A Randomized Pilot Study of the Efficacy and Safety of ABT-089, a Novel $\alpha_4\beta_2$ Neuronal Nicotinic Receptor Agonist, in Adults With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: ABT-089, an $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonist (generic name *pozanicline*), has demonstrated efficacy in adults with attention-deficit/hyperactivity disorder (ADHD) at doses of 40 mg once daily and 40 mg twice daily. The purpose of this exploratory pilot study was to obtain initial safety, tolerability, and efficacy data for an ABT-089 80-mg once-daily regimen to inform a decision of whether to include an 80-mg once-daily dose regimen in subsequent, definitive (phase 3) efficacy studies.

Method: This phase 2, randomized, double-blind, parallel-group, placebo-controlled pilot study was conducted at 12 sites from March to August 2008. A screening/washout period of up to 4 weeks was followed by an 8-week double-blind treatment period. Eligible subjects met *DSM-IV-TR* criteria for ADHD and were randomized in a 1:1:1 ratio to ABT-089 40 mg once daily, ABT-089 80 mg once daily, or placebo. The primary efficacy variable was reduction from baseline to the final evaluation in the investigator-rated Conners' Adult ADHD Rating Scale for each active treatment group versus placebo. Safety assessments and pharmacokinetic sampling were also conducted.

Results: A total of 160 subjects were randomized, with 137 (86%) completing the trial. No statistically significant treatment effects were observed with either ABT-089 dose for any efficacy measures. The most commonly reported adverse events in the active treatment groups were nasopharyngitis (6.6%), upper respiratory tract infection (6.6%), and somnolence (5.7%). The incidence of adverse events did not differ significantly between active groups and placebo. There were no clinically significant laboratory, electrocardiogram, or physical examination findings.

Conclusions: ABT-089 was generally well tolerated at doses up to 80 mg. Because ABT-089 is a weak partial neuronal nicotinic receptor agonist, the results may not predict the potential efficacy for other, more potent neuronal nicotinic receptor agonists.

Trial Registration: ClinicalTrials.gov identifier: NCT00640185

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Adults with attention-deficit/hyperactivity disorder (ADHD) experience a variety of cognitive, behavioral, and emotional symptoms that lead to significant functional impairment and negatively impact quality of life. The prevalence of ADHD in adults is estimated to be approximately 4% in the United States.[1–3] Adults with ADHD often have poor time management and organization skills, have difficulty accomplishing tasks, speak and act impulsively, are forgetful, and find it difficult to monitor their own behavior.[4] Many adults with ADHD struggle to find and keep jobs,[5] fail to have healthy social relationships,[6] and achieve lower education than their counterparts without ADHD.[7] Higher rates of comorbid psychiatric illnesses such as depression, anxiety, and substance abuse in this population confer an additional burden.[7]

Cognitive function is modulated by the cholinergic system,[8] and dysregulation of the neuronal nicotinic cholinergic pathway has been implicated in the pathophysiology of ADHD.[9] ABT-089 is an $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonist (generic name *pozanicline*) that has demonstrated efficacy in animal models of attention, learning, and memory as well as in controlled trials in adults with ADHD.[10,11] In a previous clinical trial with ABT-089—investigating once-daily regimens from 2 mg to 40 mg and a 40-mg twice-daily regimen—both the 40-mg once-daily and 40-mg twice-daily regimens were superior to placebo, with similar magnitudes of effect.[10]

The purpose of this exploratory pilot study was to obtain initial safety, tolerability, and efficacy data for an ABT-089 80-mg once-daily regimen to inform a decision of whether to include an 80-mg once-daily dose regimen in subsequent, definitive (phase 3) efficacy studies. Although the study was not powered to detect statistically significant differences in efficacy between the active doses and placebo, it was expected to guide the design of subsequent, fully powered, definitive, phase 3 efficacy studies by providing initial estimates of the magnitude and within-group variance of treatment effects in a parallel-group design.

