Adaptive, Dose-finding Phase 2 Trial Evaluating the Safety and Efficacy of ABT-089 in Mild to Moderate Alzheimer Disease

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Abstract: ABT-089, an $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonist, was evaluated for efficacy and safety in mild to moderate Alzheimer disease patients receiving stable doses of acetylcholinesterase inhibitors. This phase 2 double-blind, placebo-controlled, proof-of-concept, and dose-finding study adaptively randomized patients to receive ABT-089 (5, 10, 15, 20, 30, or 35 mg once daily) or placebo for 12 weeks. The primary efficacy endpoint was the Alzheimer's Disease Assessment Scale, cognition subscale (ADAS-Cog) total score. A Bayesian response-adaptive randomization algorithm dynamically assigned allocation probabilities based on interim ADAS-Cog total scores. A normal dynamic linear model for dose-response relationships and a longitudinal model for predicting final ADAS-cog score were employed in the algorithm. Stopping criteria for futility or success were defined. The futility stopping criterion was met, terminating the study with 337 patients randomized. No dose-response relationship was observed and no dose demonstrated statistically significant improvement over placebo on ADAS-Cog or any secondary endpoint. ABT-089 was well tolerated at all dose levels. When administered as adjunctive therapy to acetylcholinesterase inhibitors, ABT-089 was not efficacious in mild to moderate Alzheimer disease. The adaptive study design enabled the examination of a broad dose range, enabled rapid determination of futility, and reduced patient exposure to noneffacious doses of the investigational compound.

Key Words: Alzheimer disease, neuronal nicotinic receptor, partial agonist, adaptive trial design

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Alzheimer disease (AD) is a progressive, neurodegenerative disorder that accounts for 60% to 70% of progressive cognitive impairment in the elderly.[1] Because of the modest efficacy of available treatments, much attention has been focused on developing better AD medications. However, these endeavors have resulted in more failures than successes, and no new therapies have been approved for AD since 2003. Numerous recent clinical failures in AD have led some companies to abandon pursuit of treatments for this indication.[2] Novel trial designs to aid in the development of AD agents are therefore needed.

Among the reasons for failed AD trials is ineffective trial design and execution, often resulting in inadequate evaluation of a drug's full dose range.[3,4] Adaptive trial designs that use accumulating data to continuously modify specific trial aspects offer particular advantages over traditional, resource-intensive, often inefficient phase 2 trials. Predefined decision rules and frequent interim efficacy evaluations can efficiently assess success and failure. Response-adaptive randomization uses interim data to allocate patients to more informative treatment arms, allowing efficient evaluation of a wide range of doses.[5,6] Employing these tools can achieve proof-of-concept (POC) and determine an effective dose range in a single trial.

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ABT-089 is a partial agonist of the $\alpha_4\beta_2$ neuronal nicotinic receptor (NNR).[7] Multiple pharmacologically and functionally distinct NNR subtypes mediate the broad range of effects of nicotine.[8–11] Several preclinical and clinical studies have demonstrated that NNR agonists, including $\alpha_4\beta_2$ NNR agonists, improve cognitive performance.[12–14] Given the loss of cholinergic afferent terminals characteristic of the progression of AD, it was predicted that the administration of an agonist at $\alpha_4\beta_2$ receptors would provide benefit above that seen with acetylcholinesterase inhibitors (AChEIs) alone. The current study was designed to assess the safety and efficacy of ABT-089 in broad dose range in patients with mild to moderate AD as an adjunctive agent to donepezil. It is a POC study as well as a dose-finding study. To gain efficacy, response-adaptive randomization design was utilized.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consent

The study protocol was approved by the independent ethics committee or institutional review board at each study site, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.[15] All patients (or their legally acceptable representatives) provided written informed consent. Clinical trial registration (clinicaltrials.gov): NCT00555204.

Study Design

This was a phase 2, randomized, double-blind, placebo-controlled, multicenter (41 US sites) study using a Bayesian response-adaptive randomization design[5,6] conducted from November 2007 to June 2009. Subjects were on stable doses of AChEIs (donepezil, rivastigmine, or galantamine) for at least 90 days before study drug administration. The study consisted of a screening period of up to 28 days and a 12-week treatment period.

There were 7 treatment groups: 6 oral QD doses of ABT-089 (5, 10, 15, 20, 30, 35 mg) and placebo. Doses of ABT-089 were selected based on preclinical efficacy models which achieved maximum efficacy at plasma concentrations of 5 to 15 ng/mL. Phase 1 dose-escalation studies in older subjects with mild to moderate AD predicted that 10 mg QD would provide plasma concentrations above 5 ng/mL for >24 hours (AbbVie data on file). The dose of 35 mg QD was identified as the highest possible dose within safety margin suggested by phase 1 dose-escalation studies. As this study had the goal of both dose-finding and POC, it was deemed appropriate to include the highest possible dose based on phase 1 dose-escalation studies. Patients were randomized using an interactive voice response system.

