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# A Randomized Study of H3 Antagonist ABT-288 in Mild-To-Moderate Alzheimer's Dementia[1]

George M. Haig[a,*], Yili Pritchett[a,2], Andreas Meier[a], Ahmed A. Othman[a,b], Coleen Hall[a], Laura M. Gault[a] and Robert A. Lenz[a,3]
[a]*AbbVie, North Chicago, IL, USA*
[b]*Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo, Egypt*

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**Abstract**.
**Background:** ABT-288, a highly selective histamine-3 receptor antagonist, demonstrated efficacy across several preclinical cognitive domains, and safety in healthy subjects and elderly volunteers.
**Objective:** Evaluate the efficacy and safety of ABT-288 in subjects with mild-to-moderate Alzheimer's dementia.
**Methods:** The study used a randomized, double-blind, placebo- and active-controlled, parallel group design with pre-defined futility criteria to permit early study termination. A total of 242 subjects were randomized in an equal ratio to ABT-288 1 mg or 3 mg, donepezil 10 mg, or placebo once daily for 12 weeks. The primary efficacy endpoint was the change from baseline to final evaluation on the 13-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) total score.
**Results:** The study was prematurely terminated because futility criteria were met. Point estimates on the ADAS-Cog scores for both ABT-288 dose groups were numerically inferior to placebo but no statistical differences were detected. Donepezil demonstrated statistically significant improvement. Adverse events were generally mild and self-limiting.
**Conclusion:** ABT-288 did not demonstrate efficacy in the symptomatic treatment of Alzheimer's dementia.

Keywords: ABT-288, Alzheimer's dementia, cognition, drug therapy, H3 antagonists, humans

## INTRODUCTION

Alzheimer's dementia (AD) is a neurodegenerative disorder characterized by cognitive deterioration, progressive impairment of activities of daily living, and neuropsychiatric and behavioral disturbances. Approximately 25 million people worldwide have dementia, with AD being the underlying cause in 50 to 70% of the cases; the worldwide prevalence of dementia is expected to double every 20 years [1]. In the US, AD is the sixth leading cause of death and incurs costs of $148 billion annually [2].

The currently approved agents for the treatment of dementia associated with AD include the cholinesterase inhibitors, such as donepezil, and the N-methyl D-aspartate (NMDA) glutamate receptor inhibitor memantine. Cholinesterase inhibitors produce a modest improvement in cognition and are the standard of care for the treatment of cognitive

[1]Data previously presented at the Alzheimer's Association International Conference, July 14–19, 2012, Vancouver, British Columbia, Canada.

[2]Present address: Astellas Pharma Global Development Inc., Northbrook, IL, USA.

[3]Present address: Amgen, Thousand Oaks, CA, USA.

*Correspondence to: George M. Haig, PharmD, MBA, AbbVie, Neuroscience Development, Global Pharmaceutical Research and Development, One Waukegan Road, North Chicago, IL 60064, USA. Tel.: +1 847 938 1900; Fax: +1 847 937 0745; E-mail: george.haig@abbvie.com.

symptoms in mild-to-moderate AD. The identification of drugs with superior efficacy and improved side effect profiles is an active area of research.

One of the different mechanisms of action being investigated as a potential treatment for AD is inhibition of the histamine-3 (H3) receptor. H3 receptors are abundantly located in cortical regions of the brain on presynaptic terminals. Their function is inhibitory, such that activation of H3 receptors suppresses the release of histamine, acetylcholine, and norepinephrine. In contrast, pharmacological antagonism of the H3 receptor increases the release of these neurotransmitters in cortical regions of the brain [3–5]. In preclinical rodent studies, H3 antagonists improved performance across several cognitive domains [4–7] suggesting they may provide therapeutic benefit in subjects with AD [3].

ABT-288 is a highly potent and selective H3 receptor antagonist with an affinity <2 nM at the H3 receptor and little binding to most known human receptors at a concentration <10 nM [3]. In rodent behavioral models, ABT-288 demonstrated activity across several cognitive domains with a predicted efficacious plasma concentration range of 0.1 to 2 ng/mL [3]. In phase 1 studies in healthy young subjects and elderly volunteers, ABT-288 was well tolerated at doses up to 3 mg once daily. Dose-limiting adverse events included hot flashes, insomnia, nausea, and dizziness and were observed at higher doses (6 mg once daily in healthy young subjects and 5 mg once daily in elderly volunteers, respectively) [8]. This is consistent with other H3 antagonists such as bavisant where the dosing was limited by side effects, most notably those affecting sleep (e.g., insomnia, abnormal dreams) [9]. In healthy young and elderly volunteers, the pharmacokinetic profile of ABT-288 was characterized by bi-exponential disposition with an elimination half-life of approximately 50 hours and 3.4- to 4.2- fold accumulation with once-daily dosing [8]. ABT-288 exposure was dose-proportional and steady-state is reached by 10 days of dosing. There was no clinically meaningful effect of food on ABT-288 exposure [8].

Dose selection for the current study was based on data obtained from preclinical and healthy volunteer studies to achieve a plasma exposure in the range of preclinical efficacy. ABT-288 1 mg once daily resulted in exposures at or above the preclinical efficacious range and ABT-288 3 mg once daily was the maximum tolerated dose in phase 1 studies of elderly subjects [3, 8]. In positron emission tomography (PET) studies with other H3 antagonists in human volunteers, notable sleep disturbances (insomnia) were observed at a brain receptor occupancy of approximately 70% and greater [10]. Preclinical experiments suggested that the pro-cognitive effects of ABT-288 would be observed at receptor occupancy levels comparable to or lower than those that induce sleep effects. Given the *in vitro* binding affinity of ABT-288 and the predicted exposures, 1 mg and 3 mg of ABT-288 administered once-daily were estimated to achieve peak to trough H3 receptor occupancy of 40 to 25% and 70 to 50%, respectively [8].

