site, and sequence × time as covariates.

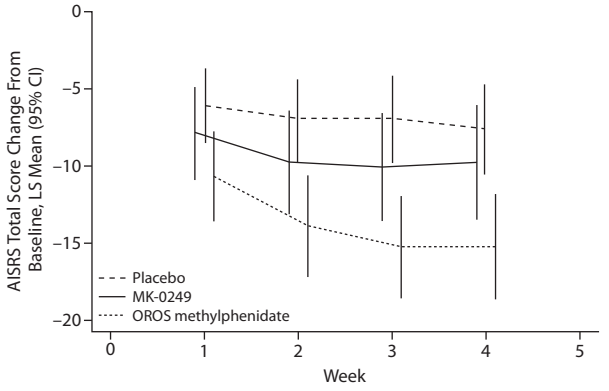
Abbreviations: AISRS = Adult Attention-Deficit/Hyperactivity Disorder Investigator Symptom Rating Scale, CAARS-O:SV = Conners Adult Attention-Deficit/Hyperactivity Disorder Rating Scales-Observer Screening Version, CPT = Continuous Performance Test, LS = least-squares, OROS = osmotic-release oral system, SE = standard error.

DISCUSSION

In this relatively brief proof-of-concept study, contrary to our hypothesis, the histamine H3 inverse agonist MK-0249 was not efficacious compared to placebo for the treatment of ADHD in adults. In contrast, OROS methylphenidate was effective compared to placebo, as expected given that other studies in adults with ADHD have demonstrated effectiveness for this medication.[27,28] Hence, we are confident that the lack of efficacy of MK-0249 was not related to the execution of the study but to the inherent properties of the drug at the dose studied.

The failure of MK-0249 to separate from placebo could potentially be related to the dose. A 10-mg/d dose was selected partly on the basis of PET data that demonstrated approximately 85% occupancy of H3 receptors in humans at the maximum blood level (Merck & Co, Inc; unpublished data on file; 2008) and demonstration that this dose had alerting effects in a sleep deprivation model in healthy adults.[16] In addition, 10-mg/d was considered to be the maximum tolerated dose, given that there were a large number of complaints of insomnia in earlier phase 1 studies in healthy subjects (Merck & Co, Inc; unpublished data on file; 2008), consistent with the increased reports of insomnia observed in the present study. This tolerability profile could be related to the relatively long half-life of MK-0249. A shorter-half-life H3 inverse agonist that allowed dosing to receptor occupancy saturation might have a different effect. However, a higher 50-mg/d dose, producing 93% receptor occupancy, had alerting effects similar to the 10-mg/d dose, suggesting that

Figure 2. Model-Based Least-Squares (LS) Mean AISRS Total Score Change From Baseline (with 95% CI) by Treatment Group at Each Week



Abbreviations: AISRS = Adult Attention-Deficit/Hyperactivity Disorder Investigator Symptom Rating Scale, OROS = osmotic-release oral system.

Table 3. Summary of Clinical Adverse Events Reported Within 14 Days After Dosing by Treatment Group

Variable	MK-0249 (n = 37)	OROS Methylphenidate (n = 44)	Placebo (n = 54)
One or more adverse events, n (%)	27 (73.0)	33 (75.0)	37 (68.5)
Drug-related adverse event, n (%)[a]	23 (62.2)	32 (72.7)	27 (50.0)
Discontinuation due to adverse event, n (%)	5 (13.5)	3 (6.8)	2 (3.7)
Common adverse events, n (%)[b]			
Insomnia	12 (32.4)	6 (13.6)	6 (11.1)
Headache	3 (8.1)	3 (6.8)	7 (13.0)
Dry mouth	1 (2.7)	10 (22.7)	1 (1.9)
Anxiety	0 (0.0)	7 (15.9)	1 (1.9)

[a]Determined by the investigator (while blinded to treatment) to be related to the drug.
[b]Incidence ≥ 10% in any treatment group.
Abbreviation: OROS = osmotic-release oral system.

higher doses may offer only limited additional benefits.[12] Stimulants appear to be effective with less-than-saturation dopamine transporter occupancy (approximately 70%),[29,30] but it may be that higher occupancy of H3 receptors is necessary for a therapeutic effect in ADHD. It is also possible that a trial of longer duration may have demonstrated efficacy of MK-0249 due to a delay in onset of action of the medication. However, inspection of our data does not indicate any significant change in response at the end of the study relative to earlier time points.

Our findings of a lack of efficacy for MK-0249 are similar to disappointing recent findings with some other nonstimulants including nicotinic agonists[31] and catecholamine multiple reuptake inhibitors[32] that failed to separate from placebo. In contrast, other nonstimulants that act predominantly via catecholaminergic reuptake inhibition, such as atomoxetine[33] and bupropion,[34] have been demonstrated to be effective for ADHD. It may be that agents with indirect dopamine and noradrenergic effects, such as reported preclinically with H3 antagonists,[11] may be insufficient to improve symptoms in ADHD.