Initially, during a fixed allocation burn-in stage, subjects were randomized to one of the 7 treatment groups with equal ratios. Once at least 5 patients had been randomized to each treatment group, the randomization probabilities for ABT-089 treatment groups were modified based on accumulated change from baseline to week 12 data on the primary efficacy measure, Alzheimer's Disease Assessment Scale, cognition portion (ADAS-Cog). At 2-week intervals, all available ADAS-Cog data were incorporated into an algorithm, generating new randomization probabilities for each ABT-089 treatment group. The randomization probability for the placebo group was fixed at 0.20 but was subsequently adjusted to 0.35 after 121 patients were randomized (after 12 interim adaptive calculations). This adjustment was made based on the recommendation of the Data Monitoring Committee and was due to the higher than usual placebo response seen in the first 12 interim efficacy evaluations. Given the observations in the first 12 interim assessments, the Data Monitoring Committee suggested that increasing the sample size of the placebo group could result in a more precise estimate of the mean change in the ADAS-Cog total score for placebo-treated patients and therefore a more precise estimation of treatment effect. The sponsor was not involved in or informed of this decision. A normal dynamic linear model (NDLM) was used to guide the estimation of the dose-response relationship among dose groups.[16] The NDLM was used because it is flexible enough to capture both monotonic and non-monotonic dose-response relationships.

The objective of the adaptive algorithm was to identify the ED_{90} (lowest dose of ABT-089 that resulted in 90% of the maximal effect compared with placebo) and the minimum effective dose (MED; lowest dose of ABT-089 that resulted in at least a 1.75-point ADAS-Cog improvement over placebo in mean change from baseline). The reason for choosing a 1.75-point improvement as the minimum clinically meaningful difference was that this amount was considered to be 75% of the monotherapy effect of donepezil on mild to moderate AD patients, which is approximately 2.33 units on the ADAS-Cog total score as reported by the Cochrane Collaboration (2006).[17] As an adjunctive therapy, it was estimated that the effect of ABT-089 would be less, and was estimated to be 75% of the effect of donepezil alone. Stopping criteria were assessed once 150 patients were randomized, and at each subsequent biweekly interim analysis. Biweekly interims are operationally easy to implement, as opposed to subject thresholds, with no loss in efficiency. The study would be stopped for success if there was $\geq 80\%$ probability that a MED had been identified; the study would be stopped for futility if there was $\geq 95\%$ probability that no ABT-089 dose group would achieve ≥ 1.38-point improvement over placebo on the ADAS-Cog total score. The cutoff value for futility was chosen to be less than the cutoff value for success to support the design intent that is to allow a protective zone for potential viable treatment effect. The value of 1.38 was determined because it provided strong operating characteristics for futility stopping as shown by trial simulations. Extensive simulations were conducted for 9 scenarios of various dose-response relationships ranging from nonefficacious to efficacious scenarios, which showed that the design had strong operating characteristics. All aspects of the design were vetted and iterated through the simulation process. The sample size, allocation rules, stopping rules, and modeling were optimized through this process (see Text, Supplemental Digital Content 1, http://links.lww.com/WAD/A114, which explains the determination of maximum trial sample size).

The ADAS-Cog was performed at day-1 and at weeks 4, 8, and 12. To allow the adaptive algorithm to use all available information, including partially observed data from subjects who were ongoing, a Bayesian longitudinal linear model[18,19] used ADAS-Cog total scores observed at weeks 4 or 8 to predict what they would be at week 12. The parameters of the longitudinal model were estimated from subjects with both completed 12-week data and early 4- and 8-week data. For those subjects who prematurely discontinued from the study, their last observed values were used without imputation. Additional information regarding longitudinal models in adaptive trials can be found in Berry

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et al[18] and Padmanabhan et al.[19] Detailed modeling parameters and other statistical details can be found in the Supplemental Digital Content 1, http://links.lww.com/WAD/A114.

Patients

All patients met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD,[20] were aged 55 to 90 years (inclusive), had Mini-Mental State Examination (MMSE) scores of 12 to 26 (inclusive) at screening, and were receiving a stable dose of an AChEI (donepezil, rivastigmine, or galantamine) for at least 90 days before study drug administration. Each patient was required to maintain their AChEI regimen throughout the study. Exclusion criteria included treatment with memantine within 28 days or varenicline within 2 weeks before study drug administration.