Preclinical efficacy data, safety and tolerability profiles obtained from phase 1 studies, and the ability to attain purportedly efficacious plasma exposures in humans with once-daily dosing provided the justification for advancing ABT-288 to a phase 2 proof-of-concept study. The objective of this study was to evaluate the efficacy and safety of ABT-288 for the symptomatic treatment of mild-to-moderate AD. Six interim efficacy evaluations were planned with predefined stopping criteria. These interim analyses provided a mechanism to discontinue an inefficacious dose of ABT-288 or terminate the entire study due to futility of both ABT-288 dose groups.

## MATERIALS AND METHODS

### *Study design*

This phase 2, randomized, multiple-dose, double-blind, placebo- and active-controlled, parallel group study (NCT number 01018875) was conducted at 10 sites in Russia and 11 sites in Ukraine from December 2009 to February 2011. Study protocol, amendments, and informed consent forms were approved by independent ethics committees. Subjects and caregivers gave voluntary, signed informed consent before any study procedures were initiated. If the subject was not fully competent, informed consent was obtained from a legal representative and assent was obtained from the subject. The study was conducted according to Good Clinical Practice guidelines.

The study consisted of a screening period of up to 28 days that included 2 screening visits, a double-blind treatment period of 12 weeks, and a 30-day follow-up period. Psychiatric scales, cognitive assessments, and safety evaluations were conducted at study visits on day –1 (randomization and baseline), and weeks 2, 4, 8 and 12. Urine drug and alcohol tests were performed during screening, at week 4, and week 12. A follow-up visit and phone contact occurred at week 14 and 30 days post-dose, respectively.

A total of 260 subjects (65 per treatment group) were planned. Subjects were randomized in an equal ratio via an interactive voice response/interactive web-based system to receive once daily doses of placebo, ABT-288 1 mg, ABT-288 3 mg, or donepezil 10 mg. The randomization schedule was computer-generated by the sponsor's Department of Clinical Statistics before the study initiation and was stratified by study site.

Study drug for all treatment arms was identical in appearance to maintain the blind. Over-encapsulated donepezil, used as an active control to assess assay sensitivity, was administered at 5 mg once daily for 4 weeks, then 10 mg once daily during weeks 5 through 12. Each morning all subjects took four capsules packaged in a blister pack.

*Study population*

Eligible subjects were male or female subjects between 55 and 90 years of age diagnosed with mild-to-moderate AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD [11]. Key inclusion criteria included a Mini-Mental Status Examination (MMSE) [12] score of 10 to 24 (inclusive), a Cornell Scale for Depression in Dementia (CSDD) [13] score $\leq$10 and a Modified Hachinski Ischemic Scale [14] score of $\leq$4 at the screening visit. A computerized tomography or magnetic resonance imaging scan within 36 months prior to randomization was also required to rule out other causes of dementia.

Exclusion criteria included a history of any significant neurologic disease other than AD, a history or evidence of substance or alcohol abuse, significant uncontrolled medical conditions, neurologic, or psychiatric illness, known donepezil treatment failure, and an inability or difficulty swallowing capsules. Subjects taking warfarin or phenprocoumon within 30 days of screening and those with known intolerance to donepezil, piperidine derivatives, or excipients in donepezil or ABT-288 were also excluded.

Subjects were not allowed to enroll in the study if they had taken any medication for dementia or underwent cognitive therapy for the treatment of AD or dementia within 60 days of screening. Investigational drugs were not allowed within 6 weeks prior to the first dose of study drug. Subjects who took part in a monoclonal antibody trial for AD were not eligible until 6 months after the last study visit for the prior study; those enrolled in an active vaccine trial for AD were excluded. Antidepressants (except tricyclics and monoamine oxidase inhibitors), melatonin, and anxiolytics, hypnotics, and antipsychotics administered at low stable doses were permitted provided they were initiated >30 days prior to screening with no subsequent dosing changes. Use of anxiolytics or hypnotics on an as needed basis was not permitted within 12 hours of efficacy assessments. Use of all other psychotropic medications within two weeks of screening was prohibited.

*Assessments*

The primary efficacy endpoint was the change from baseline to the final evaluation in the 13-item Alzheimer's Disease Assessment Scale-cognitive subscale [15, 16] (ADAS-Cog) total score. The 13-item ADAS-Cog includes all items in the 11-item ADAS-Cog scale plus delayed word recall and number cancellation subtests. The 13-item ADAS-Cog was chosen as the primary endpoint because the number cancellation subtest evaluates attention, a cognitive domain believed to improve with H3 antagonist treatment. The 11-item ADAS-Cog total score was analyzed as a secondary efficacy measure. Other secondary endpoint measures were the MMSE total score, Clinician Interview-Based Impression of Change [17] (CIBIC-plus, measured at post-baseline assessments while the Clinician Interview-Based Impression of Severity [CIBIS] was measured at baseline), Neuropsychiatric Inventory [18, 19] (NPI) total score, the Alzheimer's Disease Cooperative Study-Activity of Daily Living [20] (ADCS-ADL) total score, and the Quality of Life-Alzheimer's Disease [21] (QoL-AD) subject and caregiver totals scores.

Safety evaluations included concomitant medication review, vital signs, electrocardiograms (ECGs), physical examinations, brief neurological examinations, brief psychiatric assessments, clinical laboratory assessments, the CSDD [13] conducted at screening and the week 12/final visit, and the Physician Withdrawal Checklist (PWC-20) [22], conducted during follow-up at the week 14 visit. Relationship and severity of treatment-emergent adverse events were rated by the investigator. Laboratory data, vital signs, and ECGs were evaluated for clinical significance. An independent safety data monitoring committee reviewed safety parameters throughout the study.

Pharmacokinetic samples were collected at the week 2, 4, 8 and 12/final visits (1 sample per visit, 4 samples planned per subject). ABT-288 plasma concentrations were determined by the sponsor using a validated liquid chromatography method with tandem mass spectrometric detection as previously described [8].

