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A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of $\alpha4\beta2$ Agonist ABT-894 in Adults with ADHD

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Dysregulation of the neuronal nicotinic acetylcholine receptor (NNR) system has been implicated in attention-deficit/hyperactivity disorder (ADHD), and nicotinic agonists improve attention across preclinical species and humans. Hence, a randomized, double-blind, placebo-controlled, crossover study was designed to determine the safety and efficacy of a novel $\alpha4\beta2$ NNR agonist (ABT-894 (3-(5,6-dichloro-pyridin-3-yl)-1(*S*),5 (*S*)-3,6-diazabicyclo[3.2.0]heptane)) in adults with ADHD. Participants ($N = 243$) were randomized to one of four dose regimens of ABT-894 (1, 2, and 4 mg once daily (QD)) or 4 mg twice daily (BID) or the active comparator atomoxetine (40 mg BID) *vs* placebo for 28 days. Following a 2-week washout period, participants crossed over to the alternative treatment condition (active or placebo) for an additional 28 days. Primary efficacy was based on an investigator-rated Conners' Adult ADHD Rating Scale (CAARS:Inv) Total score at the end of each 4-week treatment period. Additional secondary outcome measures were assessed. A total of 238 patients were assessed for safety end points, 236 patients were included in the intent-to-treat data set, and 196 were included in the completers data set, which was the prespecified, primary data set for efficacy. Both the 4 mg BID ABT-894 and atomoxetine groups demonstrated significant improvement on the primary outcome compared with placebo. Several secondary outcome measures were also significantly improved with 4 mg BID ABT-894. Overall, ABT-894 was well tolerated at all dose levels. These results provide initial proof of concept for the use of $\alpha4\beta2$ agonists in the treatment of adults with ADHD. Further investigation of ABT-894, including higher doses, is therefore warranted.

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INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and/or impulsivity. ADHD has historically been considered a childhood disorder; however, work in recent years suggests that 15–65% of school-aged children diagnosed with ADHD have symptoms and related impairments that persist into adulthood (Barkley *et al*, 2002). Approximately 4.4% of US adults meet the diagnostic criteria for ADHD (Faraone and Wilens, 2007; Kessler *et al*, 2005, 2006). These adults are often forgetful, have difficulties completing tasks, struggle with prioritization, and cannot self-monitor their behavior (Culpepper, 2006). These characteristics can lead to difficulties maintaining social and marital relationships (Gudjonsson *et al*, 2009) and poor educational outcomes (Biederman, 2004; McGough *et al*, 2005). In addition, ADHD has significant psychiatric comorbidities, such as depression, anxiety, and substance abuse (Biederman, 2004; McGough *et al*, 2005).

Current US Food and Drug Administration (FDA)-approved medication options for ADHD in adults include stimulants (methylphenidates, amphetamines) and the selective norepinepherine reuptake inhibitor, atomoxetine. It is generally recommended that stimulant medications be used as first-line treatments, followed by nonstimulant medications if stimulants are not efficacious or well tolerated (Pliszka, 2007; Pliszka *et al*, 2006a). Although safety concerns, including cardiovascular risks, sleep disturbances (Adler *et al*, 2006, 2009; Weisler *et al*, 2009), and the potential for growth suppression (Biederman *et al*, 2003; Faraone *et al*, 2005; Pliszka *et al*, 2006b; Spencer *et al*, 2006, 2007; reviewed by Vitiello, 2008), have been raised for the classes of currently available medications, recent reviews of clinical trial data suggest that these treatments are effective (Faraone and Glatt, 2010) and generally well tolerated (Habel *et al*, 2011; Hammerness *et al*, 2011).

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However, for patients with underlying cardiovascular risk factors or certain psychiatric problems, currently available medications may be contraindicated (Wigal, 2009). In addition, stimulant medications for ADHD are scheduled by the US Drug Enforcement Agency (Schedule II), citing their high potential for abuse, physical dependence, and diversion. These characteristics necessitate increased vigilance by the patients, caregivers, and physicians to monitor the distribution and use of this class. Overall, there is an ongoing need to develop new classes of therapeutics for ADHD symptoms, to meet the efficacy needs of patients while reducing the safety risks and the potential for abuse and diversion associated with currently available treatments.

Dysregulation of the nicotinic acetylcholine receptor system has been implicated in the pathophysiology of ADHD (Potter *et al*, 2006), and hence, these receptors are targets for therapeutic intervention. Activation of nicotinic acetylcholine receptors improves both cognition and attention in preclinical species and in healthy human volunteers (reviewed in Levin *et al*, 2006; Newhouse *et al*, 2004). Specifically, the $\alpha_4\beta_2$ subtype of neuronal nicotinic receptors (NNR) has been investigated because of its specific localization within the cortex, hippocampus, striatum, and thalamus in rodent and human brain (reviewed in Gotti and Clementi, 2004; Perry *et al*, 2002), potentially reducing the liability for peripherally mediated side effects. Selective agonists of the $\alpha_4\beta_2$ NNRs produce procognitive effects in animal models of cognition (Buccafusco *et al*, 1995; Decker *et al*, 1994; Grottick and Higgins, 2000). In addition, ispronicline, a selective partial $\alpha_4\beta_2$ receptor agonist, improved attention after 10 days of treatment in young, healthy volunteers (Dunbar and Kuchibhatla, 2006), and produced an EEG pattern similar to that seen with drugs known to improve attention and vigilance (Dunbar *et al*, 2007).