In addition to the primary measures assessing ADHD symptomatology, there were no important differences between MK-0249 and placebo for neuropsychological outcomes. These data suggest a lack of efficacy not only for ADHD symptoms, but also for neuropsychological changes that may or may not reflect ADHD. This finding is not surprising given that only a subset of ADHD patients appear to be impaired on neuropsychological tests and that improvements on the Stroop test during atomoxetine treatment were seen only in a subset of individuals impaired on this measure at baseline.[35]

MK-0249 was relatively well tolerated, with overall adverse-event rates similar to placebo. Of interest, MK-0249 was associated with a higher rate of insomnia compared to placebo, commensurate with the prohistaminergic properties of the medication and supporting the suggestion that H3 inverse agonists may have wakefulness-promoting properties. However, in a pilot study[36] of patients with excessive daytime sleepiness, MK-0249 did not appear to help maintain daytime wakefulness on the primary assessment instrument, although improvements were seen on some neuropsychological end points. The interpretation of the increased insomnia associated with MK-0249 in the present study is not clear.

It is interesting that, despite the suggestion of an alertness-promoting effect of MK-0249 in previous studies of healthy subjects[16,17] and some patient groups,[36] there was no effect on ADHD nor any suggestion of an improved neuropsychological profile in our study of adult ADHD patients. These data suggest that enhancing the state of arousal may not in itself be adequate to treat ADHD.

There were a number of limitations to this study. It was a pilot study and, as such, was limited by the small sample sizes and relatively short duration. While attempts were made to choose a dose of medication that was appropriate, we may have underestimated or overestimated the necessary dose. Patients were carefully screened with strict inclusion and exclusion criteria, possibly limiting the generalizability of the study to clinic populations. On the other hand, the study was successful in recruiting an intended representative sample of adult ADHD patients, with a majority of the patients (86%) being of the combined ADHD subtype and the remainder (14%) being of the inattentive subtype. Due to the positive response of this sample to the active comparator, it seems likely that the results of this study, with respect to lack of efficacy for MK-0249 10-mg/d, could be reasonably generalized to the broader adult ADHD population. Whether the results are generalizable to the pediatric ADHD population is less certain. Similar efficacy across age groups is typically seen with other stimulant and nonstimulant agents efficacious in the treatment of ADHD. However, there have been instances, such as with modafinil, in which positive findings with a drug in a pediatric ADHD population[37] have not been replicated in an adult ADHD population.[38]

Despite these methodological shortcomings, our data suggest that a histamine inverse agonist, given as monotherapy, was not effective for treating ADHD in adults. It may be of value to conduct further studies to evaluate whether

the combination of a histamine H3 receptor inverse agonist with a stimulant might improve efficacy in partly stimulant-responsive patients. Animal studies have suggested a modulatory effect of H3 receptor inverse agonism on methamphetamine,[39] and a human experimental medicine study found that an H3 receptor inverse agonist enhanced the procognitive effects of a cholinesterase inhibitor.[40]

Drug names: atomoxetine (Strattera), bupropion (Aplenzin, Wellbutrin, and others), clonidine (Catapres, Duraclon, and others), ibuprofen (Caldolor, Ibu-Tab, and others), methamphetamine (Desoxyn and others), methylphenidate (Ritalin, Metadate, and others), osmotic-release oral system methylphenidate (Concerta), modafinil (Provigil), warfarin (Coumadin, Jantoven, and others).

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Potential conflicts of interest: **Drs Herring**, **Liu**, **Lines**, and **Michelson**; **Ms Baranak**; and **Mr. Snavely** are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, and own stock or stock options in Merck. **Dr Wilens** has received grant support from Abbott, McNeil, Eli Lilly, the National Institutes of Health (the National Institute on Drug Abuse), Merck, and Shire; has been a member of the speakers bureaus for Eli Lilly, McNeil, Novartis, and Shire; and has been a consultant for Abbott, McNeil, Eli Lilly, the National Institutes of Health (the National Institute on Drug Abuse), Novartis, Merck, and Shire. **Dr Adler**, in the prior year, has received grant/research support from, has consulted with, or has served on advisory boards for Shire, Eli Lilly, the National Institute on Drug Abuse, Chelsea Therapeutics, Major League Baseball, Shire, i3 Research, Merck, AstraZeneca, Otsuka, United BioSource, EPI-Q, INC Research, and the Major League Baseball Players Association and, since 2004, has received royalty payments (as inventor) from New York University for license of adult ADHD scales and training materials.

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