METHOD

Study Design

This was an exploratory phase 2 randomized, double-blind, parallel-design, placebo-controlled pilot study conducted at 12 sites within the United States. The study was conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice (GCP). Institutional review board approval and written informed consent were obtained prior to any study procedures. The study was registered on ClinicalTrials.gov (identifier: NCT00640185). The purpose of the study was to evaluate the safety and efficacy of 40-mg and 80-mg ABT-089 administered

once daily compared to placebo in adults with ADHD. Doses were chosen based upon earlier studies of ABT-089 in this population.[11]

The study consisted of a screening/washout period of up to 4 weeks, followed by an 8-week double-blind treatment period. Study visits occurred on days −1 (prerandomization baseline), 7, 14, 28, 42, and 56 during the double-blind treatment period. The primary efficacy end point was the change from baseline to the final evaluation in the investigator-rated Conners' Adult ADHD Rating Scale (CAARS-INV)[12] total score.

The sample size of 50 subjects per treatment group was chosen primarily to obtain safety and tolerability data for the 80-mg once-daily dose regimen, which had not been tested previously in outpatient studies. For adverse events that might be common within the active dose groups, this sample size was expected to provide frequency estimates that could reasonably inform decision making for doses in subsequent studies. The sample size also allowed initial estimates, albeit underpowered to demonstrate statistical significance, of the relative efficacy between the dose groups, for the purpose of determining whether once-daily dose regimens higher than 40 mg should be tested in definitive efficacy studies. Assuming 5% of the subjects would not have efficacy data postrandomization, a sample size of 50 subjects per treatment group was calculated to provide a power of 51%, 69%, 77%, and 84% to detect an effect size versus placebo of 0.35, 0.45, 0.5, and 0.55, respectively, for a 1-sided test at $\alpha = .05$. Subjects were randomized in a 1:1:1 ratio to the 3 treatment groups utilizing an interactive voice response system. The randomization schedule was generated by the Department of Clinical Statistics at Abbott.

Eligible participants were 18 to 60 years of age and in general good health based on a physical examination, medical history, laboratory tests, and a 12-lead electrocardiogram (ECG). Eligible female subjects were required to be either postmenopausal for at least 1 year, surgically sterile, or agree to practice a reliable method of birth control (eg, abstinence, hormonal contraception, intrauterine device) throughout the study. Women of childbearing potential underwent a serum pregnancy test at the first screening visit and urine pregnancy tests at all subsequent study visits. Women who were breastfeeding were excluded. In order to enroll in the trial, men had to be surgically sterile (vasectomy), be sexually inactive, or use a barrier method of birth control (condom) for the duration of the study.

Subjects had a current *DSM-IV-TR*[13] diagnosis of ADHD confirmed by the Adult ADHD Clinical Diagnostic Scale[14] version 1.28 at the first screening visit. Additionally, subjects had a Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S)[15] score ≥ 4, indicating moderate or more impairment, at each visit prior to randomization. Subjects who were newly diagnosed with ADHD at the initial screening visit had a second visit during the screening period to increase familiarity with ADHD symptoms and corresponding rating scale items. Subjects who had failed to respond to 2 or more adequate trials of an approved ADHD medication (stimulants or atomoxetine) were excluded.

Clinical Points

- Over 90% of adults with attention-deficit/hyperactivity disorder (ADHD) have some form of cognitive dysfunction.
- $\alpha_4\beta_2$ Neuronal nicotinic receptors are involved in cognitive processing, suggesting potential use of $\alpha_4\beta_2$ agonists in cognitive disorders.
- Although well tolerated, the $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonist ABT-089 did not demonstrate statistical significance on efficacy measures in ADHD.