ABT-894 (3-(5,6-dichloro-pyridin-3-yl)-1(*S*),5 (*S*)-3,6-diazabicyclo[3.2.0]heptane) is a novel, highly selective $\alpha_4\beta_2$ NNR agonist (Ji *et al*, 2007) that has demonstrated efficacy in preclinical animal models of cognition and attention (Rueter *et al*, 2011). ABT-894 has also been shown to reduce scopolamine-induced impairments of attention in healthy volunteers (Abbott unpublished data), with an observed half-life in humans of approximately 4–6 h. The objective of the current exploratory study was to evaluate the safety and efficacy of ABT-894 to improve the clinical symptoms in adults with ADHD and to inform dose selection for subsequent clinical trials.

PATIENTS AND METHODS

Participants

Adult male and female patients (aged 18–60 years) met the DSM-IV-TR criteria for ADHD, confirmed by the Adult ADHD Clinical Diagnostic Scale V 1.2 (Adler and Spencer, 2004) at Screening. Eligible individuals also demonstrated scores $\geqslant 2$ (pretty much, often) on at least 6 of 9 items on the Inattentive score or the Hyperactive/Impulsive score of the Conners' Adult Rating Scale–Investigator Rated Scale (CAARS:Inv), a total CAARS:Inv score of $\geqslant 20$, and a Clinical Global Impression-ADHD Severity (CGI-ADHD-S) score of moderate or more impairment ($\geqslant 4$) at Screening and Baseline. Potential participants were excluded if they had any history of lifetime psychotic disorder, bipolar disorder, obsessive-compulsive disorder, or mental retardation; current generalized anxiety disorder, post-traumatic stress disorder, sleep disorder requiring treatment, or a current major depressive episode; any unstable medical condition; any condition that could affect cognitive performance; or if they were a pregnant or lactating female. Excluded psychotropic medication included anxiolytics, antipsychotics, antidepressants, mood stabilizers, nicotine replacement therapies, or varenicline. The use of atomoxetine was prohibited within 3 months before screening, and subjects receiving psychostimulants required a 7-day washout before randomization. Because of the potential of past or present nicotine use to influence the response to a nicotinic receptor agonist, participants were queried about their tobacco use. Individual study subjects were designated as nontobacco user, current tobacco user, or ex-tobacco user based on each subject's self-identification as such. Tobacco use was defined as the use of cigarettes, pipes, cigars, or chewing tobacco. Current tobacco users were allowed to continue use during the study.

Approximately 200 subjects were to be randomized across 20 study sites within the United States. All study sites received approval from their respective institutional review board or independent ethics committee, and all conducted the study according to the ethical principles outlined in the Declaration of Helsinki. Before any study procedure being performed, each subject voluntarily provided written informed consent.

Study Design

This exploratory, dose-finding, multicenter study utilized a randomized, double-blind, placebo-controlled, two-period crossover design (Apostol *et al*, 2012). The crossover design was employed to achieve study objectives while minimizing the numbers of patients required for this exploratory study. Following screening, participants were randomized to receive placebo treatment and ABT-894 or atomoxetine treatment, each for 4 weeks (see Figure 1). Randomization was stratified at the study center level. To reduce randomization block size and improve logistics of performing the randomization (to achieve overall site randomization balance), study centers were divided into two cohorts, with 12 sites in Cohort A and 8 sites in Cohort B. Study sites were blind to their assigned

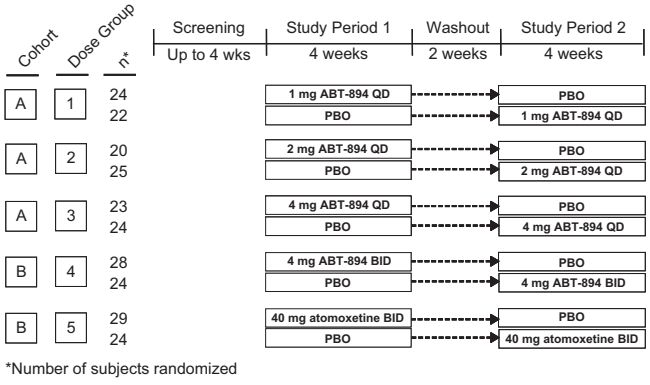

Figure 1 Study design and subject assignment.

treatment cohort. Each cohort enrolled subjects into dose groups depicted in Figure 1. Atomoxetine was an active control used to assess the assay sensitivity of the study design.

