2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-126	**Volume:**	
Name of Active Ingredient: ABT-126	**Page:**	

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of ABT-126 in Subjects with Mild-to-Moderate Alzheimer's Disease

Coordinating Investigator:

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Study Sites: Bulgaria, Czech Republic, Slovakia, South Africa, United Kingdom, and United States

Publications: None

Studied Period (Years): 1 First Subject First Visit: 03 November 2009 Last Subject Last Visit: 11 November 2010	**Phase of Development:** 2

Objective:

The objective of this study was to evaluate the efficacy and safety of 2 doses of ABT-126 (5 mg and 25 mg) in subjects with mild-to-moderate Alzheimer's disease (AD).

Methodology:

This was a Phase 2, randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group study conducted in subjects diagnosed with mild-to-moderate AD, defined as meeting the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD. This study comprised a Screening Period of up to 28 days, a 12-week double-blind Treatment Period, and a Post-Treatment Period (30 days after double-blind treatment). The Screening Period consisted of 3 visits: Screening Visit 1, Screening Visit 2, and a Day –1 Visit. At the end of the Day –1 Visit, eligible subjects were randomized in an equal ratio to 1 of 4 treatment groups (placebo, 5 mg ABT-126, 25 mg ABT-126, or donepezil, the positive control to ensure assay sensitivity). The Post-Treatment Period included a Follow-up Visit approximately 2 weeks after the Week 12 (or premature discontinuation) Visit, and telephone contact approximately 30 days after the subject's last dose of study drug.

Number of Subjects (Planned and Analyzed):

Approximately 260 subjects were planned, 65 subjects per treatment group. A total of 274 subjects were randomized at 27 sites from 358 subjects screened at 29 sites.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects at least 55 to 90 years of age, inclusive, who met the NINCDS/ADRDA criteria for probable AD, were eligible for the study if they had a reliable caregiver, had a Mini-Mental Status Examination (MMSE) score from 10 to 24, a Cornell Scale for Depression in Dementia (CSDD) score ≤ 10, and a Modified Hachinski Ischemic Scale (MHIS) score of ≤ 4 at Screening Visit 1. Additionally, subjects were to be in general good health (with the exception of a diagnosis of mild-to-moderate AD) on the basis of medical history, physical examination, vital sign measurements, laboratory profile, and a 12-lead electrocardiogram (ECG), and were to have had a CT scan within 36 months prior to randomization that did not show evidence for an alternative etiology for dementia. Potential subjects were excluded from the study if female and of child-bearing potential or pregnant or breast-feeding; were currently taking or had taken medication within 60 days prior to Screening Visit 1 for the treatment of AD or dementia or participating in cognitive therapy for treatment of AD; were currently taking or had taken warfarin, acenocoumarol, or phenprocoumon, or another vitamin K antagonist within 30 days of Screening Visit 1; or had a clinically significant abnormal ECG or an ECG with QTcB interval > 450 sec for males or > 470 sec for females, had a history of atrial fibrillation or a history of sick sinus syndrome or other supraventricular tachyarrhythmia; or met the other criteria for exclusion.

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

ABT-126, 5 mg and 25 mg, oral capsules, bulk lots 09-022230 and 09-022231

Duration of Treatment:

12 weeks, with a 2-week post-treatment Follow-up Visit, and telephone contact approximately 30 days postdose

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

Placebo for ABT-126, oral capsules, bulk lots 09-022074 and 09-022366

Active control, donepezil, 5 mg and 10 mg, oral capsules, bulk lots lot 09-022180, 09-023686, 09-022235, and 09-023690

Criteria for Evaluation

Efficacy:

The primary efficacy measure was assessment of cognitive functioning and memory impairment using the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog). Secondary efficacy measures included the MMSE, the Clinician Interview-Based Impression of Change – plus (CIBIC-plus), the Neuropsychiatric Inventory (10-item and 12-item), the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), and the Quality of Life – Alzheimer's Disease (QoL-AD). In addition, the ADAS-cog (13-item) total score was analyzed as a secondary efficacy variable.

