2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-639		
Name of Active Ingredient: ABT-639		

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study Comparing the Analgesic Efficacy and Safety of ABT-639 to Placebo in Subjects with Diabetic Neuropathic Pain

Coordinating Investigator:
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Study Sites: United States of America (USA), Mexico, the Czech Republic, Germany, and France

Publications: None

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 27 April 2011 Last Subject Last Visit: 26 October 2011	

Objective:

The primary objective of this study was to compare the analgesic efficacy and the safety of ABT-639 100 mg administered twice daily to placebo in the treatment of diabetic neuropathic pain (DNP). Pregabalin (150 mg BID), which is an approved product for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, was included in this study for assay sensitivity. This study also explored the pharmacokinetic (PK) and pharmacogenetic characteristics of ABT-639 in the DNP population.

Methodology:

This was a Phase 2, multicenter, randomized, double-blind, placebo- and active-controlled, parallel group study. For a single subject, the period of study participation was approximately 11 weeks, including a 4-week screening/washout phase, a 6-week treatment phase, and a 1-week follow-up phase. Initially, subjects were required to undergo washout of prohibited medications. Qualified subjects were then randomized in an equal ratio to 1 of 3 treatment groups: ABT-639 100 mg BID, pregabalin 150 mg BID, or placebo BID. Subjects randomized to pregabalin were titrated from 75 mg BID to 150 mg BID at the end of the first week of study drug administration. During the treatment phase, subjects returned to the study site for 3 interim visits and a final visit. The interim visits occurred at the end of Weeks 1, 2, and 4, in relation to the baseline visit. The final visit occurred at the end of Week 6 relative to the baseline visit followed by a follow-up visit 1 week later. Each subject was contacted by phone approximately 30 days after the last dose of study drug. Safety and efficacy data were obtained throughout the study.

Number of Subjects (Planned and Analyzed):

Planned: 180: 60 in each treatment group
Actual Randomized: 194 subjects: placebo, 62 subjects; ABT-639 100 mg BID, 62 subjects; pregabalin 150 mg BID, 70 subjects.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects between 18 and 75 years of age, inclusive, who had a diagnosis of diabetes mellitus type 1 or type 2 according to the American Diabetes Association criteria 2011 with hemoglobin A1c (HbA1c) level of ≤ 10% at screening were eligible for the study if they had a diagnosis of painful distal symmetric diabetic polyneuropathy and presence of pain due to diabetic peripheral neuropathy for at least 6 months. Pain should typically have been present in both feet, calves, or lower limbs with relatively symmetrical onset. Subjects must have had: a score of ≥ 2.5 on the physical assessment portion of the Michigan Neuropathy Screening Instrument (MNSI) at the screening visit; a score of ≥ 4 on the Brief Pain Inventory 24-hour average pain item at screening; an average score of ≥ 4 and < 10 on the 24-hour average pain score (0–10 numerical rating scale) collected from the daily electronic dairy over approximately 7 consecutive (minimum of 5) days prior to the baseline visit; been on a stable anti-diabetic medication regimen for 30 days prior to randomization; and, been able and willing to discontinue all current medications for DNP and other prohibited medications.

Eligible subjects could not have had: a clinically symptomatic neuropathic pain condition other than painful diabetic peripheral neuropathy (e.g., vitamin B_{12} deficiency, hypothyroidism, or focal neuropathy in lower extremities due to trauma or nerve entrapment) or presence of any other painful conditions that could not be distinguished from diabetic peripheral neuropathic pain or confounded the assessment of DNP such as symptomatic peripheral vascular disease; a functioning implanted medical device (spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator) for the treatment of neuropathic pain; a symptomatic diagnosis of fibromyalgia or regional pain caused by lumbar or cervical compression with radiculopathy; had low extremity amputation other than toes due to diabetes; a history of hypoglycemia with unconsciousness, ketoacidosis, hyperosmolar coma, or major changes in diabetes therapy (e.g., initiation of insulin treatment) during the last 3 months prior to the study; taken a strong opioid for > 20 days in the last 30 days prior to screening; an active gastrointestinal (GI) disease including any GI surgery that would interfere with the absorption of study medication; or met the other criteria for exclusion.