Dose Selection

Doses of 1, 2, and 4 mg ABT-894 once daily (QD) were expected to achieve maximum plasma concentrations below, within, and above the maximally efficacious range predicted by preclinical studies (0.2–4 ng/ml) despite the 4–6 h half-life of ABT-894. The dose selection was supported by Phase 1 pharmacodynamic data demonstrating procognitive effects at trough levels with a 2 mg daily regimen on a neuropsychological battery. Because a previous Phase 1 study had indicated that effects on heart rate and tolerability are concentration-related, the 4 mg twice-daily (BID) regimen was included to increase average plasma exposures with minimal effects on heart rate and tolerability, as the peak concentrations of a 4 mg BID regimen only slightly exceed those of a 4 mg QD regimen. Atomoxetine was dosed according to the product labeling instructions for adults with ADHD symptoms: atomoxetine was initiated at 40 mg QD for 3 days, followed by the target dose of 40 mg BID for the remainder of treatment.

Efficacy Measures

The primary outcome measure was the CAARS:Inv Total score assessed on day 28 of each 4-week treatment period. The CAARS:Inv is a 30-item, investigator-rated scale that measures the severity of symptoms of ADHD. Each item is measured on a four-point scale of 0 (not at all, never) to 3 (very much, very frequently), and separate scores can be derived for Inattentive (9 items), Hyperactive/Impulsive (9 items), and ADHD Index (12 items) subscales. The CAARS:Inv Total score is the sum of the Inattentive and Hyperactive/Impulsive Scores, with possible scores ranging from 0 to 54. Secondary outcome measures included the CAARS:Inv subscales (Inattentive, Hyperactive/Impulsive, ADHD Index), CGI-ADHD-S (rates ADHD severity from 1 (normal)–7 (among most extremely ill)), Adult ADHD Investigator Symptom Report Scale (AISRS; each of the 18 DSM-IV ADHD symptoms scored from 0 (not present)–3 (severe)), which were rated by the investigator, and the subject-rated Conners' Adult ADHD Rating Scale—Self-Rated (CAARS:Self). CAARS:Inv, CGI-ADHD-S, and AISRS were administered once during screening, at baseline, and on days 7, 14, 21, and 28 of each treatment period.

Safety and Tolerability

Adverse events (AEs) were assessed by spontaneous report at each study visit and for 30 days following discontinuation of study drug. Treatment-emergent AEs, defined as AEs that began or worsened following the first dose of any study drug, were summarized based on the treatment received. AEs that occurred during the washout period were attributed to the Period 1 treatment, and those that occurred within 30 days after the last dose in Period 2 were attributed to Period 2 treatment. Electrocardiograms were performed at baseline and at days 14 and 28 of each study period. Laboratory tests and physical exams were conducted at baseline and day 28 of each study period.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were collected on days 7, 14, 21, and 28 of both Periods 1 and 2. The time of blood sample collection relative to the previous dose was recorded.

Statistical Analyses

This exploratory study was powered to detect a treatment difference between ABT-894 dose and placebo in the primary efficacy end point (CAARS:Inv Total Score at day 28). A sample size of 40 subjects per dose group was estimated to give at least 80% power to detect a treatment difference of 3.7 on the CAARS:Inv Total score (a treatment difference achieved in earlier parallel-group studies examining atomoxetine in adult ADHD; Michelson *et al*, 2003) at a one-sided significance level of 0.05. The sample size was derived assuming: (1) a pooled standard deviation for treatment response of 10 units in a parallel-group setting; (2) a within-subject correlation of 0.7 for the Period 1 and Period 2 day 28 assessments, which yields a standard deviation of 7.7 for the difference between test drug and placebo at day 28 in the crossover setting; and (3) completion of both study periods by 75% of subjects (giving 30 completed subjects per treatment sequence). These resulted in a total sample size of 200 subjects (40 per dose group and 20 per sequence). The safety data set included all subjects who received at least one dose of study drug, and the intent-to-treat (ITT) data set included subjects from the safety data set who had at least one CAARS:Inv evaluation after dosing. Completers were defined as those subjects who completed both Periods 1 and 2, and whose last CAARS:Inv evaluation within each period was performed no more than one day after the last dose of study drug in the period.

