2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-894	**Volume:**	
Name of Active Ingredient: 3-(5,6-dichloro-pyridin-3-yl)-1(S),5(S)-3,6-diazabicyclo[3.2.0]heptane	**Page:**	

Title of Study: A Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Safety and Efficacy of ABT-894, Duloxetine and Placebo in Subjects with Diabetic Neuropathic Pain

Coordinating Investigator: Armen Arslanian, MD, Brockton, MA

Study Sites: 47 sites in Canada, France, Germany, Italy, Mexico, Puerto Rico, and the United States

Publications: None

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 09 August 2007 Last Subject Last Visit: 07 October 2008	

Objectives:

The primary objective of this study was to compare the analgesic efficacy and the safety of ABT-894 (1 mg, 2 mg, or 4 mg capsules) administered twice daily (BID) to placebo in the treatment of diabetic neuropathic pain (DNP). Duloxetine 60 mg administered once daily (QD) was assessed for assay sensitivity.

Additionally, this study also explored the pharmacokinetic and pharmacogenetic characteristics of ABT-894 in the DNP population. Details of the pharmacokinetic results are provided in a separate report ([redacted]). Redacted information – 02Sep2015

Methodology:

This was a Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel study designed to compare the analgesic efficacy and the safety of ABT-894 (1 mg, 2 mg, or 4 mg capsules) administered BID to placebo in the treatment of DNP. Duloxetine 60 mg administered once daily (QD) was assessed for assay sensitivity.

A total of 280 subjects meeting selection criteria were randomized into the study at 47 sites in the United States, Canada, Mexico, Puerto Rico, and Europe.

The study was divided into the following periods: Screening/Washout (21 days) followed by a Baseline Visit, an 8-week Treatment Period and a 1-week Follow-up Visit.

Methodology (Continued):

Subjects who met eligibility criteria during the Screening Period entered the Washout portion of the Screening Period during which they discontinued all current medications for DNP (opioid and/or non-opioid, including anti-convulsants and antidepressants). Acetaminophen was permitted as rescue medication during the Washout portion of Screening, as well as throughout the study. Rescue medication could not be taken within 24 hours prior to scheduled study visits, inclusive of the Baseline Visit. Subjects were required to washout of all analgesics for at least 5 half lives of the longest acting analgesic or 2 days, whichever was longer. Following the Washout, subjects were required to return to the site to obtain an electronic diary. Once their diary was obtained, subjects were required to complete pain assessments on a daily basis for approximately 7 consecutive days prior to the Baseline Visit. In order to be eligible for randomization, the subject must have had an average score of ≥ 4 on the 24-hour average pain score (11-Point Likert Scale) and demonstrated at least 60% compliance over approximately 7 days on the 24-hour average pain score. The maximum length of time between Screening and Baseline was 21 days.

Subjects who continued to meet all eligibility criteria following the Washout returned to the study site for the Baseline Visit. Subjects completed the Brief Pain Inventory (Short Form) (BPI-SF) assessment and must have had an average of ≥ 4 on the BPI average of pain score. Subjects who continued to be eligible were then equally randomized to 1 of 5 arms of the study in a 1:1:1:1:1 ratio.

Randomized subjects then entered an 8-week treatment period during which they received treatment with study medication BID. Subjects were permitted to take acetaminophen as rescue therapy during this Period. Acetaminophen could be taken for up to 3 days per week. The days on which rescue medication was taken were not required to be consecutive, but could not exceed 3 days per week. For each of the days rescue medication was taken, subjects could not exceed the clinically approved dosage. Subjects could not take more than a total of 3000 mg of acetaminophen per day and rescue medication could not be taken within 24 hours prior to scheduled study visits.

During the treatment period, all subjects at all sites had blood samples drawn for pharmacokinetic (PK) analysis beginning at the Baseline visit and continuing at all study visits thereafter. Additionally, at the pre termination visit, a blood sample could be collected from those subjects who prematurely discontinued study medication. An intensive PK sampling occurred at select study sites (approximately 50% of total sites). A total of approximately 6 blood samples per subject were taken at one study visit that must have occurred between Week 2, Week 4, or Week 6.