Pharmacokinetic:

ABT-126 plasma concentrations were determined from the pharmacokinetic samples collected at the specified visits.

Criteria for Evaluation (Continued)

Safety:

The safety of ABT-126 in this subject population was evaluated through the collection of adverse events, measurement for changes in laboratory variables (including hematology, chemistry, and urinalysis), assessment of vital sign measurements, and ECG evaluation.

Statistical Methods

Efficacy:

The primary efficacy analysis of the change from baseline to the final observation on the ADAS-cog (11-item) total score was performed using an ANCOVA model with treatment and study site as the main effects and baseline score as the covariate. The treatment group difference between an ABT-126 dose group and placebo and the difference between the average from all treatment groups and placebo were tested at a one-sided significance level of 0.050. Type III sum-of-squares was used to generate the least square (LS) means of treatment group differences. The LS mean difference between each ABT-126 dose group and placebo, and the average from all treatment groups and placebo, and the two-sided 90% confidence intervals were estimated from the ANCOVA model. A similar testing procedure was conducted to evaluate the treatment group difference between donepezil and placebo in the change from baseline to final observation of the ADAS-cog (11-item) total score. Distribution of the residuals was checked. When the assumptions of normality or homogeneity were violated, rank-transformed change scores (derived from PROC RANK) were analyzed using an ANOVA model with the terms of treatment and investigator. A secondary efficacy analysis of the primary efficacy variable used a mixed-effects, maximum likelihood, repeated measures (MMRM) analysis to evaluate treatment group differences for the change from baseline to Weeks 4, 8, and 12 on the ADAS-cog (11-item) total score using all observed 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. The unstructured covariance structure was used to estimate the within-subject variance-covariance structure. 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. The primary comparison for the MMRM analysis was the contrast between each ABT-126 dose, donepezil, and placebo at Week 12. The treatment group differences at Weeks 4 and 8 were also evaluated.

The secondary efficacy variables of MMSE total score, NPI (10-item and 12-item) total score, ADCS-ADL total score, and QoL-AD total subject and total caregiver scores were analyzed as described for the primary efficacy analysis. In addition, the ADAS-cog (13-item) total score was analyzed as a secondary efficacy variable. The ANCOVA model was used and an MMRM analysis performed. Distribution of the residuals was checked. When the assumptions of normality and homogeneity were violated, rank transformed change scores (derived from PROC RANK) were analyzed using an ANCOVA model with the terms of treatment and investigator. The final observation for CIBIC-plus was analyzed by an ANCOVA model with the terms of treatment and investigator, with CIBIS score collected at Day –1 as a covariate. All post-baseline assessment CIBIC-plus scores were analyzed by an MMRM analysis with the fixed effects of treatment, study site, visit, treatment by-visit interaction, with CIBIS collected at Day –1 as continuous, covariate. Distribution of the final CIBIC-plus assessment was presented for each treatment group. The percentage of subjects with any improvement in final CIBIC-plus assessment was compared between placebo and each of the other 3 treatment groups using Fisher's exact test.

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Analyses of adverse events included only treatment-emergent adverse events (TEAE), defined as any adverse event that began or worsened in severity on or after the first dose of study drug and no more than 30 days after the last dose of study drug. Adverse events were coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who reported TEAE were tabulated by primary MedDRA system organ class and preferred term for each treatment group, for the overall ABT-126 dose groups, and for all treatment groups combined. Treatment group differences between each ABT-126 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 MedDRA preferred term were analyzed by Fisher's exact test. The number and percentage of subjects experiencing treatment-emergent serious adverse events (including deaths) and adverse events leading to premature discontinuation of study drug were tabulated according to the primary MedDRA system organ class and preferred term for each treatment group, for the overall ABT-126 dose groups, and for all treatment groups combined. Treatment group differences between each ABT-126 dose group and placebo, as well as between donepezil and placebo, were analyzed by Fisher's exact test.