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

ABT-639 100 mg (two 50 mg capsules): oral administration; bulk lot number 10-004989

Duration of Treatment:

Subjects received study drug for 6 weeks; total participation time, including screening/wash-out phase, was approximately 11 weeks

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

Pregabalin 150 mg (two 75 mg capsules): oral administration; bulk lot numbers 10-003894, 11-002932, and 11-001468

Placebo: capsule; oral administration; bulk lot number 10-003893

Criteria for Evaluation

Efficacy:

The primary efficacy measure was weekly mean of 24-hour average pain score measured by an 11-point numeric rating scale (NRS) based on subject's daily diary. Secondary efficacy measurements included: worst pain during the day, night time pain, feeling about pain in the morning, daily sleep interference scale, Patient Global Impression of Change (PGI-C), Brief Pain Inventory (short form) (BPI-SF), Neuropathic Pain Symptom Inventory (NPSI), Neuropathic Pain Quality of Life (NePIQoL), EuroQol-5D-5L (EQ-5D-5L), and rescue medication usage.

Pharmacokinetics:

Blood samples were obtained at specific time points for calculation of PK parameters of ABT-639 in plasma.

Safety:

Safety assessments included the monitoring and recording of adverse events (AE) throughout the study. In addition, physical examination was performed to evaluate symptoms or AEs and clinical laboratory measurements, vital signs, and electrocardiograms (ECGs) were evaluated at screening, baseline, and routinely throughout the study.

Statistical Methods

Efficacy:

All analyses were performed on a modified intent-to-treat (mITT) data set. The mITT data set included all randomized subjects who took at least 1 dose of study drug, with the exception that subjects randomized and treated at 1 site were excluded due to data quality issues at the site.

The primary efficacy variable was weekly mean of 24-hour average pain score measured by an 11-point NRS based on subject's daily diary. Treatment group mean differences for the primary efficacy variable were evaluated using analysis of covariance (ANCOVA) with factors for treatment group, pooled study center, and the 24-hour average pain score at baseline as a covariate. The primary treatment comparison was between the ABT-639 treatment group and the placebo treatment group. The treatment group difference between pregabalin 150 mg BID and placebo was also evaluated.

The change from baseline to each post baseline assessment in the treatment period on the 24-hour average pain score was analyzed using an ANCOVA model as well as by mixed-effect, maximum-likelihood, repeated measures (MMRM) analysis.

Efficacy (Continued):

In a secondary analysis of the primary efficacy variable, the proportion of subjects who achieved at least 30% or 50% improvement from baseline to final observation in weekly mean of the 24 hour average pain score was compared between treatment groups using Fisher's exact test. In addition, change from baseline to the weekly average of each efficacy assessment measured using the subject's daily diary (i.e., weekly average pain over 24 hours, worst pain during the day, night time pain, feeling about pain in the morning) was analyzed in the same manner as was done for the primary efficacy variable. Kaplan-Meier survival curves of time-to-first 30% and 50% reduction in 24-hour average pain score were calculated by treatment group; the survival curves were compared between treatment groups by a log-rank test controlling for pooled study center.

Change from baseline to each post baseline assessment in the treatment period on secondary variables of worst pain during the day score, night time pain score, feeling about pain in the morning score, daily sleep score interference, BPI-SF, and NPSI was analyzed using the ANCOVA and MMRM models, and change from baseline to the final assessment on these variables, as well as NePIQoL and EQ-5D-5L, was analyzed using the ANCOVA model. Post-baseline data for PGI-C were analyzed using the CMH test for equal row means scores with study center as a stratification factor. Rescue medication use during the treatment period was analyzed by a Generalized Estimate Equation (GEE) model including treatment group, pooled study center, and visit (% of subjects and % of days using rescue medication) and by ANCOVA (average daily dose).