As per the protocol, a blinded interim analysis was conducted once 125 subjects (approximately 25 subjects/arm) completed the Week 6 Visit (or prematurely discontinued). Enrollment into the study continued per protocol while the interim analysis was conducted.

Methodology (Continued):

An Abbott statistician was unblinded to perform the interim analysis and was no longer involved in any other aspect of the study following the analysis. At the interim analysis, the unblinded statistician reviewed unblinded patient diary data for all subjects who had baseline assessment data and completed their Week 6 Visit or prematurely discontinued. Other Abbott statisticians, clinical project team members, site staff and Investigators who were involved in the study remained blinded to subject treatment during the analysis. Upon the completion of the analysis, a decision was made based on the pre-specified statistical criteria whether enrollment into the lowest dose group (1 mg BID) should be stopped. Subjects already enrolled into this dose group (1 mg BID) completed the study per protocol.

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 if the subject prematurely discontinued study medication. In addition, a follow-up phone call was to be conducted approximately 30 days after the last dose of study drug for all subjects. During the call, subjects were to be asked about their overall health status, including whether or not they had been hospitalized or received emergency treatment, as well as status/resolution of any adverse events ongoing since their last contact with study personnel.

Subjects were to adhere to the required study schedule. Study visits were to occur within the specified visit windows. A Baseline Visit was to occur within 21 days of the Screening Visit. The visit window for the Week 1 and Week 2 Visit was ± 2 days. For Weeks 4, 6, 8 and the 1-week Follow-up Visit; the visit window was ± 3 days. Abbott/designee was to be contacted prior to any study visits occurring outside the specified visit windows.

Subjects had the option to participate in pharmacogenetic sampling. Voluntary pharmacogenetic samples were to be taken at the Baseline Visit.

Number of Subjects (Planned and Analyzed):

Planned: 275 subjects at 50 sites

Enrolled: 280 subjects at 47 sites

Analyzed: 280 subjects

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	1 mg	Capsule	Oral	07-012041 07-012700 08-017263
ABT-894	2 mg	Capsule	Oral	07-012046 07-012701 08-017265
ABT-894	4 mg	Capsule	Oral	07-012048 07-012702 08-017267
Duloxetine	60 mg	Capsule	Oral	07-012045 07-012704 08-017286 08-017270

Duration of Treatment:

8 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:				
Test Products	**Dose/Strength**	**Formulation**	**Mode of Administration**	**Lot Numbers**
Placebo	-	Capsule	Oral	07-012044 07-012705 08-017269

Criteria for Evaluation

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.

Secondary efficacy measures include the following:

- 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, Week 4, and Week 8.

Pharmacokinetic: Plasma ABT-894 concentration were obtained at the time indicated in the time and events schedule. Population modeling techniques were 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 also estimated. Additional parameters including pharmacokinetic parameters for ABT-894 metabolites under investigation could 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 treatment group difference between duloxetine 60 mg QD and placebo was also evaluated. 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:

Individual ABT-894 plasma concentrations at each study visit were tabulated and summarized with appropriate statistical methods.

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.

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) were summarized. The overall treatment group differences were 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. Duloxetine 60 mg QD treatment showed statistically significant difference in change of mean of 24-hour average pain score from baseline to final compared to placebo ($P = 0.032$). No statistically significant differences in change from baseline to final were noted in any of the ABT-894 treatment groups (1 mg BID, 2 mg BID or 4 mg BID) when compared to placebo group.

For the secondary efficacy variables:

- No statistically significant differences were observed between placebo and any ABT-894 groups in the proportions of subjects with a ≥ 30% reduction and ≥ 50% reduction in 24-hour average pain diary score from Baseline to Final and in the proportions of sustained responders. Duloxetine group had statistically significantly higher proportion of responders with ≥ 50% pain reduction from baseline to final.
- Differences for 24-hour worst pain score change from baseline to final ($P = 0.045$) reached statistical significance in the duloxetine treatment group compared to placebo. No statistically significant difference was noted between the placebo and ABT-894 treatment groups.
- Neither duloxetine nor ABT-894 showed statistically significant change from baseline to final in night pain diary score although duloxetine and ABT-894 4 mg treatment group showed numerical decrease compared to placebo.
- No statistically significant differences were reported for morning pain change from baseline to final in either the duloxetine or any ABT-894 group compared to placebo. The change from baseline to final value for the morning pain diary score showed a numerical decrease for the duloxetine treatment group compared with the placebo group.
- Score differences from Baseline to Final for BPI-SF 24-hour worst pain score and general activity interference reached statistical significance in the duloxetine treatment group compared to placebo. The BPI-SF change from baseline to final score differences for general activity interference ($P = 0.044$), walking ability interference ($P = 0.012$), normal work interference ($P = 0.018$), and the average of 7 interference scores ($P = 0.045$) reached statistical significance in the ABT-894 4 mg treatment group compared to placebo.
- No statistically significant difference was shown between duloxetine and placebo, between ABT-894 and placebo treatment groups in the clinical global impression of severity change from baseline to final.
- No statistically significant difference shown between placebo and any other treatment groups in the patient global impression of change from baseline to final observation.
- The McGill Pain Questionnaire (sum of the 11 sensory pain scores) changes from baseline to Week 8, reached statistical significance ($P = 0.048$) for the duloxetine treatment group compared to placebo. No statistical significance was observed between the ABT-894 and placebo treatment groups at Week 4, Week 8, or final measurement.

Efficacy Results (Continued):

- Other than the duloxetine treatment group for pain intensity ($P = 0.046$), no statistically significant differences between treatment groups were reported for the Neuropathic Pain Scale.
- Statistically significant differences were observed in change from Baseline to Final in SF-36 physical functioning ($P = 0.043$), bodily pain ($P = 0.033$), general health ($P = 0.009$), and physical component summary ($P = 0.007$) between duloxetine and placebo; and in SF-36 role emotional ($P = 0.010$) between ABT-894 1 mg treatment and placebo.
- No statistically significant changes were seen in the change from baseline to Final for the EQ-5D weighted index between placebo and the duloxetine or ABT-894 treatment groups.
- A total of 64.7% subjects in the placebo group, 43.9% subjects in the duloxetine group, 52.5% subjects in the ABT-894 1 mg group, 48.2% subjects in the ABT-894 2 mg group, and 61.8% subjects in the ABT-894 4 mg group took rescue medication during the study. There were no statistically significant differences observed between the treatment groups in rescue medication average daily dose. However, duloxetine group had statistically significantly lower proportion of subjects taking rescue medicine ($P = 0.024$ versus placebo group). Change from Baseline to Final in 24-hour average pain diary score adjusting for rescue medication use demonstrated no statistically significant differences between treatment groups.

In conclusion, ABT-894 at 1 mg, 2 mg, and 4 mg BID administered 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 in the dose range of 1 mg BID to 4 mg BID were consistent with the exposures observed in Phase 1 studies with ABT-894.

Safety Results:

Of 280 subjects who received study medication, no statistically significant differences were observed in the proportions of subjects who reported at least one treatment-emergent AE, AEs at least possibly drug related, severe and serious AEs, and AEs leading to discontinuation of study drug between any ABT-894 treatment group and placebo treatment group.

Safety Results (Continued):

A total of 62.7% (32/51) of placebo subjects, 73.7% (42/57) of duloxetine subjects and 62.8% (108/172) of ABT-894 subjects reported at least one treatment-emergent AE. The most frequently reported AEs were headache, nausea, dizziness, fatigue, peripheral edema, constipation, dry mouth, diarrhea and purities in ABT-894 treated group; arthralgia, depression, headache, insomnia, nausea, fatigue, edema, diarrhea, nasopharyngitic, urinary tract infection and excoriation in placebo-treated group; and nausea, diarrhea, fatigue, somnolence, dizziness, headache, dry mouth and hyperhidrosis in duloxetine-treated group. There was no clear evidence that the overall incidence rates of AEs were dose-dependent in ABT-894 treatment groups.