Subjects with a current or past diagnosis of schizoaffective disorder, schizophrenia, obsessive-compulsive disorder, drug-induced psychosis, bipolar disorder, psychotic disorder, or mental retardation were excluded, as were those with a recent (previous 6 months) diagnosis of a major depressive episode, generalized anxiety disorder, or posttraumatic stress disorder, or a current sleep disorder requiring treatment. Subjects requiring ongoing treatment with a psychotropic medication or those receiving pharmacologic treatment for any of the aforementioned excluded disorders within the previous 6 months were not allowed to enroll in the trial. Subjects could not have taken stimulants or atomoxetine within 7 or 14 days, respectively, prior to randomization. Other psychotropic medications were to have been stopped 28 days or 5 half-lives (whichever was longer) prior to randomization.

ABT-089 was administered orally once daily in the form of 40-mg tablets and/or matching placebo. No psychotropic medications, other than short-acting nonbenzodiazepine hypnotic agents, were allowed during the study; occasional use of diphenhydramine for nonpsychotropic reasons was permitted.

Assessments

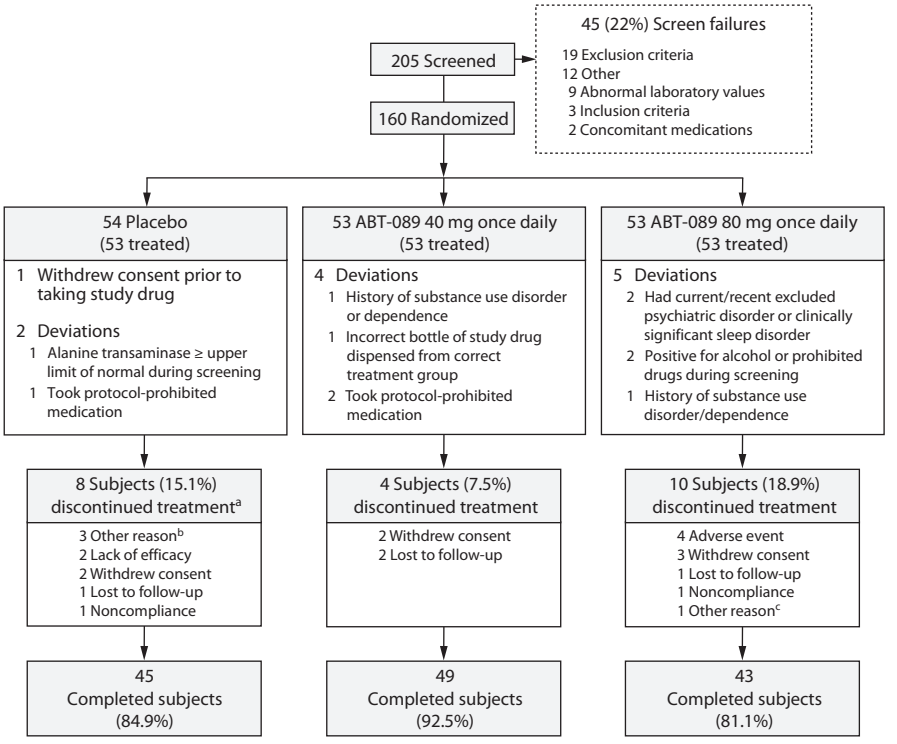
In addition to the CAARS-INV total score, the following measurements were utilized to evaluate the efficacy of ABT-089: CAARS-INV inattentive and hyperactive/impulsive subscales, CAARS ADHD Index, CGI-ADHD-S,[15] Adult ADHD Investigator Symptom Report Scale,[16] self-rated Conners' Adult ADHD Rating Scale (CAARS-Self), Time-Sensitive ADHD Symptom Scale,[17] Behavior Rating Inventory of Executive Function–Adult version,[18] Adult ADHD Quality of Life Questionnaire,[19] and the Work Productivity and Activity Impairment scale.[20] The Fagerstrom Test for Nicotine Dependence,[21] Questionnaire of Smoking Urges–Brief,[22] and the number of cigarettes smoked per day were used to explore potential study drug effects on nicotine use. Safety was evaluated through physical examinations, brief neurologic examinations, vital signs, clinical laboratory tests, ECG measurements, and adverse event monitoring throughout the study. Study drug compliance was monitored at each visit. Pharmacokinetic samples were obtained on days 7, 14, 28, 42, and 56.