Pharmacokinetics:

Individual ABT-639 plasma concentrations at each study visit were to be tabulated and summarized with appropriate statistical methods. Population PK analyses were to be performed using the actual sampling time relative to dosing. Pharmacokinetic models were to be built using a non-linear mixed effects modeling approach with the NONMEM software (Version VII, or a higher version). The structure of the starting PK model was to be based on the PK analysis of data from previous studies in pain subjects and healthy subjects.

Safety:

Analyses of adverse events included only treatment-emergent adverse events, 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 Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. The number and percentage of subjects who reported treatment-emergent adverse events were tabulated by primary MedDRA system organ class and preferred term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. Treatment group differences in the incidence rates of serious adverse events and adverse events reported as reasons for discontinuation were also evaluated using Fisher's exact test.

Laboratory measurements (hematology, chemistry, and urinalysis), vital sign measurements (pulse, systolic blood pressure, diastolic blood pressure, body temperature, and weight), and ECG variables (heart rate, PR, QRS, QT, and QTcF intervals) were analyzed for treatment differences between ABT-639 and placebo and between pregabalin and placebo in change from baseline to each post-baseline visit, minimum, maximum, and final evaluation, using 1-way ANOVA with treatment as the factor.

Safety (Continued):

Unless otherwise specified, for all safety analyses for the double-blind treatment period, "baseline" referred to the last non-missing observation prior to the first dose of study drug and "final" referred to the last non-missing observation after the first dose of study drug and no more than 3 days after the last dose of study drug. Safety data for the post-treatment period were collected up to 30 days after the last dose of study drug.

Summary/Conclusions

Efficacy Results:

Qualified subjects were randomized to ABT-639 100 mg BID, pregabalin 150 mg BID, or placebo BID for 6 weeks, with pregabalin-treated subjects receiving 75 mg BID for the first week and then escalated to 150 mg BID at the end of the first week of study drug. A total of 194 subjects received at least 1 dose of study drug: 62 received placebo, 62 received ABT-639, and 70 received pregabalin.

The primary efficacy measure was the weekly mean of 24-hour average pain score measured by the 11-point NRS and calculated from subject's daily diary. In an ANCOVA analysis of the primary variable in the mITT data set, no statistically significant difference was observed for ABT-639 compared with placebo in change from baseline to the final weekly mean of the 24-hour average pain score. The pregabalin treatment failed to show statistically significant improvement in pain, as compared to placebo, based on the primary efficacy variable analysis in this study. However, pregabalin demonstrated significant pain reduction at Week 1 and 2 compared to placebo. The addition of rescue medication use as a covariate in the ANCOVA model did not change the primary efficacy variable result with ABT-639.

In a secondary analysis of the primary efficacy variable, there were no statistically significant differences between the ABT-639 and placebo groups and between the pregabalin and placebo groups for proportions of subjects attaining $\geq$ 30% or $\geq$ 50% reduction in pain at Week 6.

Secondary efficacy variables included: weekly mean of the 24-hour average pain dairy score (change from baseline to each post-baseline visit), worst pain during the day, night time pain, feeling about pain in the morning, daily sleep interference scale, PGI-C, BPI-SF, NPSI, NePIQoL, EQ-5D-5L, and rescue medication use. No clinically meaningful or statistically significant differences were observed between ABT-639 and placebo or between pregabalin and placebo in any of the secondary efficacy variable analyses of change from baseline to the final week.

Pharmacokinetic Results: The mean plasma concentration of ABT-639 ranged from 2706 ng/mL to 3139 ng/mL when ABT-639 was administered at 100 mg BID, and these observed mean steady-state concentrations fall within the concentration range that was observed with the same dose regimen in the previous first-in-human Phase 1 study.