The approved clinical protocol and statistical analysis plan prespecified that efficacy evaluation was made on the basis of one-sided tests at $\alpha = 0.05$ comparing each ABT-894 dose group with placebo at day 28 (Apostol *et al*, 2012; Wilens *et al*, 2006, 2011). To facilitate comparisons with the published literature, *post hoc* analyses using two-sided tests for each dose group *vs* placebo were conducted for all efficacy variables and are included in the Results section and published online Supplementary Materials. Because of the nature of the crossover study design, to allow for within-subject comparison, the completers data set was used as the primary data set for efficacy analysis. Analyses were performed for each dose group separately using analysis of covariance with factors for site, treatment sequence, period, and treatment, with baseline score for each period as a covariate. SAS Proc Mixed procedure was used for the analysis. A *post hoc* calculation of effect size was also performed for treatment doses that showed superiority over placebo on the primary efficacy end point to describe the variability-adjusted treatment effect. Effect sizes were calculated by dividing the mean treatment difference at day 28 by the standard deviation of the difference without considering the order of treatment. The same statistical models were applied to assess treatment effects on prespecified

secondary efficacy end points. No corrections for multiple comparisons were made in this exploratory, dose-finding study.

To assess the robustness of the treatment effect observed for the ABT-894 4 mg BID group in light of concerns about carryover effects due to the crossover design, additional *post hoc* analyses for the primary efficacy variable were performed on data obtained from the ITT data set in Cohort B (placebo, ABT-894 4 mg BID, atomoxetine). In this approach, treatment effects were assessed separately for Periods 1 and 2 as parallel-group designs using mixed-model repeated-measures analyses (factors for site, treatment, visit, and treatment-by-visit interaction, with baseline of each period as covariate). In Period 1, the treatment response to ABT-894 or atomoxetine was compared with that of placebo. For Period 2, one cannot meaningfully compare the group differences between placebo and either ABT-894 4 mg or atomoxetine, owing to potential carryover effects from receiving different treatments during Period 1; hence, the Period 2 analysis compared ABT-894 4 mg BID to atomoxetine only, as these subjects had undergone identical procedures during Period 1 placebo treatment and washout.

All safety analyses were performed on the safety data set, and treatment group differences in safety were tested at two-sided significance level of 0.05.

RESULTS

Disposition and Demographics

A total of 353 individuals were assessed for inclusion in this study, and 243 were randomized (Figure 2, CONSORT flow diagram). Five patients who were randomized did not receive study drug, and the remaining 238 received at least one dose of study drug (safety data set). Demographics and baseline characteristics for the safety data set are shown in Table 1. A total of 36 participants discontinued treatment: 4 due to AEs (1 placebo, 3 atomoxetine), 10 were lost to follow-up, 9 due to noncompliance, 6 withdrew consent, 1 due to lack of efficacy, and 7 due to other reasons (one subject reported two reasons for discontinuing treatment, but was counted only once in the total). There were no statistically significant differences among treatment groups in the reason for discontinuation (data not shown). The ITT data set was composed of 236 patients, and 196 satisfied the criteria for inclusion in the completers data set.

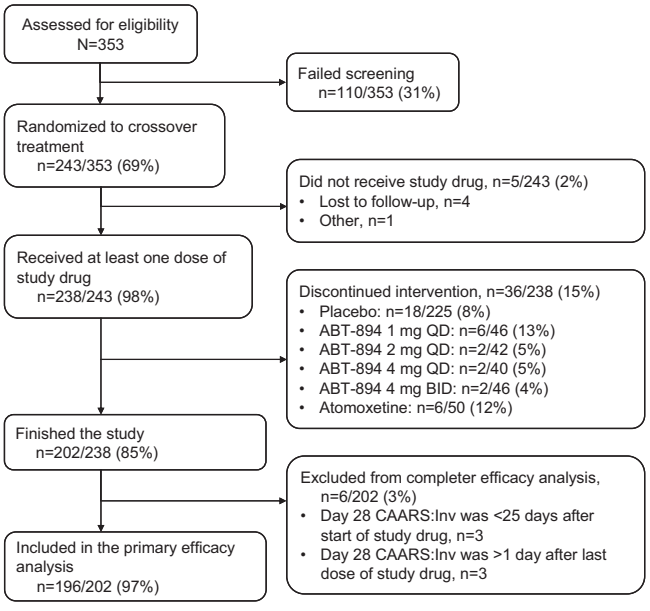

Figure 2 Subject disposition (CONSORT flow chart).

Pharmacokinetics

Mean (SD) ABT-894 plasma concentrations (ng/ml) during the window of 0–6 h after the morning dose (averaged across all visit days) were 2.09 (1.55), 4.62 (2.49), 11.32 (5.43), and 14.87 (8.91) for 1 mg QD, 2 mg QD, 4 mg QD, and 4 mg BID ABT-894 regimens, respectively. These values are consistent with those observed in previous studies.