*Statistical analyses*

*Sample size*

The planned total sample size of the study was 260 subjects. With 65 subjects per arm, the study would have 80% power to detect a treatment effect size of 0.45 at a one-sided significance level of 0.05. It was also assumed that 5% of randomized subjects would not have post-baseline data on the primary efficacy measure. A one-sided test was chosen for the primary and all secondary efficacy analyses because of the exploratory nature of the study. The intent was to test the statistical significance when an ABT-288 dose group demonstrated greater numerical improvement on the 13-item ADAS-Cog total score compared with placebo.

*Primary and secondary analyses*

All randomized subjects who took at least one dose of study drug were included in the efficacy analyses. The primary efficacy analysis was carried out using an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and baseline 13-item ADAS-Cog total score as the covariate to evaluate the treatment group difference in baseline-to-final of the 13-item ADAS-Cog total score. The treatment group difference between each ABT-288 dose group and placebo was tested at a one-sided significance level of 0.05. The difference in Type III sum-of-squares least squares (LS) mean change between an ABT-288 dose group and placebo and 2-sided 90% confidence intervals were estimated from the ANCOVA model where data from all treatment groups were included. A similar analysis was applied to assess the difference between donepezil and placebo treatment groups.

A secondary analysis of the primary efficacy endpoint was performed using a mixed-effects, maximum likelihood, repeated measures (MMRM) model utilizing all baseline and post-baseline data. The model included fixed effects of treatment, study site, visit, and treatment-by-visit interaction, with baseline score as a covariate, and the baseline-by-visit interaction. In the MMRM model, the "unstructured" variance-covariance was used, the Satterthwaite's approximation was used to estimate the denominator degrees of freedom, and the Type III sum-of-squares for the LS means was used to estimate treatment group differences for the change from baseline. Treatment group contrasts were made at each post-baseline visit where the ADAS-Cog was administered (weeks 4, 8 and 12).

Secondary efficacy endpoints included the change from baseline on the 11-item ADAS-Cog total score, MMSE, 12- and 10-item NPI, and ADAS-ADL total scores, the QoL-AD subject and caregiver rated scores, and the endpoint CIBIC-plus score. The aforementioned ANCOVA and MMRM models were used to analyze all secondary efficacy variables except for the endpoint of CIBIC-plus, which was analyzed using an ANCOVA model with the terms of treatment and study site with the day –1 CIBIS score as the covariate to adjust for baseline variability. All efficacy analyses were performed using one-sided tests at the significance level of 0.050.

*Interim efficacy analyses*

Six interim efficacy evaluations were planned when 100, 120, 140, 160, 180 and 200 subjects completed 12 weeks or prematurely discontinued from the study. The intent of planning and conducting interim efficacy evaluations was to either discontinue further enrollment to an inefficacious dose of ABT-288 or to stop the entire study if both ABT-288 dose groups met futility criteria. At each interim analysis, a Bayesian predictive probability for the event of a final one-sided p-value of $p \leq 0.050$ was calculated, comparing the ABT-288 dose group with placebo. If the predictive probabilities for 3 consecutive evaluations were all $\leq$0.10 (i.e., there was a $\leq 10\%$ chance of obtaining a statistically significant result for the primary efficacy analysis for this dose group at the final analysis), or if they showed a decreasing trend with the last one being $\leq$0.10, the dose group was considered to have met futility criteria. If an ABT-288 dose group met futility criteria, further enrollment to this group was to stop and subjects would be randomized to the remaining three groups in 1 : 1:1 ratio until the total sample size of approximately 65 per arm was reached. If both ABT-288 dose groups met futility criteria, the entire study could be terminated.

Interim efficacy evaluations were conducted in accordance with the Efficacy Data Monitoring Committee charter that was approved prior to the first interim analysis. The analyses were performed by an unblinded sponsor statistician (one who was not a member of the study team) and an unblinded external statistician.

*Pharmacokinetic analyses*

Because steady state is reached for ABT-288 by day 10 of dosing [8], plasma concentrations of ABT-288 for each dose level were combined across all visits. The plasma concentrations were categorized on the basis of time since administration of the previous dose of ABT-288.

*Safety analyses*

All randomized subjects who took at least one dose of study drug were included in the safety analyses. Overall statistical comparisons were made at a two-sided significance level of 0.050. Treatment-emergent adverse events were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA) [23] version 13.1 System Organ Class and Preferred Term. Treatment group differences in the occurrence of adverse events were assessed by Fisher's exact test.

Treatment differences between each ABT-288 dose group and placebo as well as between donepezil and placebo in the change from baseline to minimum, maximum, and final clinical laboratory evaluation, vital sign values, and ECG observations were analyzed using one-way analysis of variance (ANOVA) with treatment as the main effect. Potentially clinically significant laboratory and vital sign values, according to pre-specified criteria, were also summarized. Treatment differences between each ABT-288 dose group and placebo, as well as between donepezil and placebo in change from baseline to final observation for CSDD total score (sum of 19 items score) were analyzed using two-way ANCOVA with the terms of treatment and study site and baseline score as covariate. The PWC-20 total score was analyzed using two-way ANOVA with the terms of treatment and study site.

## RESULTS

*Interim efficacy analysis results*

Futility criteria were met for both doses of ABT-288 at the third interim efficacy evaluation, the first opportunity to determine futility as defined by the interim analysis algorithm. At the first interim efficacy evaluation ($n = 100$), the predictive probabilities of having a final $p$-value $\leq 0.05$ on the 13-item ADAS-Cog compared with placebo were 0.001 for ABT-288 1 mg, 0.036 for ABT-288 3 mg, and 0.858 for donepezil. The second analysis ($n = 120$) showed the predictive probabilities of 0.001 (ABT-288 1 mg), 0.045 (ABT-288 3 mg), and 0.970 (donepezil). Similar results were obtained in the third interim analysis ($n = 140$), with predictive probabilities of 0.004 (ABT-288 1 mg), 0.051 (ABT-288 3 mg), and 0.999 (donepezil). The study was then terminated by the sponsor. Active study subjects were instructed to discontinue study medication and return to the site for a discontinuation visit. Data from these subjects were included in the final efficacy and safety analyses.