Safety Results:

Overall, 51.0% of subjects had at least 1 treatment-emergent adverse event during the study. The proportion of subjects who experienced adverse events was lower in ABT-639 treatment group (43.5%) compared with placebo (54.8%), although the difference was not statistically significant. There were no adverse events reported by ≥ 5% subjects in the ABT-639 treatment group. The proportion of subjects who reported adverse events that were assessed as possibly or probably related to study drug was also lower, although not statistically significantly different, for the ABT-639 treatment group compared to placebo. In the pregabalin group, 54.3% of subjects reported treatment-emergent adverse events. The most frequently reported adverse events (≥ 3% of subjects) for the ABT-639 group, and at rates numerically higher than with placebo, were abdominal distension (4.8%), muscle spasms (4.8%), viral gastroenteritis (3.2%), insomnia (3.2%), nasopharyngitis (3.2%), rash (3.2%), and sinusitis (3.2%).

Seven cardiac-related adverse events were reported in a total of 6 subjects. Three subjects treated with placebo had cardiac-related adverse events, including 1 subject who experienced atrial fibrillation and tachycardia, 1 subject who experienced QT prolonged, and 1 subject who experienced tachycardia (PT = heart rate increased). Two subjects treated with ABT-639 had cardiac-related adverse events, including 1 subject who experienced angina and 1 subject who experienced coronary artery dilatation. One subject treated with pregabalin experienced a cardiac-related adverse event of MI. Most of these events were resolved at the completion of study drug.

The majority of adverse events were considered mild or moderate in severity. A total of 8 (4.1%) subjects experienced 12 adverse events that were assessed as severe: 2 (3.2%) subjects in the placebo group, 3 (4.8%) subjects in the ABT-639 mg group, and 3 (4.3%) subjects in the pregabalin group.

Across all treatment groups, 5 subjects experienced a serious adverse event: 1 subject each in the placebo and ABT-639 groups and 3 subjects in the pregabalin treatment group. One death due to pneumonia in the placebo group was reported in the study.

Nine subjects discontinued the study prematurely due to adverse events: 2 (3.2%) subjects in the placebo group, 3 (4.8%) subjects in the ABT-639 group, and 4 (5.7%) subjects in the pregabalin group. No adverse event led to premature discontinuation of study drug for more than 1 subject in any treatment group.

There were no consistent and clinically relevant changes from baseline to final in hematology, chemistry, and urinalysis laboratory tests with the exception of serum uric acid in the ABT-639 group. Consistent and statistically significant decreases in uric acid were detected in mean changes from baseline to minimum, maximum, every visit, and final when comparing ABT-639 and placebo.

No statistically significant differences between the ABT-639 treatment group and the placebo group were observed in mean changes from baseline to minimum, maximum, each visit, or final evaluation for systolic blood pressure, pulse rate, body temperature, and body weight. There was a statistically significant decrease in diastolic blood pressure in ABT-639 treatment group compared to placebo in mean change from baseline to minimum, Week 6, and final evaluation. Pregabalin also showed a similar trend. These changes were small and were not considered to be clinically meaningful.

Safety Results (Continued):

No statistically significant differences between the ABT-639 and placebo groups were observed in mean changes from baseline to minimum, maximum, each visit, or final evaluation for PR interval, QRS duration, and QT/QTc interval. For heart rate, small but statistically significant differences between the ABT-639 and placebo groups, ranging from 2.7 bpm to 3.6 bpm, were detected at Weeks 1, 4, 6 and final evaluation. No statistically significant differences between the pregabalin and placebo groups were observed in these analyses of ECG variables except mean change from baseline to Week 6 for PR interval. No subjects shifted to the abnormal clinically significant category of the ECG in any treatment group, regardless of their assessment at baseline. The proportion of subjects in the normal and abnormal nonclinically significant categories remained similar in all 3 treatment groups from baseline to the final evaluation. Overall, ABT-639 was well tolerated.

Conclusions:

In this study, treatment with ABT-639 100 mg BID for 6 weeks did not provide significant pain relief in subjects with DNP when compared to placebo, as demonstrated by the primary measure of change from baseline to the final weekly mean of the 24-hour average pain score. ABT-639 was well tolerated and there were no consistent and clinically relevant findings in physical examination, vital signs, laboratory tests, and ECG.