Outcomes

Efficacy assessments occurred on day-1, week 4, week 8, and week 12 (or at final study visit). The primary efficacy measure was the change from day-1 to week 12 on the ADAS-Cog, a subscale of the ADAS that focuses on cognitive functioning and memory.[21] ADAS-Cog total score ranges from 0 to 70, with higher scores representing greater impairment. Secondary efficacy endpoints included MMSE total score, Clinician Interview-Based Impression of Severity/Clinician Interview-Based Impression of Change-plus (CIBIS/CIBIC-plus), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) total score, Neuropsychiatric Inventory (NPI) total score, and Cornell Scale for Depression in Dementia (CSDD) total score. All sites also used the Cognitive Drug Research (CDR) battery, selected for its sensitivity to detect changes in attention. Given the reported preclinical effects of $\alpha_4\beta_2$ agonists on attention[22,23] and the lack of explicit testing of this domain by the ADAS-Cog, it was of interest to have a specific measurement for this domain. Safety assessments included incidence of adverse events (AEs), vital signs, electrocardiograms (ECG), physical examinations, brief neurological examinations, and laboratory tests.

Statistical Analysis

The maximum sample size for the trial was 400 patients. The sample size was obtained through simulations. The targeted treatment effect for ABT-089 was 1.75-point improvement from placebo on the ADAS-Cog. A conventional parallel group design, with 80% power for a 1-sided test at $\alpha = 0.05$ assuming a SD of 5.0 would have required 100 subjects per treatment group. With 6 dose groups and a placebo arm, the study would have requested a total of 700 subjects. Using response-adaptive design sample size design, as the data accumulated and interim analyses were performed, the new eligible subjects would be allocated to more informative dose group(s). That is, the sample size for each ABT-089 dose group was not fixed but was determined by the response-data driven, dynamically updated, randomization allocation probabilities aimed at determining an ED_{90} and MED. The more efficacious dose group(s) would receive more sample size allocation, and less efficacious dose group(s) would receive less or no sample size allocation as the trial continued. Extensive simulations suggested that a total of 400 subjects would allow the study design to have satisfactory operating characteristics. With prespecified futility stopping rule, the study could stop for futility, but it was specified that this would not happen before a minimum sample size of 150 patients was randomized.

Efficacy and safety analyses were conducted on the data set that included all randomized patients who took at least 1 dose of study drug (intent-to-treat data set). As specified in the study's Statistical Analysis Plan, "baseline" was the last nonmissing observation taken at or before the day-1 visit, and "final evaluation" was the last nonmissing observation in the double-blind treatment period. This approach yielded the same analysis results as analyzing change from baseline to week 12 using the last-observation-carried-forward method for subjects who prematurely discontinued from the study and thus their last observations occurred before week 12.

The primary efficacy analysis used Bayesian posterior probability distributions of the mean change and 95% credible interval for each ABT-089 dose group and placebo on the ADAS-Cog total score, using the NDLM as was used in the interim adaptive algorithm.[6] When calculating posterior probabilities, the least-squares (LS) mean change on the ADAS-Cog total score from an analysis of covariance (ANCOVA) model was used (described below). In addition, we calculated the probabilities that the mean change on the ADAS-Cog total score between each ABT-089 dose and placebo resulted in a ≥ 1.75-point improvement. Given that an improvement of 1.75 points was the prespecified, minimum clinically relevant difference in the study design, a low probability would indicate that ABT-089 was unlikely to be better than placebo.

Secondary efficacy analyses (all prespecified, unless otherwise indicated) included an analysis of the mean change from baseline to the final evaluation for ADAS-Cog total score using ANCOVA with a term of treatment and baseline score as the covariate. Estimates of the treatment group difference between each ABT-089 dose and placebo, with associated 2-sided 90% confidence intervals for baseline to final change were obtained. The change from baseline to final evaluation for the total score of MMSE, NPI, CSDD, ADCS-ADL were analyzed within the repeated-measures ANCOVA framework described above. The final evaluation on the CIBIS/CIBIC-plus was analyzed using an analysis of variance (ANOVA) model. A repeated-measures analysis was used to analyze the change from baseline for variables obtained from the CDR (analyses for the CDR were considered ad hoc analyses, as they were not described in the Statistical Analysis Plan).

Changes from baseline to final evaluation on laboratory values, vital signs, and ECG variables were analyzed using a 1-way ANOVA model. The incidence of AEs was compared using Fisher exact test. One-sided tests at significance level of 0.050 were used for all efficacy analyses, and 2-sided tests at significance level of 0.050 were used for all safety analyses.

