2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td>Individual Study Table Referring to Part of Dossier:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: ABT-894</td><td>Volume:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
ABT-894 (3-(5,6-dichloro-pyridin-3-yl)-1(S),5 (S)-3,6-diazabicyclo[3.2.0]heptane)</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study: A Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of ABT-894 versus Placebo in Subjects with Diabetic Neuropathic Pain</td></tr>
<tr><td colspan="3">Investigator: Timothy R. Smith, MD</td></tr>
<tr><td colspan="3">Study Sites: This study was conducted at 26 sites that enrolled subjects in the Czech Republic, France, Germany, Italy, Spain, the United Kingdom, and the United States. Thirty-two sites were initiated for this study; however, 6 sites did not enroll any subjects. In addition, one site replaced the Principal Investigator with a subinvestigator.</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 13 November 2007
Last Subject Last Visit: 02 December 2008</td><td>Phase of Development: Phase 2</td></tr>
<tr><td colspan="3">Objectives: The primary objective of this study was to compare the analgesic efficacy and the safety of ABT-894 (6 mg tablets) BID to placebo in the treatment of DNP. Additionally, this study explored the pharmacokinetic and pharmacogenetic characteristics of ABT-894 in the DNP population.</td></tr>
<tr><td colspan="3">Methodology:
This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study designed to compare the analgesic efficacy and the safety of ABT-894 (6 mg tablets) administered BID to placebo in the treatment of DNP.
Approximately 110 subjects meeting selection criteria were to be randomized into the study at approximately 30 sites in both the United States and Europe. Actually, 124 subjects were enrolled at 26 sites.
The study was divided into the following periods: Screening/Washout (maximum of 21 days) followed by a Baseline Visit, an 8-week Treatment Period, and a 1-week Follow-up visit.
Subjects who met the eligibility criteria during the Screening period entered a Washout period during which they discontinued all current medications for pain (opioid and/or non-opioid, including anti-convulsants and anti-depressants). Acetaminophen was permitted as rescue medication throughout the study. Subjects were not to take more than a total of 3000 mg of acetaminophen per day during the washout period. Rescue medication was not to be taken within 24 hours before scheduled study visits.</td></tr>
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Methodology (Continued):

Upon completion of the Washout portion of the study, subjects were issued an electronic diary to record pain assessments and rescue medication compliance at home. Subjects were required to complete a pain diary on a daily basis following the Washout period for 7 consecutive days prior to the Baseline Visit. The duration of the Screening period (Washout and 7 days of diary completion) was not to exceed 21 days.

At the Baseline visit, the subject had to have had an average score of 4 or greater on the 24-hour average pain score (11-point Likert Scale) collected for approximately 7 days prior to Baseline with at least 60% diary entry compliance. In addition, subjects must have had an average score greater than 4 on the site based Brief Pain Inventory (BPI) question and must have met all eligibility criteria for randomization.

Subjects were randomized to one of two arms of the study in a 1:1 ratio: 6 mg ABT-894 BID or placebo.

Randomized subjects then entered an 8-week Treatment Period during which they received treatment with either ABT-894 or placebo 1 tablet BID. Acetaminophen was permitted as rescue therapy and could have been taken for up to 3 days per week. The days on which rescue medication was taken did not need to be consecutive, but were not to exceed three days per week.

At scheduled site visits, efficacy and quality of life assessments were completed using an electronic diary. Monitoring of AEs, physical examinations, 12-lead electrocardiograms, vital signs, and laboratory testing were performed throughout the study.

All subjects at all sites were to have blood samples drawn for pharmacokinetic analysis beginning at the Baseline Visit and continuing at all study visits through the Week 8 (Final) Visit. Additionally, at the Pre-termination Visit, a blood sample may have been collected from those subjects who prematurely discontinued study medication.

Intensive pharmacokinetic sampling was to occur at selected study sites (approximately 50% of total sites). A total of approximately six blood samples per subject were to be taken at one study visit on any one of the Week 2, Week 4, or Week 6 study visits. Voluntary pharmacogenetic samples were to be taken at the Baseline visit.

All subjects were required to return to the site for a 1-week Follow-up visit after the Week 8 (Final) visit or Pre-termination visit should the subject prematurely discontinue.

Number of Subjects (Planned and Analyzed): A total of 110 subjects was planned, and 124 subjects were enrolled into the study at 26 study sites. All 124 subjects received study drug and were included in the statistical analyses.