Statistical Methods

The primary efficacy end point was the change from baseline to the final evaluation in the CAARS-INV total score (the sum of inattentive and hyperactive/impulsive subscales) for the intent-to-treat dataset, which included all randomized subjects who took at least 1 dose of study drug and had a minimum of 1 postbaseline CAARS-INV evaluation. The primary analysis was an analysis of covariance (ANCOVA) model with factors of treatment group and site, and with baseline score as a covariate. As specified in the protocol, an ANCOVA model was performed to obtain estimates of treatment differences between each ABT-089 dose and placebo as well as to determine the upper bound associated with a 1-sided test. Repeated-measures analysis of the CAARS-INV total score mean change from baseline to each study visit was also conducted. Analyses of secondary efficacy measures were carried out using similar models.

The safety population included all randomized subjects who took at least 1 dose of study drug. Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA)[23] and were summarized by system organ class, MedDRA-preferred terms, severity, and relationship to study drug. Treatment group comparisons of adverse events were performed using Fisher exact test. Treatment group differences in laboratory test values, vital signs, and 12-lead ECG measurements change from baseline to minimum, maximum, and final evaluation were analyzed using 1-way analysis of variance. For safety analyses, treatment group differences were evaluated using 2-sided tests at the significance level of .05. Mean plasma concentrations of ABT-089 were summarized by dose group and time frame.

Figure 1. Subject Disposition Flowchart



[a]In certain cases, more than 1 reason for discontinuation was reported; subjects were counted once in the total.
[b]Pregnancy (n = 1) and positive drug screen (n = 2).
[c]Positive urine drug screen (n = 1).

RESULTS

Subject Disposition

A total of 160 subjects were randomized in this study, which was conducted from March 24, 2008 (first subject first visit), to August 05, 2008 (last subject last visit). Twenty-two of the 159 subjects (14%) who took at least 1 dose of study drug prematurely discontinued treatment, with 137 subjects (86%) completing the study. A statistically significantly greater number of subjects in the ABT-089 80-mg once-daily group discontinued due to adverse events compared to placebo (n = 4 vs n = 0, respectively; $P = .034$). Subject disposition and protocol deviations are summarized by treatment group in Figure 1.

Subject Characteristics

Key subject baseline demographic and psychiatric characteristics are presented in Table 1. The majority of the subjects were white (84%) and male (62%). The overall mean age was 35.9 years (range, 18–59). Subjects were generally overweight, with a mean body mass index (kg/m^2) of 29.2. In terms of alcohol and nicotine use, 77% reported current alcohol use, 30% used nicotine at the time of study entry, and 15% had previously used nicotine.

Of the 159 treated subjects, 40% were newly diagnosed with ADHD upon entry into the trial. The overall Adult ADHD Clinical Diagnostic Scale subtype diagnoses included 75% (119/159) combined subtype, 25% (39/159) inattentive subtype, and < 1% (1/159) hyperactive-impulsive subtype. Significantly more inattentive subtype subjects were randomized to placebo (n = 20; $P = .02$) than to the ABT-089 40-mg once-daily (n = 9) or ABT-089 80-mg once-daily (n = 10) dose groups. More female subjects were in the placebo group, but this difference was not statistically significant. The mean (standard deviation) baseline CAARS-INV total scores were 36.9 (8.88) in the placebo group, 40.0 (7.40) in the ABT-089 40-mg once-daily group, and 37.3 (7.79) in the ABT-089 80-mg once-daily group; these differences

were not statistically significant. Subjects reported the following history of educational interventions: tutoring (34% of subjects); special classes, such as delayed or remedial (25%); and repeating a grade during kindergarten through grade 12 (22%). A total of 82% had attended college, with 36% overall having attained a college degree or higher.