RESULTS

This study was stopped for futility after randomization of 337 patients. Of the 334 patients who received study drug, 228 (68.3%) completed the study, 72 (21.5%) were prematurely discontinued due to study termination, and 34 (10.2%) prematurely discontinued study drug voluntarily. The most common reasons for voluntary premature discontinuation of study drug were: withdrew consent (5.4%); AE (3.6%); and lack of efficacy (1.8%; Fig. 1). The

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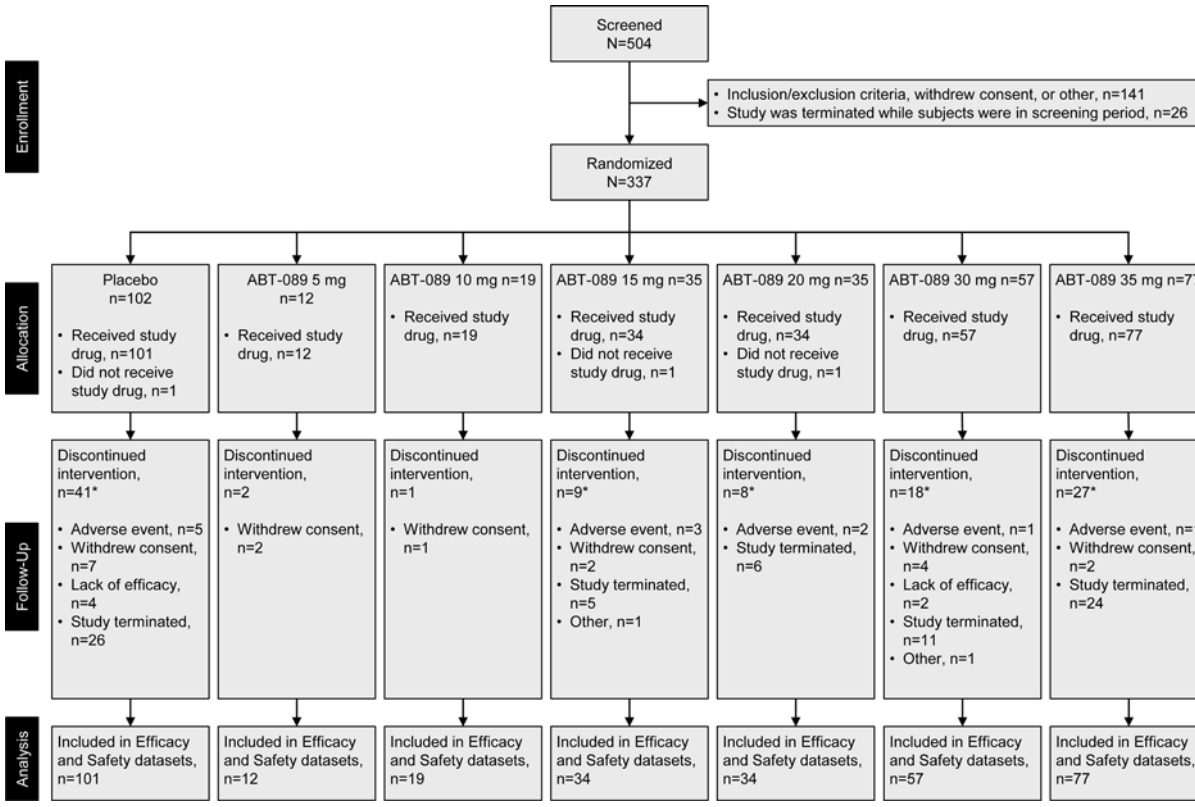

FIGURE 1. Patient disposition and flow through study. *Patients may have reported >1 reason leading to discontinuation, but are counted only once in the total.

majority of patients were white (95.2%) and female (55.1%). The median age was 77 years (range, 53 to 90 y). Baseline MMSE and ADAS-Cog total scores for the entire study population were 20.7 and 20.3, respectively. All except 1 patient (who was in the placebo group) received AChEIs for treatment of AD during the study, with the vast majority of patients receiving 5 or 10 mg donepezil (12.4%, 68.6%, respectively). There were no clinically meaningful differences among the treatment groups for any of the demographics or baseline characteristics (Table 1). Interim adaptation of randomization began after 56 patients had been randomized. Randomization probabilities were revised every 2 weeks throughout the study. Results of 5 interim efficacy evaluations and patient allocation are presented in the figures of Supplemental Digital Content 2, http://links.lww.com/WAD/A115.

At the final analysis, patients were distributed across treatment dose groups as follows: ABT-089 5 (N = 12), 10 (N = 19), 15 (N = 35), 20 (N = 35), 30 (N = 57), 35 mg (N = 77), and placebo (N = 102; Fig. 2A). The posterior mean change on the ADAS-Cog total score, the primary efficacy analysis, showed small mean decreases (improvements) from baseline in the ADAS-Cog total score for each ABT-089 dose group (range, −0.97 to −0.68) and placebo (−0.66; Fig. 2A). The difference in posterior mean change between each ABT-089 dose group and placebo ranged from −0.31 to −0.02, with the 95% credible interval all including 0 (data not shown). Bayesian posterior probabilities that ABT-089 would result in a mean improvement from baseline as compared with placebo in the ADAS-Cog of at least 1.75 points were between 0.0010 and 0.0046. Therefore, the probability that any dose of ABT-089 would achieve the targeted treatment effect on the ADAS-Cog total score was <1%.