Laboratory measurements (hematology, chemistry, and urinalysis), vital sign measurements (pulse, systolic blood pressure, diastolic blood pressure, body temperature, weight, and body mass index), and ECG variables (heart rate, PR, QRS, QT, QTcB and QTcF intervals) were analyzed for treatment differences between each ABT-126 dose group and placebo, as well as between donepezil and placebo, in change from baseline to minimum, maximum, and final clinical laboratory evaluation, using one-way ANOVA with treatment as the main effect.

Safety data collected in the Post-Treatment Period that began 7 days after the last dose day and ended 30 days after the last dose of study drug were also analyzed. Baseline was the last non-missing observation no more than 6 days after the last dose of study drug, and final observation was the last non-missing observation collected more than 6 days after the last dose of study drug and no more than 30 days after the last dose of study drug. Adverse events were analyzed for treatment group differences between each ABT-126 dose group and placebo, as well as between donepezil and placebo, by Fisher's exact test. Laboratory, vital sign, and ECG measurements were analyzed for treatment group differences between each ABT-126 dose group and placebo, as well as between donepezil and placebo, using one way ANOVA, with treatment as the main effect.

Summary/Conclusions

Efficacy Results:

ABT-126 exhibited a dose-response relationship, and improvement in cognition was observed in subjects treated with ABT-126 at the 25 mg dose, compared to placebo. Treatment with ABT-126 at 5 mg did not demonstrate statistically significant improvements in cognition, as evaluated by the primary and secondary efficacy measures. Subjects treated with donepezil demonstrated improvements over the course of the 12-week study on measures of cognition and global function.

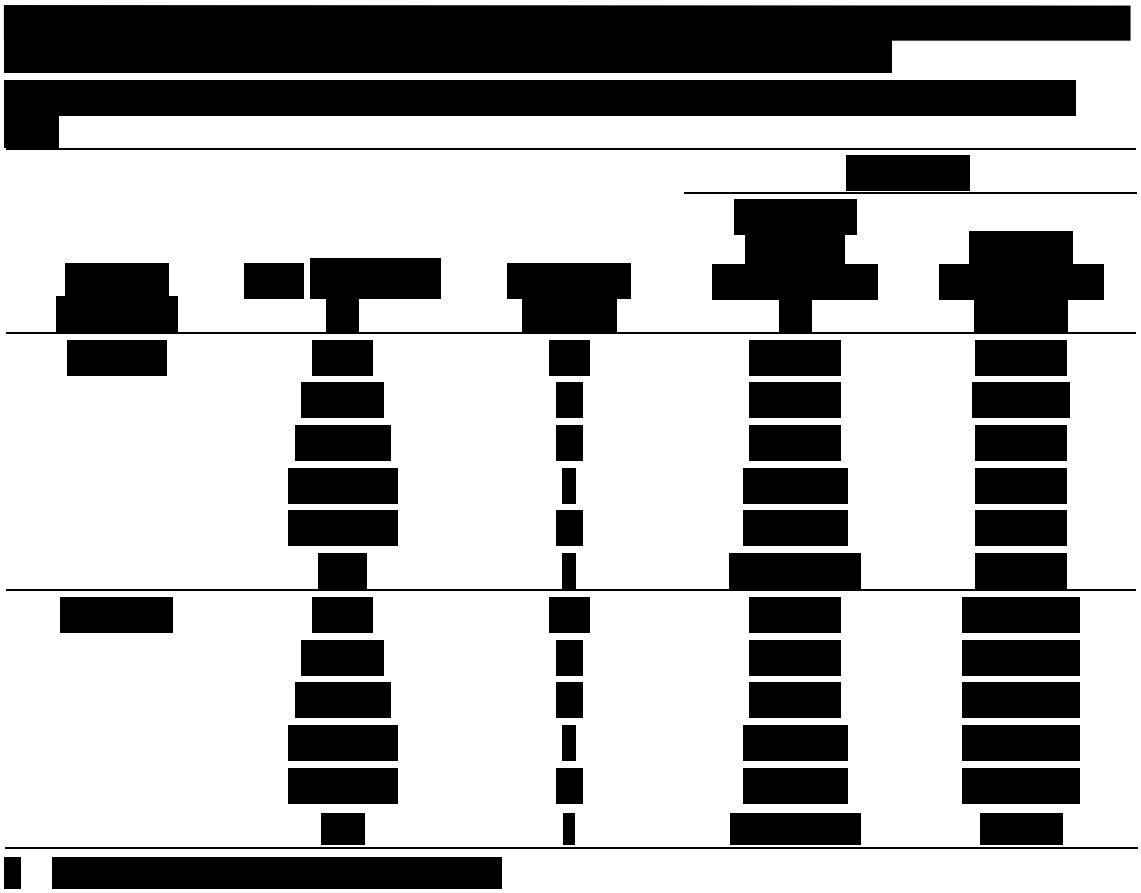
Summary/Conclusions (Continued)