The overall mean duration of study drug exposure in the 56-day double-blind period was 52.1 days in the placebo group, 54.3 days in the ABT-089 40-mg once-daily group, and 48.6 days in the ABT-089 80-mg once-daily group. Study drug compliance rates were similar among the 3 treatment groups, with 91% of placebo, 85% of ABT-089 40-mg once-daily, and 89% of ABT-089 80-mg once-daily subjects being ≥70% compliant. A total of 84% of subjects used concomitant medications during the study, the most common (>5%) being ibuprofen (28%), multivitamin (18%), paracetamol/acetaminophen (15%), acetylsalicylic acid (10%), loratadine (11%), salbutamol (8%), levothyroxine (6%), and naproxen (6%).

Efficacy Results

No statistically significant treatment effects were observed with either ABT-089 dose regimen in the primary efficacy end point or any secondary measure of efficacy. The changes from baseline to the final evaluation for each assessment by treatment group are presented in Table 2. When analyzed over time, no statistically significant treatment effect with either ABT-089 dose compared to placebo was observed in the CAARS-INV total score for mean change from baseline to each evaluation (Figure 2). No statistically significant interactions at the .10 level for previous ADHD treatment (naive versus previously treated), age, nicotine use, or ADHD subtype were observed in subgroup analyses of the CAARS-INV total score. ABT-089 plasma levels were consistent with those observed in previous studies.

A post hoc 2-tailed analysis of the CAARS-INV total score change from

Table 1. Subject Demographic Characteristics and Psychiatric History (safety dataset)

Characteristic	Placebo (n = 53)	ABT-089, 40 mg Once Daily (n = 53)	ABT-089, 80 mg Once Daily (n = 53)
Gender, n (%)			
Male	27 (51)	34 (64)	38 (72)
Female	26 (49)	19 (36)	15 (28)
Age, mean (SD), y	35.6 (10.6)	36.1 (12.1)	36.1 (9.9)
Race, n (%)			
White	42 (79)	43 (81)	49 (93)
Black	5 (9)	6 (11)	4 (8)
Other	6 (11)	4 (8)	0 (0)
Hispanic or Latino, n (%)	4 (8)	2 (4)	2 (4)
ADHD diagnosis prior to screening visit, n (%)			
Yes	34 (64)	32 (60)	29 (55)
No	19 (36)	21 (40)	24 (45)
ADHD subtype by adult ACDS diagnosis at initial screening visit, n (%)			
Predominantly inattentive[a]	20 (38)	9 (17)	10 (19)
Predominantly hyperactive-impulsive	1 (2)	0	0
Combined	32 (60)	44 (83)	43 (81)
ADHD medication history, n (%)			
Stimulants	23 (43)	29 (55)	26 (49)
Atomoxetine	8 (15)	3 (6)	3 (6)
Antidepressant	3 (6)	5 (9)	4 (8)
Other	11 (21)	6 (11)	6 (11)

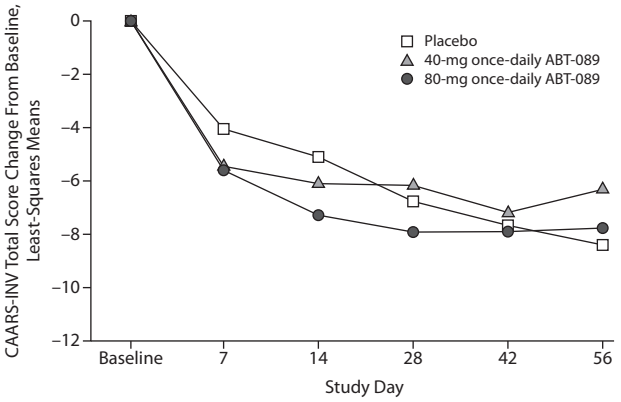
[a]There were significantly more inattentive subjects in the placebo group compared to the ABT-089 groups ($P = .02$).
Abbreviations: ACDS = ADHD Clinical Diagnostic Scale, ADHD = attention-deficit/hyperactivity disorder.