Table 1 Demographics and Baseline Characteristics

Characteristic	Safety data set ($N = 238$)
Age (years), mean (SD)	36.2 (11.85)
Sex, n (%)	
Female	112 (47%)
Male	126 (53%)
Race, n (%)	
White	207 (87%)
Black	23 (10%)
Other	8 (3%)
History of psychiatric disorders, n (%)	
Major depression	51 (21%)
Anxiety disorder	7 (3%)
Conduct disorder	2 (<1%)
Age of first diagnosis (years), mean (SD)	29.6 (15.97)
Receipt of past pharmacological treatment, n (%)	
Stimulants	117 (49%)
Atomoxetine	28 (12%)
Antidepressants	20 (8%)
Other	19 (8%)
ADHD DSM-IV diagnosis subtype, n (%)	
Inattentive	60 (25%)
Hyperactive/impulsive	1 (<1%)
Combined	177 (74%)
Tobacco use, n (%)	
Nontobacco user	152 (64%)
Current tobacco user	44 (18%)
Ex-tobacco user	42 (18%)

Efficacy

Administration of 4 mg BID ABT-894 for 28 days significantly improved the CAARS:Inv Total score compared with placebo (LS mean difference (SE): −6.69 (2.30), $P=0.003$; *post hoc* two-sided *P*-value: $P=0.006$). A similar result was found with atomoxetine treatment (LS mean difference (SE): −7.98 (2.65), $P=0.002$; *post hoc* two-sided *P*-value: $P=0.005$). Calculated effect sizes were 0.45 for ABT-894 4 mg BID and 0.57 for atomoxetine compared with placebo. There were no statistically significant improvements seen with the lower doses of ABT-894 (Figure 3). Table 2 shows the change from placebo at day 28 for all doses of ABT-894 and atomoxetine for the secondary efficacy end points. The 4 mg BID ABT-894 dose group performed significantly better than placebo on all subscales of the CAARS:Inv, CGI-ADHD-S, AISRS, and CAARS:Self. Atomoxetine treatment produced similar results (significant improvements on all but one of the subscales of the CAARS:Self). There were no significant effects of treatment with the lower doses of ABT-894.

As a sensitivity analysis, data from Cohort B were analyzed separately for period 1 and for period 2. This analysis intended to evaluate treatment differences without the potential impact of carryover effects from the crossover design. Using data from Period 1, the repeated-measures analysis revealed that 4 mg BID ABT-894 demonstrated a significant improvement from baseline in ADHD symptoms at day 28 compared with placebo treatment ($P=0.04$; Figure 4, left panel; a trend only ($P=0.08$) for *post hoc* two-sided analysis), while atomoxetine significantly improved symptoms from baseline to each postbaseline time point ($P<0.002$ for each time point; Figure 4, left panel). For those subjects who received placebo in Period 1, the change from Period 2 baseline to day 28 for ABT-894 4 mg BID was similar to that for atomoxetine (−11.3 for both groups; Figure 4, right panel).

In the completers data set, 32 patients (16%) identified themselves as tobacco users and 36 (18%) identified themselves as ex-tobacco users. Given the small numbers of patients in these categories, the sample size within each of the five treatment regimens was too small to meaningfully assess differential effects of past or present tobacco use on the response to ABT-894.

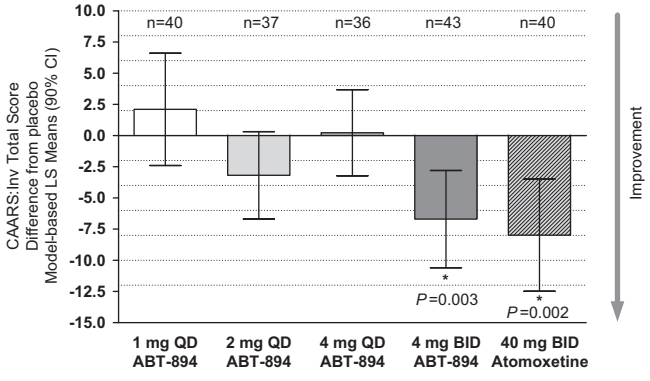

Figure 3 Mean difference from placebo on primary efficacy end point: Inattentive score or the Hyperactive/Impulsive score of the Conners' Adult Rating Scale–Investigator Rated Scale (CAARS:Inv) Total score at day 28 by dose group (completers data set). ABT-894 (3-(5,6-dichloro-pyridin-3-yl)-1(*S*),5 (*S*)-3,6-diazabicyclo[3.2.0]heptane) at 4 mg twice daily (BID) significantly improved symptoms of attention-deficit/hyperactivity disorder (ADHD). Treatment with 40 mg BID atomoxetine resulted in a similar improvement in symptoms. No significant improvements were detected with lower doses of ABT-894.

Safety

There were no deaths, serious AEs, or premature discontinuations due to AEs for any dose of ABT-894. AEs occurring in >2 participants in any treatment group are presented in Table 3. The most common AEs (≥5%) reported for all ABT-894 doses combined were nausea, dizziness, headache, and fatigue. These were all reported at higher rates for atomoxetine than for the efficacious dose of ABT-894 (4 mg BID). Four subjects discontinued the study because of treatment-emergent AEs ($n=1$ for placebo, $n=3$ for atomoxetine). Heart rate was significantly increased ($P<0.05$) at the final visit compared with placebo by 4 mg QD ABT-894 (3.14 b.p.m.) and atomoxetine (4.74 b.p.m.). The efficacious dose of ABT-894 (4 mg BID) did not significantly elevate heart rate (0.98 b.p.m.).