Efficacy Results (Continued):

The primary efficacy analysis indicated a trend toward a statistically significant difference in change from baseline to the final observation in the ADAS-cog (11-item) total score for both the ABT-126 25 mg treatment group and the donepezil treatment group, compared to placebo, suggesting improvement in cognition ($P < 0.100$, both groups). There was no statistically significant LS mean difference observed for the ABT-126 5 mg treatment group when compared to placebo. Similar results were also obtained for each of these treatment groups in an MMRM analysis of the primary efficacy measure that indicated decreasing LS mean differences from placebo in the ADAS-cog (11-item) total score at Weeks 4 and 8 for the ABT-126 25 mg group and a statistically significant difference in LS mean from placebo at Week 12 for the donepezil treatment group.

Subgroup analyses by baseline MMSE category, age, country, and ApoE-ε4 allele status indicated that there was a statistically significant treatment-by-subgroup variable interaction noted only for the baseline MMSE category. In subjects with more severe impairment in cognition at baseline (MMSE values ≤ 19), improvements compared to placebo were demonstrated in the ABT-126 25 mg and donepezil treatment groups. In subjects with less severe impairment in cognition at baseline (MMSE values ≥ 20), the ABT-126 25 mg treatment group exhibited a numerical improvement relative to placebo, whereas the donepezil treatment group did not.

Results of the analyses of secondary efficacy variables indicated statistically significant improvements in the ADAS-cog (13-item) total score for the ABT-126 25 mg dose group and the donepezil group, compared to placebo. On the CIBIC-plus evaluation, a global impression of change in severity of dementia, the donepezil group showed a statistically significant trend in the percentage of subjects with any improvement compared to placebo, whereas the results for the ABT-126 25 mg group were not statistically significant and were intermediate in magnitude between those observed in the donepezil and placebo groups. Other secondary efficacy measures indicated no statistically significant differences from placebo for any treatment group. Although this study was not designed to assess the efficacy of ABT-126 relative to donepezil, it was noted that the magnitude of the ABT-126 25 mg effects on cognitive measures and the consistency of the treatment response across secondary outcome measures were less than that observed for donepezil.



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Safety Results:

The overall rate of adverse events was low and comparable across treatment groups. There was no statistically significant difference in the incidence of adverse events or adverse events considered possibly or probably related to study drug in subjects treated with ABT-126 compared to subjects treated with placebo. Most adverse events were considered mild or moderate in severity. The most frequently reported adverse events (≥ 3%) for the total ABT 126-treated subjects, at rates that were also higher than placebo, were diarrhea (4.3%), fall (4.3%), urinary tract infection (4.3%), headache (3.6%), and nausea (3.6%). The incidence rate of these adverse events in the donepezil treatment group was: diarrhea (7.4%), fall (2.9%), urinary tract infection (4.4%), headache (5.9%), and nausea (8.8%).

Safety Results (Continued):

There were 2 deaths reported in the study: One subject on placebo completed suicide, and 1 subject from the ABT-126 25 mg treatment group died 18 days postdose of cardiac failure, which was assessed as not related to study drug. The number of other serious adverse events was similar across treatment groups, occurring in a total of 13 subjects, and in 9 of those subjects while on double-blind treatment.
Three subjects in the ABT-126 treatment groups reported serious adverse events, including 1 subject with hyponatremia, 1 subject with bradycardia, nausea, and vomiting, and 1 subject with hypotension. All serious adverse events were assessed by the investigator as not related or probably not related to study drug. Nine subjects experienced adverse events that resulted in premature discontinuation from the study. Two premature discontinuations were in the ABT 126 treatment groups and were those subjects reporting serious adverse events of hyponatremia and bradycardia, nausea, and vomiting.