Table 2. ABT-089 Efficacy Results: Mean Change From Baseline to Final Evaluation (intent-to-treat dataset)

Assessment[a]	Placebo, Mean (SE)	ABT-089 40 mg Once Daily, Mean (SE)	ABT-089 80 mg Once Daily, Mean (SE)
n	53	53	53
Primary measure			
CAARS-INV total score	−8.0 (1.5)	−6.1 (1.6)	−7.5 (1.5)
Secondary measures			
CAARS-INV inattentive subscale score	−4.2 (0.8)	−3.2 (0.8)	−3.4 (0.8)
CAARS-INV hyperactive/impulsive subscale score	−3.9 (0.8)	−3.1 (0.8)	−3.8 (0.8)
ADHD Index	−3.9 (0.9)	−2.6 (0.9)	−2.4 (0.9)
CGI-ADHD-S score	−0.57 (0.15)	−0.55 (0.14)	−0.60 (0.15)
AISRS score	−7.7 (1.6)	−6.4 (1.6)	−7.5 (1.6)
CAARS-Self total score	−8.9 (1.8)	−4.8 (1.9)	−6.5 (1.8)
BRIEF-A global executive composite score	−11.7 (2.8)	−8.8 (2.9)	−8.7 (2.9)
TASS score			
11 AM	−5.1 (1.7)	−1.5 (1.8)	−4.2 (1.8)
4 PM	−6.5 (1.7)	−1.5 (1.8)	−4.4 (1.8)
10 PM	−6.4 (1.8)	−2.1 (1.9)	−4.5 (2.0)
AAQoL score	9.3 (2.0)	7.0 (2.1)	6.0 (2.1)
WPAI score	−0.11 (0.03)	−0.08 (0.03)	−0.11 (0.03)
Smoking measures	n[b]	n[b]	n[b]
FTND	12 −0.2 (0.3)	11 −0.0 (0.4)	11 0.6 (0.4)
QSU-Brief	13 −13.7 (5.4)	13 3.6 (5.4)	15 −5.3 (5.2)
No. of cigarettes smoked/d	12 −6.4 (6.7)	13 4.7 (6.4)	15 1.3 (5.9)

[a]Least-squares model-based means.
[b]Smokers within the intent-to treat dataset who provided assessments.
Abbreviations: AAQoL = Adult ADHD Quality of Life Questionnaire, ADHD = attention-deficit/hyperactivity disorder, AISRS = Adult ADHD Investigator Symptom Report Scale, BRIEF-A = Behavior Rating Inventory of Executive Function—Adult version, CAARS-INV = investigator-rated Conners' Adult ADHD Rating Scale, CAARS-Self = self-rated Conners' Adult ADHD Rating Scale, CGI-ADHD-S = Clinical Global Impressions-ADHD-Severity scale, FTND = Fagerstrom Test for Nicotine Dependence, QSU = Questionnaire of Smoking Urges, SE = standard error, TASS = Time-Sensitive ADHD Symptom Scale, WPAI = Work Productivity and Activity Impairment.

Figure 2. Mean Change From Baseline to Each Visit for CAARS-INV Total ADHD Score (intent-to-treat dataset)



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS-INV = investigator-rated Conners' Adult ADHD Rating Scale.

baseline to the final evaluation did not indicate any significant effects compared to placebo for ABT-089 40-mg once-daily ($P = .40$) or ABT-089 80-mg once-daily ($P = .81$) regimens. Additionally, a post hoc posterior probability analysis for the CAARS-INV total score indicated that the probability of a treatment effect of 3.5 points greater than placebo was less than .05 for both ABT-089 dose groups.