In the secondary efficacy analysis of the ADAS-Cog total score, which used an ANCOVA of the mean change from baseline to final evaluation, small LS mean improvements were observed for each ABT-089 dose group (range, −2.63 to −0.34) and placebo (−0.77; Fig. 2B). No statistically significant or clinically meaningful treatment differences were observed for any of the ABT-089 dose groups versus placebo. Although the 5 mg group appeared to have a substantial improvement of −2.63 compared with baseline and −1.87 compared with placebo, it was assigned to only 12 patients because the dose-response algorithm largely discounted this observation. Indeed, 1 patient in the 5 mg ABT-089 dose group had a substantially larger improvement from baseline to final evaluation than the other patients. When this patient was excluded from the analysis, the difference in the LS mean (SE) improvement from baseline between the 5 mg dose group and placebo changed from −1.87 (1.49) ($P = 0.106$) to −0.64 (1.53) ($P = 0.338$), indicating that the majority of benefit observed in the 5 mg dose group was driven by a single patient.

There were no statistically significant changes from baseline to final evaluation on secondary efficacy scales (Table 2). At week 8, ABT-089 30 mg was significantly improved compared with placebo on the CDR battery Power of Attention composite score, comprised of Simple Reaction Time, Choice Reaction Time, and Digit Vigilance (LS mean difference, −170.94; $P = 0.044$). No other CDR

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TABLE 1. Patient Demographics and Baseline Cognitive Scores

		ABT-089 Dose Group					
	Placebo (n = 101)	**5 mg (n = 12)**	**10 mg (n = 19)**	**15 mg (n = 34)**	**20 mg (n = 34)**	**30 mg (n = 57)**	**35 mg (n = 77)**
Age [mean (SD)] (y)	75.0 (8.56)	71.3 (9.85)	76.4 (6.24)	77.8 (7.48)	75.6 (7.56)	75.4 (7.55)	76.0 (7.87)
Sex [n (%)]							
Female	60 (59.4)	7 (58.3)	12 (63.2)	18 (52.9)	20 (58.8)	28 (49.1)	39 (50.6)
Race [n (%)]							
White	94 (93.1)	12 (100)	18 (94.7)	31 (91.2)	32 (94.1)	57 (100)	74 (96.1)
Black	4 (4.0)	0	1 (5.3)	2 (5.9)	2 (5.9)	0	1 (1.3)
Other	3 (3.0)	0	0	1 (2.9)	0	0	2 (2.6)
Nicotine use [n (%)]							
User	9 (8.9)	0	0	3 (9.1)	3 (8.8)	3 (5.3)	7 (9.1)
Exuser	46 (45.5)	4 (33.3)	12 (63.2)	14 (42.4)	11 (32.4)	29 (50.9)	27 (35.1)
Nonuser	46 (45.5)	8 (66.7)	7 (36.8)	16 (48.5)	20 (58.8)	25 (43.9)	43 (55.8)
Unknown	0	0	0	1 (2.9)	0	0	0
ADAS-Cog total score [mean (SD)]	20.2 (7.95)	23.5 (9.93)	20.1 (8.10)	18.1 (7.65)	21.5 (8.66)	21.1 (10.22)	19.9 (8.63)
MMSE [mean (SD)]	20.4 (3.96)	20.3 (4.11)	21.4 (3.96)	21.5 (4.15)	20.6 (4.01)	20.3 (4.53)	21.1 (4.18)
CSDD [mean (SD)]	2.5 (2.43)	2.0 (1.71)	3.5 (2.67)	2.0 (2.35)	2.2 (2.40)	2.3 (2.29)	3.1 (2.77)
ADCS-ADL [mean (SD)]	61.6 (12.01)*	61.3 (13.36)	62.4 (14.60)	64.8 (11.49)	58.4 (12.86)†	62.8 (11.96)‡	60.8 (12.45)§
NPI [mean (SD)]	7.8 (9.53)	6.3 (10.06)	6.7 (12.46)	7.1 (9.34)	7.7 (8.10)	8.7 (11.11)	7.2 (8.40)
CIBIS [mean (SD)]	3.6 (0.73)	3.4 (0.67)	3.5 (0.90)	3.5 (0.79)‖	3.5 (0.86)	3.6 (0.81)	3.6 (0.78)

*n = 97.
†n = 31.
‡n = 54.
§n = 71.
‖n = 33.
ADAS-Cog indicates Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; CIBIS, Clinician Interview-Based Impression of Severity; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

results achieved significance and no patterns suggesting a dose response were observed (data not shown).