Twenty-five subjects experienced adverse events of special interest: falls, tremor, evidence of an altered mental state (e.g., agitation or aggression), and depression-related events such as depressed mood, negative thoughts, tearfulness, and suicide. The incidence of these adverse events was distributed similarly across treatment groups. Most of the adverse events were considered to be mild or moderate in severity by the investigator. Three adverse events (completed suicide and 2 falls) were assessed as severe but not related to study drug, and most of the adverse events were considered by the investigator as probably not or not related to study drug. Those adverse events assessed as possibly or probably related to study drug were tremor, aggression, tearfulness, and depression.

There were no consistent, clinically significant changes in laboratory, vital sign, or ECG measurements across treatment groups. Statistically significant increases in mean white blood cell, neutrophil, and basophil counts for the ABT-126 5 mg group compared to placebo were not noted at the higher dose and are of undetermined clinical significance. Urine specific gravity was observed to increase with statistical significance for both ABT 126 treatment groups, compared to placebo, but the increases were small and not considered to be clinically meaningful.

Some statistically significant increases in ECG mean values for the QTcB interval and QTcF interval were noted for the ABT-126 25 mg group, compared to placebo, at a single time point. The statistically significant differences from placebo emerged at Week 12, and were driven both by increases in mean values in the ABT-126 treatment group, as well as by decreases in these intervals in the placebo group. In the Post-Treatment Period, the increases in QTcB and QTcF values were reversed, due to an increase in values in the placebo group and decrease in the ABT-126 25 mg treatment group. The incidence of potentially clinically significant increases in QTc values was low in the ABT-126 treatment group and similar to that observed across all of the treatment groups. The emergence of QTc changes after several months of treatment is not typical of drug-induced QTc changes, and thus, are not considered to be related to ABT-126 treatment.

Safety Results (Continued):

Several statistically significant changes in ECG parameters were noted for the donepezil treatment group, including a statistically significant decrease in mean value for the heart rate with a corresponding numerical increase in the PR interval. Additionally, a statistically significant increase in the QT interval for the donepezil treatment group compared to the placebo group was noted at the final visit. There was no statistically significant change in the QTcB interval or QTcF interval in the donepezil treatment group during the Treatment Period, perhaps due to the decrease in heart rate in this group. The changes in ECG intervals noted during the Treatment Period for the donepezil group were reversed in the Post-Treatment Period, with group mean values in the Post-Treatment Period that were similar to baseline values. The incidence of potentially clinically significant changes in ECG parameters in the donepezil treatment group was low and similar to that observed across all of the treatment groups. The changes in ECG parameters noted in this study are consistent with those previously reported for donepezil.

The ABT-126 25 mg treatment group showed a statistically significant increase in withdrawal symptoms on the Physician's Withdrawal Checklist (PWC-20) compared to placebo. Most of the symptoms endorsed were of mild severity, and there was no difference in the quantitative or qualitative nature of spontaneously reported adverse events in the Post-Treatment Period across treatment groups. No withdrawal effects have been noted in Phase 1 studies at doses up to 100 mg for ABT-126. The magnitude of the effect observed in the ABT-126 25 mg treatment group is less than that typically observed on the PWC-20 for drugs with known withdrawal syndromes, suggesting that this finding is unlikely to be of clinical significance.

Conclusions:

The safety and tolerability of ABT-126 was successfully evaluated in this Phase 2 study in subjects with mild-to-moderate AD. Results of the study indicate that ABT-126 exhibited a favorable safety profile. There was evidence for a treatment effect on measures of cognition demonstrated by ABT-126 25 mg. ABT-126 exhibited a dose-response relationship, with no efficacy for the lower dose evaluated (5 mg), but evidence for efficacy at the higher dose (25 mg).