Safety Results

Of the 159 subjects who received at least 1 dose of study drug, 109 (69%) reported at least 1 treatment-emergent adverse event. There was no statistically significant difference in the overall incidence of treatment-emergent adverse events between ABT-089 40 mg once daily (79%), ABT-089 80 mg once daily (62%), and placebo (64%). There were no specific adverse events for which the incidence was statistically significantly higher for either ABT-089 dose group when compared to placebo. The most commonly reported adverse events for ABT-089 (≥ 5% in either active treatment group and > placebo) were nasopharyngitis (6.6%), upper respiratory tract infection (6.6%), and somnolence (5.7%).

Two subjects experienced a serious adverse event (SAE) during the study. A subject in the placebo group had an SAE of colitis that required hospitalization. The event was moderate in severity and was considered to be not related to study drug. One subject taking ABT-089 80 mg once daily for 12 days experienced an SAE of suicidal ideation leading to psychiatric hospitalization and premature discontinuation of study drug. The subject was found to have a history of polysubstance abuse, depression, and posttraumatic stress disorder related to a history of abuse, which was not disclosed during screening, and the subject had experienced an acute psychosocial stressor prior to the event. He improved rapidly upon admission to the psychiatric unit and was subsequently discharged to outpatient treatment. Prior to the psychosocial stressor, the subject had not experienced any worsening of depressive symptoms while taking study drug. The investigator considered this SAE severe and probably not related to study drug.

Three additional subjects in the ABT-089 80-mg once-daily group discontinued study drug prematurely due to an adverse event. All 3 events (depression, irritability, and erectile dysfunction) were considered possibly related to study drug. Although abstinence or the use of adequate birth control was a requirement for participation in the study, 2 subjects in the placebo group became pregnant during the study; both delivered healthy babies. There were no apparent dose-related changes in laboratory values or vital signs with ABT-089. Analysis of mean changes from baseline in ECG parameters revealed no evidence suggesting QT prolongation in either ABT-089 dose group.

DISCUSSION

ABT-089 dose regimens of 40 mg once daily and 80 mg once daily were well tolerated in this study population. As this study failed to replicate the positive findings from prior ABT-089 studies that suggested this agent is efficacious for the treatment of ADHD in adults,[10,11] it is important to examine factors that may explain these results. Day-to-day study conduct and dose selection are unlikely factors. The study sites were experienced in adult ADHD trials and were selected by the sponsor after participating in 1 or 2 clinical trials in this population with positive results using the same rating scales. In a previous dose-ranging clinical trial with ABT-089, in which doses as low as 2 mg once daily were tested, only the 2 highest dose regimens were efficacious, with the 40-mg once-daily and 40-mg twice-daily regimens showing a similar magnitude of effect.[10] Improving efficacy by using significantly higher doses than the ones tested is not clinically feasible, as phase 1 studies indicate that tolerability to ABT-089 declines at doses greater than 120 mg once daily. Furthermore, ABT-089 plasma levels in this study were in the expected range based on observations from previous phase 1 and 2 studies in this population. Overall, these findings suggest that the clinical sites and dose selection were appropriate and subjects were dosed adequately in this study.

An active comparator was not included in this study to confirm whether negative findings may have resulted from methodological issues. However, the placebo response in this study was comparable to placebo response rates reported in other trials in adults with ADHD. In 2 large multicenter studies of atomoxetine versus placebo in adults with ADHD, the placebo response rates in the CAARS-INV total score were −6.0 and −6.7,[24] compared with −8.0 in our study. The ADHD inattentive subtype population may have distinct responses to pharmacologic agents, including higher placebo responses.[25,26] In the current study, a disproportionate number of inattentive subjects were randomized to the placebo group compared to the ABT-089 groups, which may have affected the magnitude of the placebo response.