DISCUSSION

The 4 mg BID dose of ABT-894 significantly reduced ADHD symptoms in adults as measured by the primary outcome measure, the CAARS:Inv Total score (Figure 3), as well as numerous secondary outcome measures, including other investigator-rated scales (CGI-ADHD-S, AISRS) and a self-rated scale (CAARS:Self; Table 2). Atomoxetine was also efficacious, providing evidence that the study was well executed and sensitive for detecting improvements in ADHD symptoms. The response to ABT-894 4 mg BID was comparable to that of atomoxetine on the primary analysis of CAARS:Inv and on all other ADHD efficacy measures. These results build on the body of literature demonstrating the ability of NNR agonists to improve attention (Levin *et al*, 2006). The positive result provides additional support for the notion that specific agonists of the $\alpha4\beta2$ receptor subtype may be an attractive target for ADHD because of the anatomical location within the brain, resulting in improved attention with an acceptable safety and tolerability profile.

Because this was an exploratory, dose-finding study, the prespecified statistical plan dictated the use of one-sided tests of significance for primary and secondary efficacy measures; this choice did not affect our interpretation, as *post hoc* two-sided tests supported the statistically significant improvement by 4 mg BID ABT-894 (Supplementary Figure S1 and Supplementary Table S1). The 4 mg BID dose also maintains significance on the primary outcome measure when Bonferroni corrections are made for multiple comparisons of five dose groups.

The use of a crossover design limits the ability to compare the magnitude of treatment response with that obtained from a parallel-group design, as treatment effects are susceptible to the influence of carryover effects. However, the ability to significantly reduce sample size can dramatically increase the efficiency of exploratory studies such as this one. To study the treatment effect of ABT-894 assuming the same parameters for effect size, power, and statistical

Table 2 Summary of Secondary Efficacy End Points (Completers Data Set)

Efficacy end point	Mean difference from placebo (90% CI) at day 28 (Periods 1 and 2, completers data set)[a]				
	ABT-894				Atomoxetine
	1 mg QD ($n=40$)	2 mg QD ($n=37$)	4 mg QD ($n=36$)	4 mg BID ($n=43$)	40 mg BID ($n=40$)
CAARS:Inv					
Total score	2.11 (−2.4, 6.6)	−3.18 (−6.7, 0.3)	0.23 (−3.2, 3.7)	−6.69 (−10.6, −2.8)*	−7.98 (−12.5, −3.5)*
Inattentive score	0.94 (−1.5, 3.4)	−1.92 (−3.8, −0.1)*	0.60 (−1.5, 2.7)	−4.08 (−6.4, −1.7)*	−3.89 (−6.3, −1.5)*
Hyperactive score	1.43 (−0.8, 3.7)	−1.24 (−3.0, 0.5)	−0.21 (−1.9, 1.5)	−2.69 (−4.4, −1.0)*	−4.04 (−6.2, −1.8)*
ADHD Index	0.52 (−2.0, 3.0)	−2.01 (−4.4, 0.4)	0.90 (−1.0, 2.8)	−3.89 (−6.3, −1.5)*	−3.70 (−6.0, −1.3)*
CGI-ADHD-S	0.04 (−0.3, 0.4)	−0.31 (−0.6, 0.0)	−0.06 (−0.3, 0.2)	−0.58 (−1.0, −0.2)*	−0.45 (−0.8, −0.1)*
AISRS					
Total score	3.19 (−1.2, 7.6)	−2.72 (−6.4, 1.0)	−0.13 (−3.6, 3.4)	−8.07 (−12.2, −3.9)*	−7.18 (−11.5, −2.9)*
Inattention score	1.72 (−0.6, 4.1)	−1.59 (−3.6, 0.4)	0.81 (−1.2, 2.8)	−4.26 (−6.6, −1.9)*	−3.81 (−6.1, −1.6)*
Hyperactivity score	1.53 (−0.8, 3.8)	−1.11 (−3.0, 0.7)	−0.81 (−2.6, 1.0)	−3.58 (−5.6, −1.6)*	−3.29 (−5.4, −1.2)*
CAARS:Self					
Total score	3.57 (−0.4, 7.5)	−2.64 (−6.6, 1.3)	−1.13 (−5.2, 2.9)	−7.34 (−11.6, −3.1)*	−7.12 (−10.9, −3.3)*
Inattention/memory score	0.60 (−0.5, 1.7)	−0.23 (−1.2, 0.8)	0.11 (−0.9, 1.2)	−1.40 (−2.5, −0.3)*	−1.56 (−2.5, −0.6)*
Hyperactivity score	0.93 (−0.2, 2,0)	−0.55 (−1.4, 0.3)	−1.07 (−2.1, −0.0)*	−1.90 (−3.0, −0.8)*	−1.43 (−2.4, −0.4)*
Impulsivity score	0.65 (−0.1, 1.4)	−0.48 (−1.3, 0.3)	−0.02 (−0.9, 0.9)	−0.70 (−1.4, −0.0)*	−1.17 (−1.9, −0.5)*
Problem with self-concept score	0.51 (−0.2, 1.2)	−0.57 (−1.6, 0.5)	0.33 (−0.7, 1.4)	−1.39 (−2.5, −0.3)*	−0.70 (−1.5, 0.1)
ADHD index	1.84 (−0.0, 3.7)	−1.52 (−3.3, 0.2)	−0.12 (−1.8, 1.5)	−3.37 (−5.3, −1.4)*	−3.00 (−4.9, −1.1)*