*Subjects*

When the study was terminated, 342 subjects had been screened for the study and 242 subjects had been randomized. Of the 242 randomized subjects 153 (63.2%) completed the study and 89 subjects (36.8%) prematurely discontinued; 76.4% ($n = 68$) of the premature discontinuations were due to the termination of the study. All randomized subjects received at least 1 dose of study drug and were included in the efficacy and safety analyses. Subject disposition is illustrated in Fig. 1.

Demographic characteristics were not significantly different among treatment groups. All participants were white and 64.5% were female. The mean age was 70.2 years (range 55 to 87); 144 (59.5%) were 70 years or older. The mean age at AD diagnosis was $69.2 \pm 8.54$ years, while the mean duration of AD diagnosis (time elapsed from diagnosis to first dose of study drug) was $1.1 \pm 1.6$ years. Approximately half of the subjects with genotype testing results were carriers of the apolipoprotein E (APOE) $\varepsilon 4$ allele, and 10.7% overall reported a family history of AD. Overall, 47 subjects (19.4%) had been previously treated for AD with a cholinesterase inhibitor or memantine. The most common medications subjects had previously used for AD included "Other" (e.g., piracetam, gingko biloba; vinpocetine, citicoline; 25.2%), memantine (11.2%), and galantamine (5.0%). Baseline demographic characteristics are presented in Table 1.

*Final efficacy analysis results*

Thirty of the 242 randomized subjects (12.4%) were not included in the primary efficacy analysis because they either did not have a baseline ($n = 1$) or a post-baseline ($n = 29$) ADAS-Cog total score. The LS mean change from baseline for both ABT-288 1 mg (–0.54) and 3 mg (–1.14) dose groups were numerically worse than placebo (–1.6) at the final evaluation, while donepezil had a statistically significant greater decrease (improvement) compared with placebo (–4.32, $p = 0.008$; Table 2).

The secondary MMRM analysis of the 13-item ADAS-Cog was in general agreement with the primary ANCOVA analysis. Improvements from baseline to weeks 4, 8 and 12 were observed in all treatment groups, with greater LS mean decreases at each time point in both the donepezil and placebo groups when compared with either ABT-288 dose group (Fig. 2). The LS mean difference from placebo for donepezil was statistically significant at week 8 ($p = 0.021$) and week 12 ($p = 0.023$).

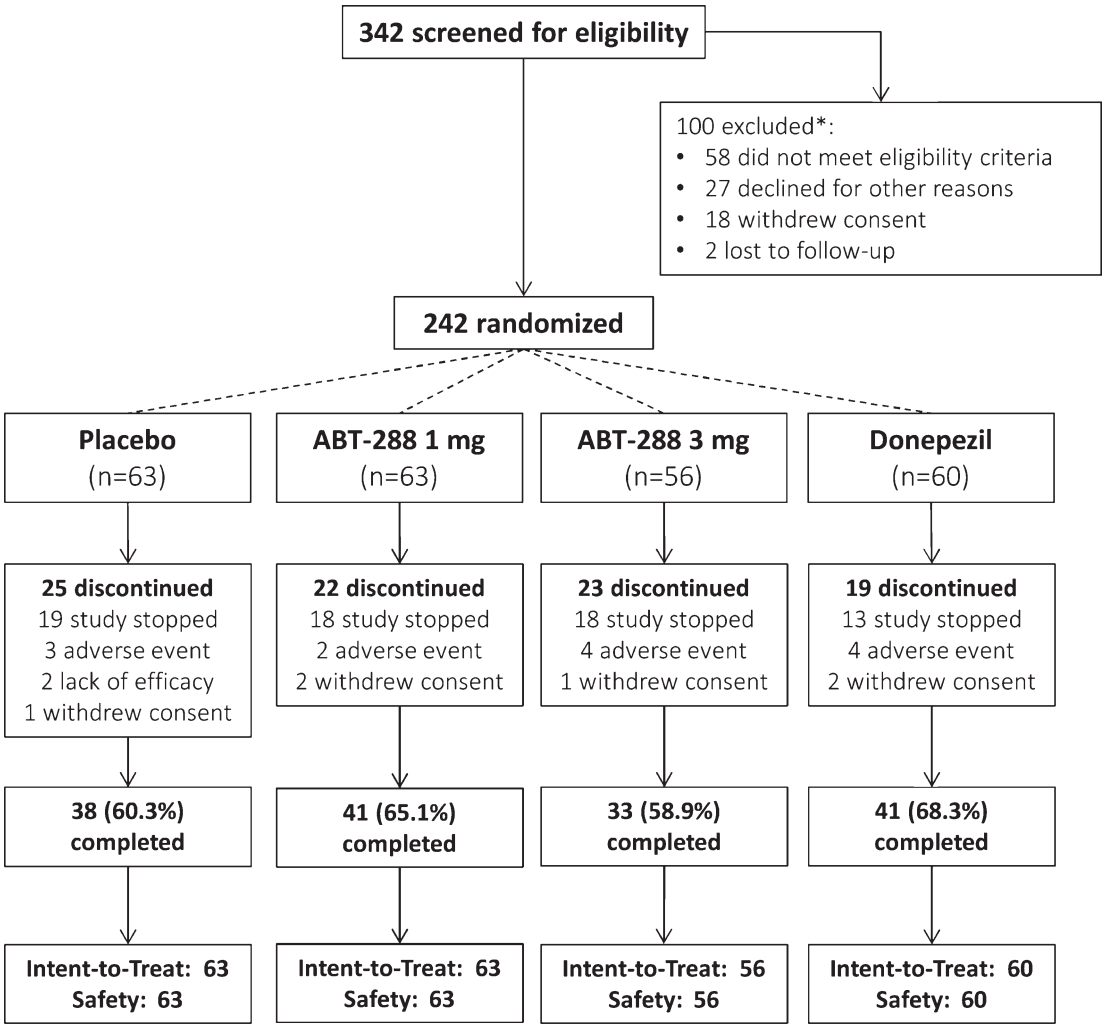


Fig. 1. Subject disposition.