Although this pilot study was not designed or adequately powered to detect a treatment difference compared to

placebo, the results with the current study sample nevertheless suggest a low likelihood that ABT-089 efficacy in the overall population would be comparable to that of existing treatments. Mean improvements relative to placebo in the CAARS-INV Total Score ranged from 3.5 to 3.8 points in phase 3 studies of atomoxetine using parallel-group designs in adults with ADHD.[24] In addition, stimulant medications generally produce larger effect sizes than those seen with atomoxetine. Based on the probability distribution for the sample means in this study, the probability that a true mean treatment effect for the population samples would be at least 3.5 points greater than placebo is less than .05 for both ABT-089 dose groups. Furthermore, in 2 randomized controlled studies[27] of ABT-089 in children with ADHD, no statistically significant effect compared with placebo was observed with any ABT-089 dose. One of these studies included atomoxetine as an active comparator; in that study, atomoxetine was significantly better than placebo in most efficacy outcome measures.[27] Taken together, the evidence available from all studies suggests that an inadequate ABT-089 treatment effect, rather than methodological deficiencies or an unusually high placebo response, led to the negative outcome,

Unlike the previous studies with positive results using ABT-089 in adults with ADHD, the current study utilized a parallel-group study design that does not allow for within-subject treatment comparisons. The dose-ranging study described earlier used a crossover design, while the earlier proof-of-concept study employed a placebo-controlled, 4×4 Williams design testing doses of 2 mg, 4 mg, and 20 mg twice daily.[10,11] While the possibility exists that both of the previous trials produced false-positive results, it is also conceivable that study designs employing within-subject treatment comparisons have greater sensitivity for detecting treatment effects of ABT-089.

Patients with ADHD are more likely to smoke than controls without ADHD. The severity of ADHD symptoms reportedly has a positive association with an increase in smoking as measured by the modified Fagerstrom Tolerance Questionnaire,[28] the likelihood of becoming a regular smoker, age at smoking onset, and the number of cigarettes smoked per day.[29] Although stopping or reducing smoking was not a treatment objective for this study, measures related to smoking were included. In smokers taking ABT-089, there were no changes in the number of cigarettes per day or the Questionnaire of Smoking Urges–Brief, which measures the urge to smoke.

Because ABT-089 is a weak partial agonist of $\alpha_4\beta_2$ neuronal nicotinic receptors, the negative results reported here should not be assumed to predict the potential efficacy of other $\alpha_4\beta_2$ nicotinic receptor agonists. Additional investigation with neuronal nicotinic receptor agonists that have greater intrinsic agonist activity is warranted.

Drug names: atomoxetine (Strattera and others), diphenhydramine (Benadryl and others), ibuprofen (Caldolor, Ibu-tab, and others), levothyroxine (Tirosint, Synthroid, and others), naproxen (Naprosyn, Ec-Naprosyn, and others).

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Potential conflicts of interest: **Drs Bain** and **Robieson** and **Ms McNeill** are employees of Abbott, receive salary and other compensation from Abbott, and hold Abbott stock options and/or stock of Abbott. **Dr Bain** is an inventor on Abbott patent applications. **Dr Apostol** was an employee of Abbott when this study was performed; is currently a full-time employee of Novartis AG; and is a stock shareholder in Pfizer, GlaxoSmithKline, and Bristol-Myers Squibb. **Dr Sangal** is a consultant to Abbott and has received grant/research support from Merck, Sunovion, Eli Lilly, Sanofi-Aventis, and Shire. **Dr Abi-Saab** was an employee of Abbott when this study was performed; is currently a full-time employee of Shire; owns equity in Abbott, Novartis, and Shire; and is an inventor on patents from Abbott. **Dr Saltarelli** was an employee of Abbott when this study was performed; is currently a full-time employee of Shire; owns equity in Abbott and Shire; and is an inventor on Abbott patent applications and Pfizer patents.

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