[a]LS model-based means are presented; *$P<0.05$, one-sided tests; from ANCOVA with factors for site, sequence, subject within sequence, period, and treatment, and with baseline score of each period as a covariate.

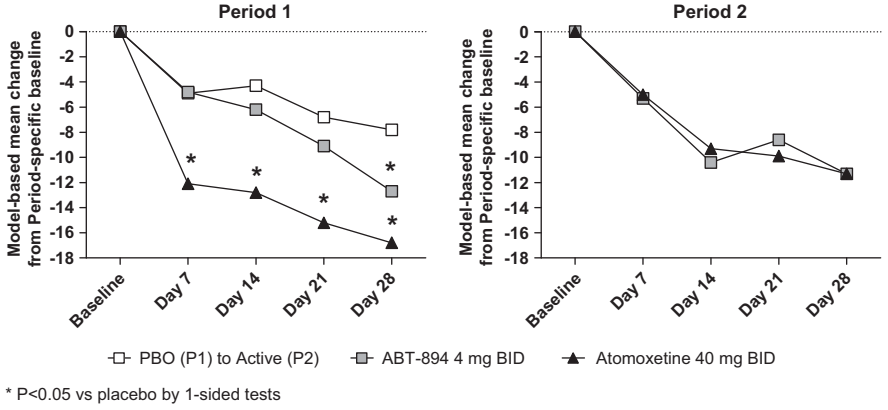

Figure 4 Crossover results analyzed as two parallel-group periods (Cohort B). Model-based mean change from period-specific baseline during treatment with 4 mg twice daily (BID) ABT-894 (3-(5,6-dichloro-pyridin-3-yl)-1(*S*),5 (*S*)-3,6-diazabicyclo[3.2.0]heptane) or atomoxetine at each study visit (intent-to-treat (ITT) data set) in Period 1 (left panel; *$P<0.05$ *vs* placebo) and Period 2 (right panel). The patients who received placebo graphed in the left panel are shown receiving active treatment in the right panel (treated with either 4 mg BID ABT-894 or atomoxetine). In Period 1, both active treatments demonstrated significant improvement compared with placebo. In Period 2, the magnitudes of treatment response to ABT-894 4 mg BID and atomoxetine were similar. No placebo group is shown in Period 2 because of potential carryover effects from receiving active treatment in Period 1.

significance in a parallel-group setting, we predicted a requirement of 90 subjects per treatment arm, yielding a total study sample of 540 subjects. The period-by-period repeated-measures analyses in this study provided parallel-group comparisons that generally supported the overall conclusion that 4 mg BID ABT-894 is efficacious in this population of adults with ADHD. The 4 mg BID ABT-894 showed a magnitude of effect that was consistent in Periods 1 and 2 (change from baseline = −12.7 and −11.3 for Period 1 and Period 2, respectively) (Figure 4). Despite being significantly underpowered as a parallel-group design, the treatment effect for ABT-894 was statistically