Among the secondary efficacy variables, no statistically significant difference between each ABT-288 dose group and placebo was observed from the ANCOVA for the mean change from baseline to final evaluation (Table 2). The donepezil treatment group had statistically significant improvements compared with placebo in the 11-item ADAS-Cog total score ($p = 0.019$) and the CIBIC-plus score ($p = 0.002$) at the final evaluation. Results from MMRM analyses of secondary efficacy measures were generally in agreement with those obtained from the ANCOVA analyses.

A *post hoc* analysis of the 13-item ADAS-Cog total score was conducted on the dataset that excluded the 68 subjects who prematurely discontinued due to study termination. The results were similar to those obtained from the primary analysis. Greater improvements in both the donepezil ($n = 43$, –5.17) and placebo ($n = 43$, –1.68) groups were observed compared with the ABT-288 1 mg ($n = 41$) and 3 mg ($n = 36$) dose groups (–0.48 and –1.21, respectively). The treatment group difference between donepezil and placebo was statistically significant (difference in LS mean change −3.49; $p = 0.005$).

### *Pharmacokinetics*

The observed ABT-288 plasma concentrations (mean and 5th to 95th percentiles) versus time since

Table 1
Baseline demographic characteristics

| Characteristic | Placebo $n=63$ | ABT-288 1 mg $n=63$ | ABT-288 3 mg $n=56$ | Donepezil 10 mg $n=60$ | Total $n=242$ |
|---|---|---|---|---|---|
| Age, mean (SD), years | 70.3 (7.84) | 71.2 (8.00) | 68.8 (9.17) | 70.5 (8.31) | 70.2 (8.32) |
| *Age distribution, n (%)* | | | | | |
| 55 to < 70 years | 23 (36.5) | 21 (33.3) | 29 (51.8) | 25 (41.7) | 98 (40.5) |
| ≥70 years | 40 (63.5) | 42 (66.7) | 27 (48.2) | 35 (58.3) | 144 (59.5) |
| *Gender, n (%)* | | | | | |
| Female | 39 (61.9) | 46 (73.0) | 35 (62.5) | 36 (60.0) | 156 (64.5) |
| Male | 24 (38.1) | 17 (27.0) | 21 (37.5) | 24 (40.0) | 86 (35.5) |
| Race = white, n (%) | 63 (100) | 63 (100) | 56 (100) | 60 (100) | 242 (100) |
| BMI, mean (SD), kg/m$^2$ | 25.4 (3.30) | 25.3 (3.77) | 25.9 (3.17) | 25.3 (2.94) | 25.4 (3.31) |
| Genotype, *n* (%) | *n*,= 53 | *n* = 53 | *n* = 46 | *n* = 48 | *n* = 200 |
| APOE ε4 carrier | 28 (52.8) | 25 (47.2) | 21 (45.7) | 24 (50.0) | 98 (49.0) |
| APOE ε4 non-carrier | 25 (47.2) | 28 (52.8) | 25 (54.3) | 24 (50.0) | 102 (51.0) |
| Age at AD symptom onset, mean (SD), years | 66.3 (8.08) | 67.0 (8.05) | 64.8 (9.09) | 66.4 (8.38) | 66.2 (8.37) |
| Years since AD symptom onset*, mean (SD) | 4.1 (2.71) | 4.2 (2.47) | 4.0 (2.80) | 4.1 (3.23) | 4.1 (2.79) |
| Age at AD diagnosis, mean (SD), years | 69.2 (8.15) | 70.0 (8.14) | 67.8 (9.49) | 69.4 (8.47) | 69.2 (8.54) |
| Years since AD diagnosis, mean (SD) | 1.1 (1.6) | 1.1 (1.4) | 1.1 (1.6) | 1.1 (1.7) | 1.1 (1.6) |
| Family history of AD, *n* (%) | 9 (14.3) | 5 (7.9) | 6 (10.7) | 6 (10.0) | 26 (10.7) |
| ADAS-Cog (13-item), mean (SD) | 43.8 (11.7) | 47.9 (12.1) | 41.5 (12.7) | 46.3 (13.9) | 45.0 (12.8)† |
| MMSE, mean (SD) | 18.2 (3.9) | 17.0 (4.0) | 18.6 (3.9) | 18.1 (4.1) | 18.0 (4.0) |

AD, Alzheimer's dementia; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; APOE, apolipoprotein E; BMI, body mass index; MMSE, Mini-mental Status Examination; SD, standard deviation *Time from onset of AD symptoms to first dose of study drug. †$n=241$ as one assessment was missing in the ABT-288 1 mg group.

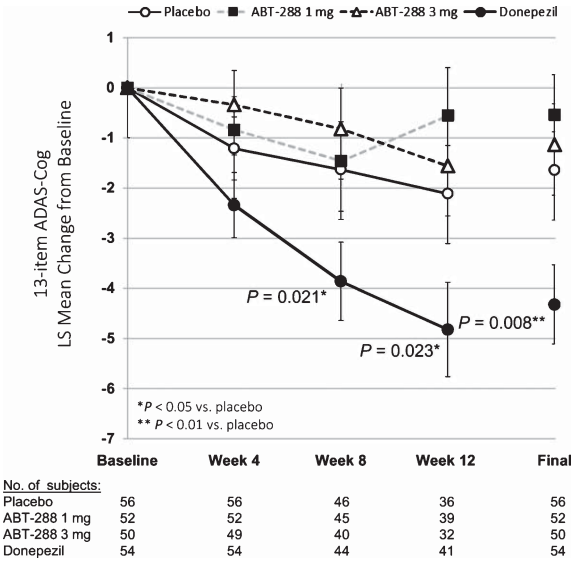


Fig. 2. 13-Item Alzheimer's Disease Scale-cognitive subscale (ADAS-Cog) total score: Least squares (LS) mean change from baseline over time. Mixed-effect model repeated-measures analysis of change from baseline to each visit and the primary analysis of covariance of change from baseline to the final evaluation for the ADAS–Cog 13-item total score. Error bars represent the standard error of the least squares means.

administration of the previous dose of ABT-288 for the 1 and 3 mg once-daily doses are presented in Fig. 3. ABT-288 1 mg once daily resulted in plasma concentrations within the preclinical pro-cognitive efficacy range while ABT-288 3 mg once daily exceeded this range in most of the subjects during the majority of the 24-hour dosing interval. The observed ABT-288 mean plasma concentrations were comparable to the predicted exposures based on the phase 1 studies of healthy adult and elderly subjects [8].