The incidence of AEs was 59.2% (138/233 patients) in the total ABT-089 group and 60.4% (61/101 patients) in the placebo group (safety data set). Across all doses of ABT-089, the AE profiles were similar to placebo. AEs were predominantly mild to moderate in severity. The most commonly reported AEs (ie, occurring in $\geq 3.0\%$ of patients in either the placebo group or the overall ABT-089 treatment group) are summarized in Table 3. Chest pain was the only individual AE which occurred in a statistically significantly higher proportion in an ABT-089 dose group (30 mg dose group, 3/57 patients) versus placebo (0/101 patients) ($P = 0.045$). Nausea was the only treatment-related AE for which a statistically significant treatment difference was observed, with a lower proportion in the total ABT-089 group (2/233 patients) than in the placebo group (5/101 patients) ($P = 0.028$). One patient (ABT-089

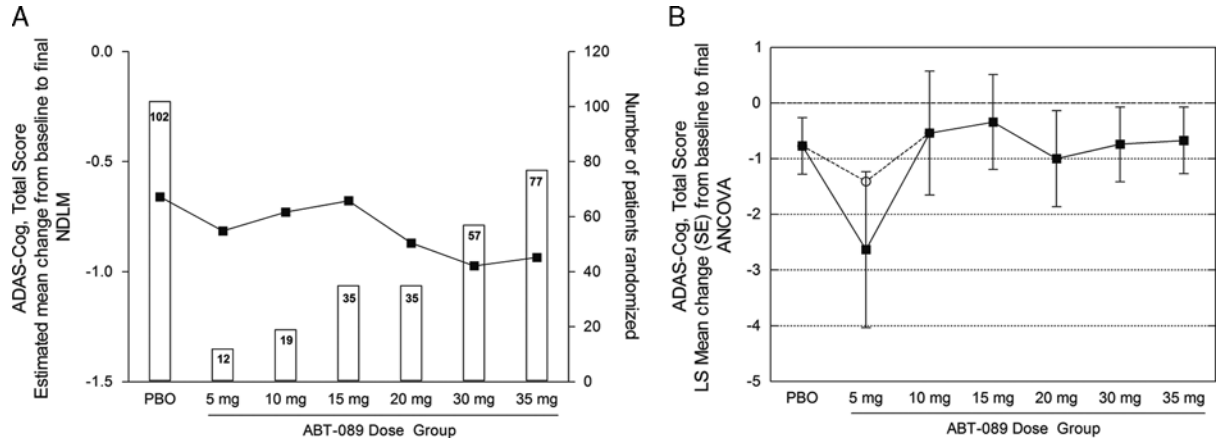

FIGURE 2. A, Line graph = ADAS-Cog total score (estimated mean change from baseline to final evaluation), analyzed by NDLM; bar graph = number of patients randomized. B, ADAS-Cog total score, analyzed by ANCOVA. Open symbol with dotted line represent data with 1 outlier removed from 5 mg ABT-089 group. Decrease in ADAS-Cog total score represents improvement in clinical measure. ADAS-Cog indicates Alzheimer's Disease Assessment Scale-cognitive subscale; ANCOVA, analysis of covariance; NDLM, normal dynamic linear model.

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TABLE 2. Summary of Secondary Efficacy Analysis: Difference in Mean Change (LS Mean by ANCOVA) From Baseline to Final Evaluation With 90% CI