Table 3 AEs Occurring in >2 Subjects Receiving Any Dose of ABT-894

	Placebo	ABT-894					Atomoxetine
	(*n* = 225)	1 mg QD (*n* = 46)	2 mg QD (*n* = 42)	4 mg QD (*n* = 40)	4 mg BID (*n* = 46)	Total (*n* = 174)	40 mg BID (*n* = 50)
Any AE, *n* (%)	126 (56%)	32 (69.6%)	26 (61.9%)	26 (65.0%)	25 (54.3%)	109 (62.6%)	41 (82.0%)
AEs occurring in >2 subjects receiving any dose of ABT-894, n *(%)*							
Nausea	5 (2.2%)	2 (4.3%)	6 (14.3%)	9 (22.5%)	4 (8.7%)	21 (12.1%)	10 (20.0%)
Headache	23 (10.2%)	4 (8.7%)	5 (11.9%)	5 (12.5%)	4 (8.7%)	18 (10.3%)	7 (14.0%)
Dizziness	6 (2.7%)	2 (4.3%)	4 (9.5%)	4 (10.0%)	1 (2.2%)	11 (6.3%)	4 (8.0%)
Insomnia[a]	15 (6.7%)	2 (4.3%)	4 (9.5%)	3 (7.5%)	1 (2.2%)	10 (5.7%)	8 (16.0%)
Fatigue	11 (4.9%)	2 (4.3%)	1 (2.4%)	2 (5.0%)	4 (8.7%)	9 (5.2%)	6 (12.0%)
Somnolence	7 (3.1%)	6 (13.0%)	0	0	2 (4.3%)	8 (4.6%)	4 (8.0%)
Upper respiratory tract infection	6 (2.7%)	1 (2.2%)	3 (7.1%)	3 (7.5%)	0	7 (4.0%)	2 (4.0%)
Diarrhea	5 (2.2%)	0	2 (4.8%)	3 (7.5%)	1 (2.2%)	6 (3.4%)	1 (2.0%)
Vomiting	1 (0.4%)	0	1 (2.4%)	4 (10.0%)	1 (2.2%)	6 (3.4%)	1 (2.0%)
Muscle strain	1 (0.4%)	3 (6.5%)	0	0	0	3 (1.7%)	0
Nasal congestion	0	0	0	0	3 (6.5%)	3 (1.7%)	2 (4.0%)

[a]Includes insomnia, initial insomnia, middle insomnia, and sleep disorder.

significant ($P = 0.04$ using one-sided analysis; a trend only ($P = 0.08$) for two-sided analysis) in the Period 1-only analysis, while in the Period 2-only analysis, the estimate for the treatment effect was similar to that of the approved treatment atomoxetine. Overall these findings suggest that the efficacy observed for the ABT-894 4 mg BID dose was not simply an artifact resulting from the crossover study design.

While the 7-day washout of stimulant medications before dosing with study drug is longer than that used in some reports (eg, Verster *et al*, 2010), a longer stimulant washout may have decreased variability in baseline measurements and treatment response to ABT-894. However, given that subjects were randomized across treatment sequences, this should not have affected the ability to adequately identify doses of ABT-894 for subsequent trials in ADHD.

All doses of ABT-894 were well tolerated, and there was no evidence of dose-limiting toxicity in the study. No serious AEs were reported, and none of the AEs in those treated with ABT-894 resulted in premature study discontinuation. The most commonly reported AEs, including nausea, dizziness, headache, and fatigue, are consistent with the profiles of other nicotinic agonists (Mills *et al*, 2010). Of interest, these events were less common numerically in the 4 mg BID group than in the 4 mg QD group (Table 2). The most efficacious dose of ABT-894 demonstrated no significant differences from placebo in side effects that have been associated with available ADHD medications, such as insomnia or increased heart rate.

Some elements of the study design limited our ability to draw conclusions about the safety and tolerability profile of ABT-894. Atomoxetine was included as a positive control to assess the sensitivity of the study design and its conduct; the study was neither designed nor powered to compare the safety profiles of ABT-894 and atomoxetine. In addition, the atomoxetine titration schedule described in the product labeling instructions for adults with ADHD and used in this study—40 mg QD for 3 days followed by 40 mg BID for the remainder of treatment—may be more aggressive than what is typically used in clinical practice, and thus may have resulted in higher rates of AEs and discontinuations. Detection of adverse advents was based on spontaneous subject self-reports, and the use of a structured side-effect rating scale may have elicited a greater number of AEs and possibly a different AE profile for ABT-894. Also, because the once-daily ABT-894 regimens were tested at different sites (in Cohort A) than the ABT-894 4 mg BID and atomoxetine regimens (in Cohort B), the ability to compare safety and tolerability across cohorts is limited.

The current results suggest that there may be room to improve the efficacy of ABT-894, while maintaining an acceptable safety and tolerability profile, by using higher doses. ABT-894 4 mg BID appeared to be better tolerated and associated with a smaller increase in heart rate than the same dose administered once daily. Despite achieving only modestly higher peak plasma concentrations, BID dosing may improve efficacy relative to once-daily dosing without significantly compromising tolerability by increasing average plasma concentrations and minimizing the fluctuations in plasma levels throughout the day. In earlier Phase 1 studies, 6 mg BID yielded plasma exposures approximately twofold higher than the 4 mg BID regimen. These plasma levels were well tolerated but were associated with an average heart rate increase of 3 b.p.m., comparable to that reported for stimulant medications (3 b.p.m.; Ritalin package insert, Adderall package insert) and for atomoxetine in adults (5 b.p.m.; Strattera package insert). A recent Phase 2 study of ABT-894 in peripheral diabetic neuropathic pain found no significant safety signals at doses up to 6 mg BID (Rowbotham *et al*, 2012). Taken together, these findings suggest that higher doses of ABT-894, with BID dosing or perhaps a sustained-release formulation, may yield improved efficacy while maintaining an acceptable safety and tolerability profile for adults with ADHD.

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DISCLOSURE

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