### *Safety*

The overall mean (SD) duration of treatment was 68.1 (25.26) days and ranged from 3 to 105 days. A total of 235 subjects (97.1%) were ≥70% compliant with study medication as determined by the investigators.

A summary of adverse events is presented in Table 3. A total of 111 subjects (45.9%) experienced at least one treatment-emergent adverse event, 39.7% in the placebo group, 47.1% in the combined ABT-288 group, and 50.0% in the donepezil group. When combining both ABT-288 dose groups, the most frequent adverse events (≥5.0%) occurring at a greater incidence than placebo included anxiety ($n=10$, 8.4%), dizziness ($n=7$, 5.9%), and agitation, irritability, and asthenia ($n=6$, 5.0% each). The rate of agitation in the ABT-288 3 mg dose group was approximately 11%. In addition, a clear treatment-related effect was observed in adverse events of anxiety and irritability. Most adverse events were mild or moderate in severity. Five subjects (2.1%) had one or more treatment-emergent

Table 2
Efficacy results, analysis of covariance

| Primary Efficacy Measure<br>Assessment | Placebo<br>$n=56$ | ABT-288 1 mg<br>$n=52$ | ABT-288 3 mg<br>$n=50$ | Donepezil<br>$n=54$ |
|---|---|---|---|---|
| *13-item ADAS-Cog Total Score* | | | | |
| Baseline mean (SD) | 44.0 (11.89) | 48.5 (12.09) | 41.9 (13.06) | 47.2 (13.76) |
| LS mean change to final (SE) | −1.6 (0.76) | −0.54 (0.80) | −1.14 (0.82) | −4.32 (0.79)** |
| Secondary Efficacy Measures | Placebo<br>$n=56$ | ABT-288 1 mg<br>$n=53$ | ABT-288 3 mg<br>$n=50$ | Donepezil<br>$n=54$ |
| *11-item ADAS-Cog Total Score* | | | | |
| Baseline mean (SD) | 31.9 (10.22) | 35.7 (10.74) | 30.2 (11.21) | 34.9 (11.93) |
| LS mean change to final (SE) | −1.3 (0.69) | −0.2 (0.72) | −0.9 (0.74) | −3.4 (0.71)* |
| *MMSE Total Score* | | | | |
| Baseline mean (SD) | 18.0 (3.91) | 16.7 (3.98) | 18.5 (4.05) | 17.9 (4.01) |
| LS mean change to final (SE) | 1.1 (0.36) | 0.5 (0.37) | 0.7 (0.38) | 1.4 (0.37) |
| *NPI (12-item) Total Score* | | | | |
| Baseline mean (SD) | 10.8 (11.74) | 12.8 (11.92) | 11.0 (9.54) | 12.0 (11.17) |
| LS mean change to final (SE) | −0.9 (0.93) | −1.8 (0.97) | −2.2 (0.99) | −0.7 (0.96) |
| *NPI (10-item) Total Score* | | | | |
| Baseline mean (SD) | 9.1 (9.98) | 11.3 (11.15) | 9.5 (8.26) | 10.8 (10.33) |
| LS mean change to final (SE) | −1.0 (0.83) | −1.9 (0.86) | −2.0 (0.88) | −0.7 (0.85) |
| *ADCS-ADL Total Score* | | | | |
| Baseline mean (SD) | 44.4 (15.72) | 41.7 (15.35) | 42.8 (14.40) | 40.7 (15.34) |
| LS mean change to final (SE) | 0.4 (0.88) | 0.6 (0.91) | 2.0 (0.94) | 2.2 (0.90) |
| *CIBIS* | | | | |
| Mean (SD) | 3.9 (0.77) | 4.1 (0.81) | 3.7 (0.79) | 4.1 (0.82) |
| *CIBIC-plus* | | | | |
| LS Mean (SE) | 4.0 (0.08)<br>$n=41$ | 4.0 (0.09)<br>$n=41$ | 3.9 (0.09)<br>$n=38$ | 3.7 (0.08)**<br>$n=43$ |
| *QoL-AD Total Score (Subject)* | | | | |
| Baseline mean (SD) | 27.6 (5.45) | 28.1 (5.80) | 26.8 (4.85) | 28.1 (5.28) |
| LS mean change to final (SE) | 0.2 (0.62) | 0.5 (0.61) | −0.2 (0.64) | 0.6 (0.60) |
| *QoL-AD Total Score (Caregiver)* | | | | |
| Baseline mean (SD) | 25.9 (6.09) | 25.1 (4.32) | 24.5 (3.94) | 25.5 (3.92) |
| LS mean change to final (SE) | 0.3 (0.5) | −0.2 (0.52) | 0.1 (0.54) | −0.3 (0.5) |

ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activity of Daily Living; CIBIC-plus, Clinician Interview-Based Impression of Change; CIBIS, Clinician Interview-Based Impression of Severity; LS, least squares; MMSE, Mini-Mental Status Examination; NPI, Neuropsychiatric Inventory; QoL-AD, Quality of Life-Alzheimer's Disease; SD, standard deviation; SE, standard error. *$p<0.05$ from one-sided test versus placebo using a significance level of 0.05; **$p<0.01$ from one-sided test versus placebo using a significance level of 0.05. Note: No efficacy measures were for either dose of ABT-288 were significantly different when evaluated with a two-sided test using an alpha of 0.05.

serious adverse events, including 3 deaths that occurred during the study. One of the deaths (coronary disease, ABT-288 1 mg group) was considered possibly related to study drug.