Diagnosis and Main Criteria for Inclusion: Subject was male or female between 18 and 75 years of age who met the following key criteria.

At the Baseline Visit the subject had met the following criteria:

- An average score of 4 or greater on the 24-hour average pain score (11-point Likert Scale) collected for approximately 7 days prior to the Baseline Visit, with a compliance rating of no less than 60%.
- Subject was to have had an average of 4 or greater on the BPI average of pain score at the Baseline Visit.
- Subject must have voluntarily signed and dated an ICF, approved by an IEC/ IRB, prior to the conduct of any study-specific procedures.
- Subject had a diagnosis of diabetes mellitus and a diagnosis of painful distal symmetric diabetic polyneuropathy.
- Subject had painful distal symmetric diabetic polyneuropathy present for at least 6 months.
- Subject was to have had a score of 3 or greater on the physical assessment portion of the Michigan Neuropathic Screening Instrument (MNSI) at the Screening Visit.

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

Test Products	Dose/Strength	Formulation	Mode of Administration	Lot Numbers
ABT-894	BID/6 mg	Tablet	Oral	07-010963

Duration of Treatment:

Eight weeks of treatment and a 1 week follow-up.

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

Test Products	Dose/Strength	Formulation	Mode of Administration	Lot Numbers
Placebo for ABT-894 6 mg	BID	Tablet	Oral	07-010964

Criteria for Evaluation

Efficacy:

The primary efficacy measure was a weekly mean of 24-hour average pain score measured by the 11-point Likert Scale and calculated from subject's daily diary.

The secondary efficacy variables were:

- Proportions of treatment responders, defined as subjects achieving ≥ 30% improvement from Baseline to final observation evaluation in weekly mean of 24-hour average pain score. The scenario of using ≥ 50% as the cutoff value was analyzed.
- The weekly mean of 24-hour worst pain severity measured by the 11-point Likert scale and calculated from subject's daily diary (abbreviated as 24-hour worst pain score hereafter).
- The weekly mean of night pain severity measured by the 11-point Likert scale and calculated from subject's daily diary (abbreviated as night pain score hereafter).
- The weekly mean of feeling of pain in the morning measured by the 5-point Likert scale and calculated from subject's daily diary (abbreviated as feeling of morning pain hereafter).
- Brief Pain Inventory Short Form (BPI SF) including Severity (4 items: worst, least, average, and current) and Interference (7 items: general activity, mood, walking ability, normal work, relations to others, sleep, and enjoyment of life) at each of the visits from Baseline to Week 8.
- Clinician Global Impression-Severity (CGI-S) at each visit from Baseline to Week 8.
- Patient Global Impression-Change (PGI-C) at each of the visits from Week 1 to Week 8.
- The sensory portion of the McGill assessment (SF-MPQ) at the Baseline Visit, the Week 4 Visit, and the Week 8 Visit (the sensory component consists of 11 pain descriptors: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting).
- Neuropathic Pain Scale (NPS) aspects of pain measured: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface versus deep pain at the Baseline Visit, the Week 4 Visit, and the Week 8 Visit.
- The Medical Outcome Study Short Form-36 (SF-36v2) Questionnaire: Assessments at Baseline, Week 4, and Week 8.
- The EuroQol instrument version (EQ-5D): Assessments at Baseline, Week 4, and Week 8.

An additional variable was:

- Fagerström Test for Nicotine Dependence (FTND): Assessments at Baseline, Weeks 4, and Week 8.

Pharmacokinetic:

Population modeling techniques were to be used to estimate population central values for ABT-894 clearance (CL/F) and volume of distribution (V_{ss}/F) and post hoc values of these parameters for the individual subjects were estimated. Additional parameters including pharmacokinetic parameters for ABT-894 metabolites under investigation may have been measured if sufficient concentrations were found and if useful in the interpretation of the data.

Safety:

Safety was evaluated throughout the study by adverse event monitoring, vital signs, electrocardiograms (ECGs), physical examinations, and laboratory tests.

