2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
ABT-384</td></tr>
<tr><td>Name of Active Ingredient:
4-{2-Methyl-2-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-propionylamino}-adamantane-1-carboxylic acid amide</td></tr>
<tr><td colspan="3">Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of ABT-384 in Subjects with Mild-to-Moderate Alzheimer's Disease</td></tr>
<tr><td colspan="3">Coordinating Investigator: Felix Potocnik, MD</td></tr>
<tr><td colspan="3">Study Sites: Thirty sites in Great Britain, Ukraine, South Africa, and Russia</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 26 May 2010
Last Subject Last Visit: 20 July 2011</td><td>Phase of Development: 2</td></tr>
<tr><td colspan="3">Objective:
The objective of this study is to evaluate the efficacy and safety of 2 dose levels of ABT-384 in subjects with mild-to-moderate Alzheimer's disease (AD).</td></tr>
<tr><td colspan="3">Methodology:
This was a Phase 2, multicenter, randomized, double-blind, placebo- and active-controlled parallel group study designed to evaluate the efficacy and safety of ABT-384 in subjects diagnosed with mild-to-moderate AD, defined as meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD.

This study consisted of a Screening Period of 14 to 28 days, a 12-Week Treatment Period, and a Follow-up Visit. The Screening Period consisted of 3 visits: Screening Visit 1, Screening Visit 2, and a Day –1 Visit. Screening Visit 1 was to take place within 28 days of the Day –1 Visit. Screening Visit 1, Screening Visit 2, and the Day –1 Visit were to be separated by at least 7 days. The Follow-up Visit was to occur 21 days after the Week 12 or Premature Discontinuation Visit.</td></tr>
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Methodology (Continued):

After completion of the Day –1 Visit, eligible subjects were randomized through an Interactive Voice Response/Interactive Web Response system. Subjects were to be randomized in approximately equal proportions (65 subjects/group) to 1 of the 4 treatment groups: placebo; ABT-384 10 mg; ABT-384 50 mg; and donepezil. Subjects randomized to donepezil were to take donepezil 5 mg once daily (QD) for the first 4 weeks of the treatment period and then donepezil 10 mg QD for the remainder of the 12-week treatment period.

Each subject was instructed to take study drug once daily in the morning. The subject and investigator were blinded to the randomized treatment assignment throughout the Treatment Period.

Number of Subjects (Planned and Analyzed):

260 planned/267 analyzed: 66 subjects were randomized to the placebo treatment group; 70 subjects were randomized to the ABT-384 10 mg treatment group; 65 subjects were randomized to the ABT-384 50 mg treatment group; and 66 subjects were randomized to the donepezil treatment group.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects between the ages of 55 and 90 years of age who met the NINCDS/ADRDA criteria for probably AD, who had computerized tomography or magnetic resonance imaging scan (within 36 months prior to Day –1) interpreted by a radiologist or neurologist as not showing evidence of an alternative etiology for dementia, who had a Mini-Mental Status Examination (MMSE) score of 10 to 24 (inclusive), a Cornell Scale for Depression in Dementia (CSDD) score ≤ 10, and a Modified Hachinski Ischemic Scale score ≤ 4 at Screening Visit 1. Other than the AD diagnosis, the subject could have stable medical conditions and was to be in general good health based on medical history, physical examination, vital signs, laboratory profile, and 12-lead ECG.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

ABT-384 10 mg capsule for oral administration: 09-025408

ABT-384 50 mg capsule for oral administration: 09-025409

Duration of Treatment: 12 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Study Drug	Formulation	Administration	Lot Number
Placebo for ABT-384	Placebo capsule	Oral	09-022074
Donepezil (Aricept®) 5 mg capsule	Contained 1 × 5 mg donepezil tablet	Oral	09-025422
Donepezil (Aricept®) 10 mg capsule	Contained 2 × 5 mg donepezil tablets	Oral	09-025423

Criteria for Evaluation

Efficacy:

The primary efficacy measure was the assessment of cognitive functioning and memory impairment using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog); the primary efficacy endpoint was the change from baseline to final evaluation on the ADAS-cog 13-item total score.

Secondary efficacy measures included the ADAS-cog 11-item total score, MMSE total score, 12-item Neuropsychiatric Inventory (NPI) total score, 10-item NPI total score, Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) total score, Quality of Life – Alzheimer's Disease (QoL-AD) total subject score, QoL-AD total caregiver score, CSDD, and the Clinician Interview-Based Impression of Change (CIBIC plus).

Pharmacokinetic:

Blood samples for assay of ABT-384, its active metabolite A-847082, and possible metabolites of ABT-384 were collected.

Pharmacodynamic:

Urine samples were analyzed for tetrahydrocortisol, allotetrahydrocortisol and tetrahydrocortisone.

Pharmacogenetic:

APOE-ε4 allele status (carrier/non-carrier) was determined for each subject.

Safety:

The following safety evaluations were performed at specified time points during the study: adverse event monitoring, vital signs, electrocardiograms (ECGs), physical examinations, brief neurological examinations, brief psychiatric assessments, laboratory test assessments, and Physician's Withdrawal Checklist (PWC-20).