	ABT-089 Dose Group					
	5 mg	10 mg	15 mg	20 mg	30 mg	35 mg
ADAS-Cog [LS mean (90% CI)]	−1.87 (−4.33, 0.60) n = 12	0.22 (−1.79, 2.24) n = 19	0.43 (−1.20, 2.06) n = 33	−0.23 (−1.88, 1.42) n = 32	0.03 (−1.36, 1.41) n = 53	0.10 (−1.20, 1.40) n = 66
MMSE [LS mean (90% CI)]	−0.14 (−1.58, 1.30) n = 12	−0.89 (−2.07, 0.30) n = 19	−0.59 (−1.55, 0.37) n = 33	−0.43 (−1.40, 0.53) n = 32	−0.19 (−1.00, 0.62) n = 53	−0.12 (−0.88, 0.64) n = 66
CSDD [LS mean (90% CI)]	0.29 (−1.22, 1.80) n = 11	0.44 (−0.80, 1.68) n = 18	0.08 (−1.02, 1.17) n = 25	−0.26 (−1.32, 0.80) n = 27	0.56 (−0.38, 1.50) n = 39	0.28 (−0.60, 1.16) n = 49
ADCS-ADL [LS mean (90% CI)]	−0.21 (−3.78, 3.36) n = 12	−0.03 (−2.97, 2.91) n = 19	2.26 (−0.12, 4.64) n = 33	0.68 (−1.82, 3.18) n = 29	−0.10 (−2.17, 1.96) n = 50	−0.72 (−2.66, 1.22) n = 62
NPI [LS mean (90% CI)]	3.77 (−0.06, 7.60) n = 12	1.80 (−1.34, 4.95) n = 19	−2.15 (−4.68, 0.38) n = 33	−1.15 (−3.71, 1.41) n = 32	0.99 (−1.16, 3.15) n = 53	1.50 (−0.52, 3.52) n = 66
CIBIC-plus [LS mean (90% CI)]*	0.09 (−0.30, 0.49) n = 12	−0.09 (−0.42, 0.23) n = 19	0.01 (−0.25, 0.27) n = 33	−0.08 (−0.35, 0.18) n = 32	−0.01 (−0.23, 0.22) n = 53	−0.02 (−0.23, 0.19) n = 66

*Final observations analyzed by ANOVA.

ADAS-Cog indicates Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CIBIS, Clinician Interview-Based Impression of Severity; CI, confidence interval; CSDD, Cornell Scale for Depression in Dementia; LS, least-squares; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

35 mg) died during the study. The patient had a history of coronary artery disease and experienced fatal atherosclerotic heart disease. The investigator attributed the event to the patient's underlying condition and did not consider it to be related to the study drug. No statistically significant or clinically meaningful treatment differences were observed between any ABT-089 dose group and placebo in the proportion of patients who experienced a serious AE or who were prematurely discontinued due to an AE (Table 3). Changes in laboratory values, vital signs, and ECG variables were similar between placebo and ABT-089 groups and were not clinically meaningful.

DISCUSSION

There have been a number of recent clinical trial failures for the symptomatic treatment of AD.[3,24–27] Some of these failures may have been due to the ineffectiveness of the specific mechanism tested, whereas others may have been the result of the inability to select the proper dose range or clinical design for successful testing of the mechanistic hypothesis. It is likely that in several of these trials, the investigational compound could have been deemed ineffective at an earlier time in the trial, or even an earlier phase of development, leading to a reduction in the number of patients taking an ineffective medication and saving resources that could be redeployed towards a more promising therapy in development. This observation highlights the need for clinical studies to be performed more effectively and more efficiently, both for the patients requiring effective new treatments and for the study sponsors.

The current phase 2, double-blind, randomized, placebo-controlled, dose-finding study employed an adaptive design for patient randomization to examine a wide dose range and increase the size of treatment groups at the doses that were most likely to result in clinical benefit (based on the results obtained to date). Although this approach did require revision to the patient allocation algorithm (increased allocation to the placebo group) at the 12th interim analysis, it ultimately allowed the more efficient assessment of whether the experimental mechanism possessed the potential to meaningfully improve cognition. The use of a Bayesian response-adaptive design allowed the maximal sample size to be reduced from 700 (100/arm for a traditional parallel group design) to 400 patients. Further, the predefined criteria for futility allowed the trial to stop when 337 patients were randomized, resulting in an additional 63 patient savings, 16% of the planned maximum sample size. Such interim analyses for futility should be routine in POC trials for the symptomatic treatment of AD.

ABT-089 failed to demonstrate efficacy when administered as adjunctive therapy to AChEIs in patients with mild to moderate AD. The rationale for the use of a selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor agonist was to increase the activation of this putatively procognitive receptor subtype, without the activation of α_3 or muscarinic subtypes, thereby avoiding the potential dose-limiting toxicities observed with nonselective cholinergic agonists.[28,29] However, the current results raise the question as to whether nicotinic receptor agonists can provide therapeutic benefit in this population when administered on the background of increased cholinergic tone. It is possible that the partial agonist property of ABT-089 does not provide enough activation of $\alpha_4\beta_2$

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TABLE 3. Summary of Adverse Events (Safety Data Set)