Statistical Methods

Efficacy:

The primary efficacy measure was the weekly mean of the 24-hour average pain score (abbreviated as 24-hour average pain score hereafter) measured by the 11-point Likert Scale and calculated from subject's daily diary. The primary efficacy analysis was to evaluate treatment group differences between ABT-894 and placebo for the mean change from Baseline to Final on the 24-hour average pain score, after accounting for differences in baseline scores. The evaluation was based on the difference between ABT-894 and placebo from an ANCOVA model, with the terms of treatment, site, and baseline scores. Site means pooled investigator sites. In a separate model where the treatment-by-investigator interaction was added to the ANCOVA as described above, the treatment-by-investigator interaction was tested at a significance level of 0.10 (two-sided). The distribution of the residuals from ANCOVA model was checked for the assumption of normality and homogeneity of variance. The normality assumption was tested with PROC UNIVARIATE using the Shapiro-Wilk test. The homogeneity of variances was tested using HOVTEST in PROC GLM. When the assumptions of both normality and homogeneity were violated, in addition to the rank-transformed ANOVA, Monte-Carlo exact Kolmogorov Smirnov test (using PROC NPAR1WAY) was used to evaluate the treatment group difference in the distribution of the baseline-to-final change in 24-hour average pain score. The EXACT KS/MC option of PROC NPAR1WAY was used with the seed set to 894014, and the number of samples for Monte-Carlo estimation set to 10,000.

For secondary efficacy analyses, all continuous variables were analyzed in a similar way as primary variables. The categorical variables were analyzed by Fisher's exact test. Log-rank test was used for time-to-event variables.

ANOVA model was used for testing whether the demographic and baseline disease characteristics were comparable between treatment groups at baseline.

For primary and secondary efficacy variables, only subjects with both Baseline and post-Baseline efficacy assessments were included in the corresponding efficacy analysis. For change from Baseline to Final observation, the last non-missing data completed at or before the final visit of the 8-week treatment period were used.

Pharmacokinetic:

Population pharmacokinetic analyses were performed using the actual sampling times relative to dosing.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA® Version 11.0). Treatment-emergent AEs (i.e., those which began or worsened in severity after initiation of study drug in each period) were tabulated by system organ class (SOC) and MedDRA preferred term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular AE. A summary of the severity and relationship to study drug of all treatment-emergent AEs, tabulated by MedDRA preferred term, and SOC was presented for each treatment group. Subjects reporting more than one AE for a given MedDRA preferred term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Safety (Continued):

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the mean changes from baseline to the final values for each laboratory variable. Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Additionally, the number and proportion of subjects with shifts from baseline to the final values using the Data Analysis Criteria for Potentially Clinically Significant Laboratory Findings to define categories (low, normal, high, and missing) were summarized.

For vital signs, mean changes from baseline to the minimum, maximum, and final values were analyzed using a 1-way ANOVA with treatment as the main effect.

For ECGs, the number and proportion of subjects with shifts from baseline to the final evaluation using assessment categories (normal, abnormal – not clinically significant, abnormal – clinical significant, and missing) will be summarized. The overall treatment group differences will be evaluated using Fisher's exact test.

Summary/Conclusions

Efficacy Results: The primary efficacy measure was the weekly mean of 24-hour average pain score measured by the 11-point Likert Scale and calculated from subject's daily diary. There was no statistically significant difference in mean change from Baseline to Final observation in the 24-hour average pain diary score between ABT-894 6 mg BID treatment group (–1.83) and placebo treatment group (–1.69) ($P = 0.347$).

For the secondary efficacy variables:

- No statistically significant differences were observed between the proportions of subjects in the placebo and ABT-894 groups with a ≥ 30% reduction and ≥ 50% reduction in 24-hour average pain diary score from Baseline to Final or for the proportions of sustained responders.
- Mean change from Baseline to Final for the 24-hour worst pain diary score was not statistically significantly different between the placebo and ABT-894 groups.
- Mean change from Baseline to Final value for the night pain diary score showed a larger decrease numerically for the ABT-894 group compared with the placebo group, but the difference was not statistically significant; however, upon repeated measures analysis, the night pain score was statistically significantly different between the placebo and ABT-894 groups at Weeks 2, 3, and 6, and Overall.
- No statistically significant differences were observed between the placebo and ABT-894 groups for mean change in morning pain from Baseline to Final; yet, upon repeated measures analysis, the morning pain score was statistically significantly different between the placebo, and the ABT-894 group at Weeks 1, 2, 3, and Overall.
- More than 50% of subjects took rescue medication during the study. There were no statistically significant differences observed between the two groups in rescue medication use or percent of days using rescue medication. The mean change from Baseline to Final in the 24-hour average pain diary score adjusting for rescue medication use demonstrated no statistically significant differences between the treatment groups.
- There were no statistically significant differences between the placebo and ABT-894 groups in mean change from Baseline to Final in BPI-SF individual pain severity and interference scores, and the average interference score.