Statistical Methods

Efficacy:

The primary efficacy endpoint was the change from baseline to the final observation on the ADAS-cog total score. The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) model with treatment and study site as the main effects and baseline score as the covariate. The treatment group difference between an ABT-384 dose group and placebo was tested at a one-sided significance level of 0.050. A similar testing procedure was performed to evaluate the treatment group difference between donepezil and placebo on the change from baseline to final observation of the ADAS-cog total score. The distribution of the residuals was checked. When the assumptions of normality or homogeneity were violated, rank transformed change scores were analyzed using an analysis of variance (ANOVA) model with the terms of treatment and study site.

Statistical Methods (Continued):

As a secondary analysis of the primary endpoint, a mixed-effects, maximum likelihood, repeated measures (MMRM) analysis was performed to evaluate treatment group differences for the change from baseline to Weeks 4, 8, and 12 on the ADAS-cog 13-item total score using all observed data. The primary comparison for the repeated measures analysis was the contrast between each ABT-384 dose, donepezil, and placebo at Week 12. The treatment group differences at Weeks 4 and 8 were also evaluated.

The secondary efficacy measures were analyzed using the ANCOVA model described for the primary efficacy analysis. The ADAS-cog 11-item total score, CSDD total score, MMSE total score, 12-item NPI total score, 10-item NPI total score, and ADCS-ADL total score also were analyzed by a repeated measures analysis as described above for the secondary efficacy analysis of the ADAS-cog 13-item total score.

Pharmacokinetic:

Individual ABT-384 and A-847082 plasma concentrations at each study visit were to be tabulated and summarized with appropriate statistical methods and population pharmacokinetic analyses were to be performed using the actual sampling time relative to dosing; however, due to the discontinuation of the development program for this product, the pharmacokinetic samples from this study were not analyzed.

Pharmacodynamic:

The primary variable (measure of HSD-1 activity) was the following ratio:

(tetrahydrocortisol + allotetrahydrocortisol)/tetrahydrocortisone

To examine whether baseline values of 11-beta-hydroxysteroid dehydrogenase type 1 (HSD-1) activity had an impact on response to treatment, an analysis of the change from baseline to final observation on the ADAS-cog 13-item total score was conducted. The analysis was performed using an ANCOVA model with the terms of treatment and study site and covariates of baseline ADAS-cog 13-item total score and baseline HSD-1 activity.

Pharmacogenetic:

To examine whether *APOE*-ε4 allele status (carrier, non-carrier) had an impact on response to treatment, a subgroup analysis of the change from baseline to final observation on the ADAS-cog 13-item total score was conducted using an ANCOVA model with the terms of treatment, study site and *APOE*-ε4 allele status, and the treatment-by-*APOE*-ε4 allele status interaction.

Safety:

All safety analyses were performed on the Safety data set, which included all randomized subjects who took at least one dose of study drug; subjects were analyzed according to the study drug they received.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. The number and percentage of subjects who reported treatment-emergent adverse events (TEAEs) were tabulated by primary MedDRA system organ class (SOC) and preferred term (PT) for each treatment group, for the combined ABT 384 dose groups, and for all treatment groups combined. Treatment group differences between each ABT-384 dose group and placebo as well as between donepezil and placebo in the percentage of subjects who reported at least 1 TEAE and for each PT were analyzed by Fisher's exact test.

The number and percent of subjects experiencing treatment-emergent serious adverse events (SAEs) (including deaths) and adverse events leading to premature discontinuation of study drug were tabulated according to the primary MedDRA SOC and PT for each treatment group, for the overall ABT-384 dose groups, and for all treatment groups combined. Treatment group differences between each ABT-384 dose group and placebo as well as between donepezil and placebo were analyzed by Fisher's exact test.

Clinical Laboratory and Vital Sign Assessments: Treatment differences between each ABT-384 dose group and placebo as well as between donepezil and placebo in change from baseline to minimum, maximum, and final clinical laboratory and vital sign evaluation were analyzed using one-way ANOVA with treatment as the main effect.

For each treatment group, shift tables for clinical laboratory measurements were generated showing the number and percentage of subjects with low, normal, high, and missing values at baseline and final observation based on the reference ranges provided by the central laboratory.

The number and percentage of subjects in each treatment group who had values meeting predefined criteria for potentially clinically significant laboratory and vital sign values at any time after the first dose of study drug and no more than 10 days after the last dose of study drug were summarized.

ECG Variables included heart rate, PR, QRS, QT, QTcB and QTcF intervals. Treatment differences between each ABT-384 dose group and placebo as well as between donepezil and placebo in change from baseline to minimum, maximum, and final ECG observation were analyzed using one-way ANOVA with treatment as the main effect. The number and percentage of subjects in each treatment group who had values meeting predefined criteria for potentially clinically significant values at any time after the first dose of study drug and no more than 10 days after the last dose of study drug were summarized.

Physician's Withdrawal Checklist:

Each item score on the PWC-20 and the total score were summarized. The mean total score for each ABT-384 dose group and for the donepezil treatment group was compared to the mean total score for the placebo group using a two-way ANOVA with treatment and study site as factors.