Sixteen subjects (6.6%) discontinued from the study due to adverse events, 7 (5.9%) ABT-288-treated subjects, 6 subjects (10.0%) taking donepezil, and 3 (4.8%) from the placebo group. The rate of discontinuation due to adverse events was higher in the ABT-288 3 mg dose group ($n=5$) than in the ABT-288 1 mg group ($n=2$; Table 3). Adverse events leading to discontinuation of two or more ABT-288-treated subjects were agitation ($n=2$) and insomnia ($n=2$) in the ABT-288 3 mg group. The incidence of adverse events considered possibly or probably related to study drug as assessed by the investigator was generally similar across treatment groups (range 20.6% to 26.8%).

No clinically meaningful effects were observed in analyses of laboratory values, vital signs, ECG measurements, CSDD, or PWC-20, nor were any trends observed for ABT-288.

## DISCUSSION

This phase 2, proof-of-concept study was designed to evaluate the efficacy and safety of two doses of ABT-288 in the symptomatic treatment of subjects with mild-to-moderate AD. While the total score of the 13-item ADAS-Cog decreased from baseline to

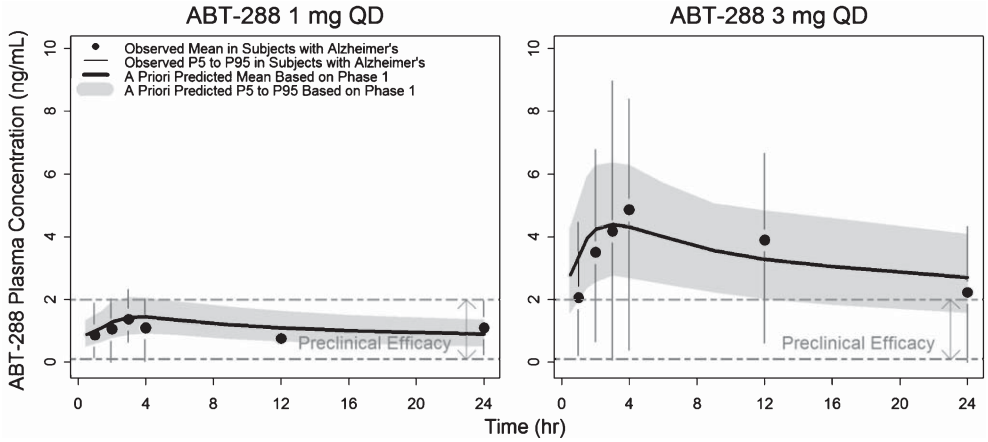


Fig. 3. Observed ABT-288 plasma concentrations compared with preclinical efficacious concentrations and the predicted concentrations from the phase 1 studies. Observed ABT-288 plasma concentrations in subjects with AD (mean and 5th to 95th percentiles) versus time since administration of the previous dose of ABT-288 are compared to the preclinical efficacy concentration range as well as the a priori predicted ABT-288 concentrations based on data from phase 1 pharmacokinetic evaluations in healthy young and elderly subjects. hr, hours; P5, 5th percentile; P95, 95th percentile; QD, once daily.

Table 3
Summary of adverse events

| Overall, *n* (%) | Placebo *n* = 63 | ABT-288 1 mg *n* = 63 | ABT-288 3 mg *n* = 56 | Donepezil 10 mg *n* = 60 | Total *n* = 242 |
|---|---|---|---|---|---|
| Any adverse event | 25 (39.7) | 34 (54.0) | 22 (39.3) | 30 (50.0) | 111 (45.9) |
| Discontinued due to AE | 3 (4.8) | 2 (3.2) | 5 (8.9) | 6 (10.0) | 16 (6.6) |
| Severe AE | 3 (4.8) | 4 (6.3) | 3 (5.4) | 3 (5.0) | 13 (5.4) |
| Serious AE | 2 (3.2) | 2 (3.2) | 0 | 1 (1.7) | 5 (2.1) |
| Adverse Events Reported by ≥2.5% of Subjects Overall (MedDRA Preferred Term), *n* (%) | | | | | |
| Headache | 7 (11.1) | 4 (6.3) | 5 (8.9) | 2 (3.3) | 18 (7.4) |
| Anxiety | 3 (4.8) | 6 (9.5) | 4 (7.1) | 2 (3.3) | 15 (6.2) |
| Dizziness | 1 (1.6) | 5 (7.9) | 2 (3.6) | 3 (5.0) | 11 (4.5) |
| Asthenia | 3 (4.8) | 4 (6.3) | 2 (3.6) | 1 (1.7) | 10 (4.1) |
| Aggression | 1 (1.6) | 2 (3.2) | 1 (1.8) | 4 (6.7) | 8 (3.3) |
| Irritability | 2 (3.2) | 3 (4.8) | 3 (5.4) | 0 | 8 (3.3) |
| Decreased appetite | 4 (6.3) | 2 (3.2) | 0 | 1 (1.7) | 7 (2.9) |
| Insomnia | 2 (3.2) | 2 (3.2) | 2 (3.6) | 1 (1.7) | 7 (2.9) |
| Agitation | 0 | 0 | 6 (10.7)* | 0 | 6 (2.5) |
| Hypertension | 1 (1.6) | 1 (1.6) | 2 (3.6) | 2 (3.3) | 6 (2.5) |
| Nausea | 1 (1.6) | 0 | 1 (1.8) | 4 (6.7) | 6 (2.5) |

AE, adverse event; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities. *$p = 0.009$ versus placebo.

the final measure in all 4 treatment groups, neither dose of ABT-288 demonstrated a pro-cognitive effect by separating from placebo on the change score. In contrast, donepezil showed significant improvement in the primary endpoint compared with placebo (2.68, $p = 0.008$). While other H3 antagonists have failed in large-scale multicenter cognition studies, this is the first AD study to conclusively demonstrate a positive assay with an active control.

The study was prematurely discontinued by the sponsor after the protocol-specified interim efficacy analyses met predefined futility criteria for both doses of ABT-288. Secondary evaluations of ABT-288 including the 11-item ADAS-Cog, MMSE, 12- and 10-item NPI, and ACDS-ADL total scores, the QoL-AD total subject and caregiver scores, and the CIBIC-plus were consistent with the primary efficacy results. An analysis excluding subjects that had prematurely discontinued due to study termination yielded results similar to those obtained from all randomized subjects.