Efficacy Results (Continued):

- For the CGI-S change from Baseline to Final score, differences between the groups were not statistically significant.
- There was no statistically significant difference in the proportion of subjects who reported "much better" or "better" in the PGIC at any time point evaluated between treatment groups.
- No statistically significant differences were observed between the placebo and ABT-894 group in mean change from Baseline to Week 4, Week 8, and Final observation in the McGill Pain Questionnaire (sum of the 11 sensory pain scores) or in each descriptor from the Neuropathic Pain scale.
- There were no statistically significant differences observed between the placebo and ABT-894 groups in mean change from Baseline to Week 4, Week 8, and Final in any of the domains of SF-36 except for physical functioning (mean change from Baseline to Week 4).
- No statistically significant differences were observed between the placebo and ABT-894 group in mean change from Baseline to Week 4, Week 8, and Final in EQ-5D.

In conclusion, ABT-894 at 6 mg BID administrated for 8 weeks was not efficacious for treatment of DNP in this study.

Pharmacokinetic Results: ABT-894 plasma concentrations and pharmacokinetic parameters observed in this study for the 6 mg BID dose were consistent with the exposures observed in the Phase 1 studies with ABT-894.

Safety Results: Evaluation of treatment emergent AEs demonstrated that 32 (49.2%) placebo subjects and 23 (39.0%) ABT-894 subjects reported at least one treatment-emergent AE. The most frequently reported AEs in both treatment groups were headache [5 subjects (7.7%) in placebo, and 4 (6.8%) in the ABT-894 group], and fatigue [placebo 2 (3.1%), and 4 (6.8%) in the ABT-894 group]. Nausea occurred only in the placebo group (5 subjects [7.7%]). Nightmare (2 subjects [3.4%]), and bronchitis (2 subjects [3.4%]) occurred only in the ABT-894 group. Most events were mild or moderate in severity and were not related or probably not related to study drug as per the Investigator's assessment. Treatment-emergent AEs considered by the Investigator to be at least possibly related to study drug occurred in 15 (23.1%) placebo-treated subjects, and 9 (15.3%) ABT-894-treated subjects. Events assessed as probably-related to study drug by the Investigator in the ABT-894 group included fatigue, pain, somnolence, and nightmare. Events assessed as probably-related to study drug by the Investigator in the placebo group included fatigue, dry mouth, and peripheral oedema. Severe AEs were reported in 3 subjects of each treatment group. Severe events in the ABT-894 group were rhinitis, hypoglycemic coma, and pulmonary embolism. Only rhinitis was considered possibly related by the Investigator. Subjects in the placebo group had severe events of arthralgia, muscle spasms, and diverticulitis.

One subject (1.5%) in the placebo group, and 4 subjects (6.8%) in the ABT-894 group reported SAEs. The SAEs in the ABT-894 group were hypoglycaemic coma (1 subject), cystitis, pyelonephritis, and sepsis (1 subject), nerve compression (1 subject), and pulmonary embolism (1 subject). One placebo subject had an SAE of diverticulitis. All of the SAEs were considered not related to study drug by the Investigator. No deaths occurred during the study.

Four (6.2%) subjects in the placebo group discontinued study drug due to AEs of hypertension, diarrhea, nausea, and QT prolongation. Five (8.5%) subjects in the ABT-894 group discontinued study drug due to AEs of vertigo and hypotension, cystitis, fatigue and pain, nerve compression, and pulmonary embolism.

Safety Results (Continued):

No statistically significant differences between placebo and ABT-894 treatment groups in mean changes from Baseline to Final visit were observed in all parameters of hematology, clinical chemistry and urinalysis except for percent neutrophil, percent lymphocyte, BUN, and triglycerides. None of these changes were considered clinically meaningful.

There were no consistent trends between placebo and ABT-894 treatment groups for the percent of subjects who had shifts from normal Baseline values to low or high values at Final Visit in hematology, clinical chemistries, and urinalysis.

No statistically or clinically significant differences between placebo and ABT-894 treatment groups in mean change from Baseline to Final visit were observed in vital signs. No subject in the ABT-894 group that had a change in ECG that was judged to be clinically significant.

No pregnancy was reported during the study.

Conclusions: ABT-894 at 6 mg BID administered for 8 weeks was not efficacious in treatment of DNP. ABT-894 at 6 mg BID was well tolerated in this study. ABT-894 pharmacokinetic parameters for the 6 mg BID dose in this study were consistent with values observed in the Phase 1 studies.

Date of Report: 24Aug2009