Treatment-emergent AEs considered by the Investigator to be at least possibly related to study drug occurred in 31.4% of placebo subjects, 52.6% of duloxetine subjects, and 31.4% of ABT-894 subjects. For ABT-894 treated subjects, the most frequently reported events assessed as possibly or probably-related to study drug by the Investigator included headache, fatigue, nausea, dizziness and constipation. Tremor, abnormal dreams, and anxiety occurred only in ABT-894 treatment groups. There appeared no dose-dependent manner in treatment-related AEs among ABT-894 groups. For placebo-treated subjects, the most frequently reported treatment related events were depression, vertigo, nausea and headache. For duloxetine-treated subjects, the most frequently reported treatment related events were nausea, diarrhea, fatigue, somnolence, dizziness and headache.

Most of the AEs were mild or moderate in severity. Severe adverse events reported in subjects who received ABT-894 included coronary artery stenosis, abdominal pain upper, cellulitis, diverticulitis, arthralgia, intervertebral disc degeneration, muscle spasms, pain in extremity, burning sensation, agitation, erythema, and pruritus. Severe adverse events reported in subjects who received placebo included infected skin ulcer and arthralgia. Severe adverse events reported in subjects who received duloxetine included dyspepsia, nausea, chest pain, influenza, electrolyte imbalance, pruritus, rash, and dizziness.

One subject (2.0%) in the placebo group, 1 subject (1.8%) in the duloxetine group, and 4 subjects (2.3%) in the ABT-894 groups reported SAEs. The SAEs in the ABT-894 groups were coronary artery stenosis, cellulitis, diverticulitis, pneumonia, third degree burns, benign lung neoplasm, benign neoplasm, and nephrolithiasis. One placebo subject had an SAE of infected skin ulcer and 1 duloxetine subject had an SAE of electrolyte imbalance. All of the SAEs were considered not related or probably not related to study drug by the Investigator.

One subject in the duloxetine treatment group died due to pancreatic cancer with metastases to liver which was reported as a post-study serious adverse event and was considered not related to study drug by the investigator.

AEs leading to discontinuation occurred in a greater number of subjects who received duoxetine (11/57 [19.3%] subjects) versus placebo (3/51 [5.9%] subjects) or ABT-894 (8/172 [4.7%] subjects. Discontinuation rate among ABT-894 treatment groups did not appear to be dose-dependent. Adverse events that lead to discontinuation included tachycardia, diarrhea, dry mouth, gastritis, diverticulitis, infected skin ulcer, blood pressure increased, intervertebral disc degeneration, headache, tremor, mood altered, ejaculation disorder, dyspnea, and hot flush in the ABT-894 treatment groups; vertigo, nausea, hypersensitivity, infected skin ulcer, heart rate increased, pain in extremity, headache, depression, sleep disorder, dyspnea, and hyperhidrosis in the placebo treatment group, and palpitations, gastritis, nausea, fatigue, influenza, arthralgia, muscle spasms, dizziness, somnolence, insomnia, restlessness, erythema, and skin burning sensation in the duloxetine treatment group.

Safety Results (Continued):

Overall, mean changes from Baseline to Final visit in hematology parameter values, clinical chemistry parameter values and urinalysis and were clinically unremarkable. There was no statistically significant difference between placebo and any ABT-894 treatment group for most hematology, clinical chemistry and urinalysis parameters except for red blood cell count in the ABT-894 4 mg treatment group and glycosylated hemoglobin (HbA1c) in the ABT-894 1 mg group. These changes were not considered clinically significant. 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 chemistry parameter and urinalysis.

No statistically or clinically significant differences in mean change from Baseline in heart rate, systolic and diastolic blood pressure and body temperature were observed at the Final visit between placebo and ABT-894 treatment groups. The shifts in ECG between categories (normal, abnormal-not clinically significant, abnormal-clinically significant) from Baseline to Final were clinically unremarkable.

No pregnancy was reported during the study.

Conclusions:

ABT-894 at a 1 mg, 2 mg, or 4 mg BID dose administered for 8 weeks did not demonstrate efficacy in treatment of DNP. The 1 mg, 2 mg, and 4 mg BID doses of ABT-894 were generally safe and well tolerated. Duloxetine 60 mg QD administered for 8 weeks was efficacious in the treatment of DNP in this study and the safety profile was consistent with published data.