The adverse events reported in this study were generally mild and self-limiting. The safety and tolerability of ABT-288 1 mg and 3 mg administered once

daily for 12 weeks were consistent with data from the phase 1 program and sufficient for continued study if warranted. The dose-dependent withdrawals due to adverse events and the rate of putative mechanistically-related adverse events such as anxiety, irritability, and agitation suggest that higher doses may not have been well tolerated. The pharmacokinetic results (Fig. 3) indicated that the exposures achieved in the trial were comparable to the predicted exposures from phase 1 healthy adult and elderly studies and were at or above the exposures where preclinical efficacy was observed. ABT-288 is a highly permeable compound with concentrations in the cerebrospinal fluid that are at least equal to free plasma concentrations [24]. Additionally, plasma protein binding of ABT-288 is moderate and comparable across species [8]. Therefore, benchmarking relative to plasma concentrations is adequate. While a direct assessment of the receptor occupancy was not performed, target H3 occupancy levels were more than likely reached based on extrapolations from published PET data with another H3 antagonist [10]. Based on these data, the highest dose used in this study (3 mg once daily) was the maximum dose that could have been tested and yielded plasma exposures that provided an adequate test of the hypothesis.

The positive results obtained with the active comparator donepezil and other aspects of the study suggest that the design and conduct of this trial were sufficient to detect a possible H3 antagonist treatment effect. The statistical variance on the primary endpoint (standard deviation of 5.9) was in agreement with the variance observed in multinational AD trials of cholinesterase inhibitors using the 11-item ADAS-Cog [25]. In addition, the retention rate of >90% prior to sponsor termination of the study was higher than retention rates of other 12-week placebo-controlled trials in subjects with AD [26–28].

The effects of several H3 receptor antagonists have been studied in adults with attention deficit hyperactivity disorder (ADHD), cognitive impairment associated with schizophrenia (CIAS), as well as AD. ABT-288 is not the first H3 antagonist that failed to show efficacy in a proof-of-concept study for a cognitive disorder. In a double-blind, placebo-controlled, 4-week trial of MK-0249 in 144 subjects with mild-to-moderate AD, no meaningful improvement in cognitive measures was observed [29], nor did MK-0249 show meaningful effects in patients with CIAS [30]. In a 16-week, phase 2a study of 194 subjects with mild-to-moderate AD, once daily doses of up to 80 mcg of the H3 antagonist GSK239512 led to limited efficacy in the CogState neuropsychological test battery and showed no significant difference versus placebo in the ADAS-Cog at 16 weeks [31]. No significant effects on cognition were observed in another study of GSK239512 in subjects with schizophrenia [32]. Additionally, the H3 antagonist PF-03654746 did not demonstrate efficacy in studies of AD, ADHD, and CIAS [33–35]. Neither ABT-288 nor any other H3 antagonists, to our knowledge, have been evaluated as adjunctive therapy to cholinesterase inhibitors.

None of the aforementioned studies utilized an active comparator, so the impact of lack of assay sensitivity on the study conclusions was not possible to determine. However, data from an adult ADHD with two active controls were recently reported. This was a large trial of 430 adult subjects with ADHD in which all three bavisant dose groups failed to demonstrate a treatment effect after 6 weeks of treatment, while statistically significant improvement was achieved with the active controls atomoxetine and methylphenidate (both $p < 0.005$) [9]. Similarly, an earlier study of adults with ADHD showed no effect with MK-0249 treatment while statistically significant results were obtained with OROS-methylphenidate ($p < 0.001$) [36].

The apparent discrepancy between the efficacy demonstrated in preclinical models of cognition and that observed in the clinic may have arisen from differences in duration of dosing and the possibility of tachyphylaxis to the beneficial effects with chronic dosing. Evidence of ABT-288 preclinical efficacy was demonstrated in models similar to those that have shown pro-cognitive effects with cholinesterase inhibitors. Dosing of ABT-288 in these preclinical studies was acute or up to 5 days. In addition, improvement in attention and impulsivity was observed with dosing of up to 14 days duration in phase 1 studies in subjects with schizophrenia (data on file). Overall, short-term dosing in both preclinical and subjects with schizophrenia was associated with pro-cognitive effects, demonstrating translation of the preclinical findings to humans. However, 12 weeks of treatment with ABT-288 did not improve cognition in stable subjects with schizophrenia [37]. A similar phenomenon was observed with modafinil, where short-term dosing in patients with schizophrenia resulted in pro-cognitive effects that could not be reproduced with long-term dosing [38–41]. In the current study, the earliest assessment was at 4 weeks, and no pro-cognitive effects were detected with longer term administration. Tachyphylaxis to the pro-cognitive effects with chronic dosing is therefore possible. This idea is further supported by the observation that many of the H3-related adverse events

occurred early in treatment and appeared to decrease over time.

Despite the negative data in disorders of cognition such as AD, ADHD, and CIAS, H3 antagonists may not be completely devoid of useful pharmacologic activity. Efficacy of H3 antagonists has been shown trials of wakefulness-promoting effects. Two different doses of MK-0249 had significant increases in sleep latency compared with placebo in a sleep deprivation model [42]. Subjects treated with pitolisant also experienced significant improvement in excessive diurnal sleepiness associated with Parkinson's disease [43], narcolepsy [44] and sleep apnea [43].

In conclusion, ABT-288 did not demonstrate cognitive enhancing effects in subjects with mild-to-moderate AD, but was safe and generally well tolerated. The adaptive dropping-arm design created for this study was advantageous as it enabled the early termination of the study, reduced subjects' exposure to an inefficacious investigational agent, and saved time and resources for the clinical investigation. However, given our findings and those from other H3 antagonist studies of cognition, we conclude that H3 receptor antagonism is not a viable target for the treatment of cognitive disorders such as AD, ADHD, and CIAS in humans.

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