		ABT-089 Dose Group						
	Placebo (n = 101)	5 mg (n = 12)	10 mg (n = 19)	15 mg (n = 34)	20 mg (n = 34)	30 mg (n = 57)	35 mg (n = 77)	Overall (n = 233)
Total AEs [n (%)]	61 (60.4)	4 (33.3)	12 (63.2)	26 (76.5)	19 (55.9)	32 (56.1)	45 (58.4)	138 (59.2)
Serious AEs [n (%)]	6 (5.9)	0	0	2 (5.9)	2 (5.9)	6 (10.5)	4 (5.2)	14 (6.0)
Premature discontinuation due to an AE [n (%)]	6 (5.9)	0	0	3 (8.8)	1 (2.9)	1 (1.8)	1 (1.3)	6 (2.6)
Most common treatment-emergent AEs [n (%)]*								
Diarrhea	4 (4.0)	0	3 (15.8)	4 (11.8)	3 (8.8)	3 (5.3)	3 (3.9)	16 (6.9)
Fall	8 (7.9)	1 (8.3)	1 (5.3)	2 (5.9)	2 (5.9)	0	6 (7.8)	12 (5.2)
Upper respiratory tract infection	3 (3.0)	1 (8.3)	1 (5.3)	3 (8.8)	2 (5.9)	1 (1.8)	3 (3.9)	11 (4.7)
Dizziness	5 (5.0)	0	0	3 (8.8)	0	3 (5.3)	4 (5.2)	10 (4.3)
Urinary tract infection	7 (6.9)	0	1 (5.3)	2 (5.9)	2 (5.9)	2 (3.5)	2 (2.6)	9 (3.9)
Cough	2 (2.0)	0	1 (5.3)	1 (2.9)	1 (2.9)	2 (3.5)	4 (5.2)	9 (3.9)
Headache	4 (4.0)	0	2 (10.5)	2 (5.9)	0	2 (3.5)	2 (2.6)	8 (3.4)
Nasopharyngitis	6 (5.9)	0	1 (5.3)	2 (5.9)	1 (2.9)	0	2 (2.6)	6 (2.6)
Nausea	6 (5.9)	0	1 (5.3)	1 (2.9)	0	2 (3.5)	1 (1.3)	5 (2.1)
Agitation	4 (4.0)	0	0	0	1 (2.9)	3 (5.3)	0	4 (1.7)
Rash	3 (3.0)	0	0	0	0	2 (3.5)	1 (1.3)	3 (1.3)
Vomiting	4 (4.0)	0	0	0	0	1 (1.8)	1 (1.3)	2 (0.9)
Fatigue	3 (3.0)	0	0	1 (2.9)	0	0	1 (1.3)	2 (0.9)
Hypertension	3 (3.0)	0	0	0	0	0	2 (2.6)	2 (0.9)

*Occurring in $\geq 3.0\%$ of patients in either the placebo group or the overall ABT-089 treatment group.
AE indicates adverse event.

receptors to provide benefit past that resulting from the cholinesterase inhibitor. Recent data have also demonstrated little benefit with ispronicline (another partial $\alpha_4\beta_2$ receptor agonist) when given as a monotherapy in AD patients.[30] However, the ispronicline results are inconclusive, as there was also no significant improvement detected in those treated with the positive control, donepezil. These results along with the current data suggest that the activation of $\alpha_4\beta_2$ receptors by partial agonists may be too weak to provide therapeutic benefit in AD.

In a preclinical experiment, improvements were observed when a suboptimal dose of ABT-089 was added to a suboptimal dose of donepezil, suggesting an additive effect (AbbVie data on file). It is possible that this effect was negated when an optimal dose of donepezil was administered, or that a more favorable result could have been obtained with ABT-089 monotherapy. Another explanation for the negative results is that ABT-089 did not adequately engage the $\alpha_4\beta_2$ receptor. However, this seems unlikely given the findings from a phase 1 study in healthy subjects in which ABT-089 demonstrated procognitive effects as assessed by the CDR battery.[31] ABT-089 attenuated the scopolamine-induced deficits in the domain of attention, with the 40 mg dose showing the most robust results, although the study was not powered to evaluate dose response. Further evidence that a 35 mg dose adequately engaged the $\alpha_4\beta_2$ receptor was the finding that a dose of 40 mg resulted in statistically significant improvement in adult patients with ADHD.[32]

Previous work has demonstrated that NNR agonists induce significant improvements on measures of cognition, including working memory, learning, and attention. In the current work, ABT-089 showed improvement on the Power of Attention measure in the CDR battery, one of the secondary endpoints. This is in line with previous results demonstrating improved attention with $\alpha_4\beta_2$ agonists in preclinical species[33,34] and in healthy subjects. ABT-089 did not improve performance on the primary outcome measure, the ADAS-Cog. While this is also the primary outcome measure for nearly all late phase clinical trials of AD, this scale does not contain specific test items for attention. The lack of a positive effect on either the global or functional outcome measures despite having proattentional effects on the CDR battery suggests that improvement of attention by ABT-089 was not sufficient to positively impact mild to moderate AD patients.

The response-adaptive trial design that was employed, which utilized interim success and futility criteria, allowed timely termination of the study. These results demonstrate the value of appropriately utilizing adaptive trial designs to efficiently evaluate novel therapeutics in AD.

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