Summary/Conclusions

Efficacy Results:

For the primary efficacy endpoint, change from baseline to the final observation on the ADAS-cog 13-item total score, the differences in change from baseline scores between each ABT-384 treatment group and the placebo treatment group were not statistically significant. The distribution of the residuals was checked for normality and homogeneity of variance; it was found that the assumption of normality was violated ($P = 0.001$ from Shapiro-Wilk method). As a result, rank-transformed change scores were analyzed using an ANOVA model with the terms of treatment and study site as the main effects. The results of the ANOVA analysis were similar to the ANCOVA analysis; the differences in change from baseline scores between each ABT-384 treatment group and the placebo treatment group were not statistically significant. In both analyses, the donepezil 10 mg treatment group had a statistically significant mean decrease in scores compared with the placebo treatment group, indicating more improvement.

For the analyses of secondary efficacy variables, the differences in change from baseline between each ABT-384 treatment group and the placebo treatment group were not statistically significant for any measure.

Pharmacokinetic Results:

Not applicable.

Pharmacodynamic Results:

A non-significant HSD-1 activity-by-treatment interaction *P* value was observed, suggesting that HSD-1 activity did not have a significant impact on response to treatment.

Pharmacogenetic Results:

Subjects in the donepezil 10 mg treatment group who were *APOE*-ε4 allele carriers had a statistically significant mean decrease in the ADAS-cog 13-item total score compared with the placebo treatment group, while no statistically significant differences in mean changes from baseline were observed for any treatment group in non-carriers.

Safety Results:

More than 50% of subjects in each treatment group reported 1 or more TEAEs. The ABT-384 treatment groups were similar to the placebo group in proportions of subjects who reported at least 1 TEAE and at least 1 severe TEAE but had higher proportions of subjects with TEAEs leading to discontinuation of study drug: 11.4% (8 subjects) and 7.7% (5 subjects) in the ABT-384 10 mg and 50 mg treatment groups compared with no subjects in the placebo treatment group. The ABT-384 10 mg treatment group also had a higher proportion of subjects (8.6%; 6 subjects) with at least 1 SAE compared with the placebo treatment group (0 subjects). One subject (in the ABT-384 50 mg treatment group) experienced an AE of the PT: pneumonia aspiration on Day 87 (5 days after the last dose of study drug) and died on Day 89; the event was assessed by the investigator as not related to study drug. Headache was the only TEAE that occurred in ≥ 5% of all ABT-384-treated subjects; headache also was reported by 6.1% of subjects in the placebo treatment group (4 subjects). Lymphocyte count decreased, headache, dizziness, lymphopenia, and WBC count decreased were assessed as possibly or probably drug related in ≥ 3 subjects who received ABT-384. No statistically significant differences were observed between an active treatment group and the placebo treatment group in proportions of subjects with possibly or probably drug-related TEAEs.

Safety Results (Continued):

Approximately 30% and 21% of subjects receiving ABT-384 10 mg and 50 mg experienced ≥ 1 PCS low reticulocyte value, compared with approximately 46% of subjects in the placebo treatment group. Approximately 7% and 18% of subjects receiving ABT-384 10 mg and 50 mg experienced ≥ 1 PCS high reticulocyte value, compared with 10% of subjects in the placebo treatment group. Approximately 25% of subjects receiving ABT-384 experienced ≥ 1 PCS low lymphocyte values, compared with approximately 12% of subjects in the placebo treatment group. Potentially clinically significant direct bilirubin values were the most frequent clinical chemistry abnormalities, reported in 5 subjects (7.4%) and 8 subjects (12.7%) in the ABT-384 10 mg and 50 mg treatment groups.

Seven of 267 subjects (2.6%: 4 subjects in the ABT-384 50 mg, 1 in the ABT-384 10 mg, 1 in the placebo, and 1 in the donepezil 10 mg treatment groups) met one or more criteria for the hepatic monitoring plan; however, only 2 subjects met these criteria due to increases in ALT or AST > 2 × ULN after being started on the ABT 384 50 mg dose, and only 1 subject had ALT > 3 × ULN. All values returned to normal or near normal without any intervention beyond more frequent liver function test monitoring.

Less than 5% of subjects in any treatment group had PCS vital signs or weight values. An increase > 60 msec in Bazett QTc interval was the most frequent PCS value in subjects who received ABT-384, reported in 3 subjects (4.4%) and 1 subject (1.6%) in the ABT-384 10 mg and 50 mg treatment groups.

Conclusions:

The study was discontinued prematurely based on the results of interim analyses of efficacy data, which indicated a high likelihood of futility for both ABT-384 doses. On the primary efficacy outcome measure, the differences in change from baseline scores between each ABT-384 treatment group and the placebo treatment group were not statistically significant. Donepezil showed statistically significantly greater improvements compared with placebo, demonstrating assay sensitivity of the study design and conduct. The futility of ABT-384 treatment was further confirmed by analysis of secondary measures.

None of the safety results raised concerns regarding the safety of either dose of ABT-384. Overall ABT-384 was generally safe and well tolerated.