2.0 Synopsis

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

Title of Study: A Randomized, Double-Blind, Placebo and Active Controlled Study of the Electrophysiological Effects of ABT-639 on Spontaneous Activity in C-Nociceptors in Patients with Diabetic Peripheral Neuropathy

Rationale for Abbreviated Study Report: ABT-639 is no longer under development by AbbVie.

Investigator: Dr. Jordi Serra, Principal Investigator

Study Site: [redacted]

Publications: None.

Studied Period (Years): First Subject First Visit: 19 April 2012 Last Subject Last Visit: 13 November 2012	**Phase of Development:** 2

Objectives:

The objectives of this study were to assess: the effect of a single dose of ABT-639 and intravenous (IV) lidocaine 3 mg/kg on spontaneous activity in peripheral C-nociceptors measured through microneurography in subjects with painful diabetic peripheral neuropathy (DPN) compared to placebo; and the safety, tolerability, pharmacodynamic and pharmacokinetics of a single dose of ABT-639.

Methodology:

This was a Phase 2, single-dose, double-blind, parallel group and randomized study designed to assess the electrophysiological effects of ABT-639 on spontaneous activity in C-nociceptors in subjects with painful diabetic peripheral neuropathy. The safety, tolerability, pharmacodynamic and pharmacokinetics of a single dose of ABT-639 were evaluated. Lidocaine 3 mg/kg IV infused over 30 minutes was included as a comparator. Subjects with neuropathic pain associated with diabetic peripheral neuropathy were selected to participate in the study according to the selection criteria. Microneurography was used to record C-fiber action potentials from the superficial peroneal nerve at the ankle. A subcutaneous reference electrode was inserted in the skin approximately 2 cm outside the nerve trunk.

This study required Screening Visits within 30 days of Day 1. Subjects were required to washout of any exclusionary medications prior to receiving a paper diary. After the subject completed washout, the subjects were required to complete a paper diary for about 7 days (minimum 5 days) prior to Day 1 to record their pain intensity on an 11-point numerical rating scale (NRS). The subjects were required to have an average daily pain score of at least 4 collected over approximately 7 consecutive (minimum of 5) days prior to Day –1.

Methodology (Continued):

Eligible subjects returned on Day –1 and were confined until the end of the study procedures on Day 1. On Day 1 microneurography was performed. Approximately 10 to 15 minutes of baseline activity of C-fibers was recorded. Only subjects who had spontaneous C-nociceptor activity identified were randomized into the study.

Upon meeting the selection criteria, subjects were randomly assigned in a 2:1:1 ratio to receive a single dose of ABT-639, placebo, or lidocaine as listed below. The investigator and the study subjects remained blinded to the treatment throughout the study.

Regimen	Oral Dose	IV Dose
A	100 mg ABT-639 (two 50 mg capsules)	IV Placebo (glucose), infused over 30 minutes
B	2 placebo capsules for ABT-639	3 mg/kg Lidocaine IV, infused over 30 minutes
C	2 placebo capsules for ABT-639	IV Placebo (glucose), infused over 30 minutes

Microneurography recording continued up to about 3 hours following the oral dose or until the signal was lost.

Subjects received an oral dose and an IV dose of study medication on Study Day 1 under fasting conditions. Each oral dose of study drug was taken with enough water to swallow the capsules. The oral dose of study medication was administered at 0 hour. The IV dose of study medication was administered 30 minutes following the oral dose at 0.5 hours. The IV dose was infused over 30 minutes.

On Day 1 the intensity of ongoing pain related to diabetic neuropathy was assessed by the subject using an 11-point NRS and was collected at baseline (immediately prior to microneurography) and every hour following the oral study drug administration until the microneurography procedure was complete.

Blood samples for pharmacokinetic evaluation were taken at 0.50, 0.75, 1, 1.5, 2, 3 and 4 hours after oral dosing.

Subjects were released on Day 1 following completion of all scheduled procedures. There was a follow-up phone call approximately 3 days after discharge.

Plasma concentrations of ABT-110 were determined using a validated 96-Well Salting-out Assisted Liquid/Liquid Extraction Tandem Mass Spectrometric Method at [redacted]. The lower limit of quantitation for ABT-639 was established at 1.05 ng/mL. Plasma concentrations of lidocaine were determined using a validated HPLC with MS/MS detection method at [redacted]. The lower limit of quantitation for lidocaine was established at 0.200 ng/mL.

Number of Subjects (Planned and Analyzed):

Planned: 48; Entered: 39; Completed: 36; Evaluated for Safety: 39, Evaluated for Pharmacokinetics: 26. For the 39 subjects who participated in the study, the mean age was 51.5 years (ranging from 23 to 73 years), the mean weight was 81.1 kg (ranging from 56 to 109 kg) and the mean height was 171 cm (ranging from 156 to 191 cm).

Diagnosis and Main Criteria for Inclusion:

Subjects were male and female between 18 and 75 years. Subjects had a diagnosis of diabetes mellitus type 1 or type 2, clinical evidence of diabetes-related peripheral neuropathy in the distal lower extremities, presence of pain due to diabetic peripheral neuropathy in the distal lower extremities for at least 6 months prior to study entry, and an average daily pain score of (greater than or equal to) ≥ 4 on an 11-point (0 – 10) NRS collected via paper diary over approximately 7 consecutive (minimum of 5) days prior to the Day –1 visit and on Day –1.

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

	ABT-639	Placebo	Lidocaine	Glucose
Dosage Form	Capsule (Size 00)	Capsule (Size 00)	Ampules 2 ml, 5 ml, 10 mL or 20 mL	Bags of 50, 100, 150, 250, 500 or 1000 mL
Strength (mg)	50	0	2% w/v	Glucose Monohydrate for Parenteral Use BP 5,5% w/v
Bulk Lot Number	10-004989	10-003893	11341041	13FBS262
Retest/Expiration Date	[redacted]	[redacted]	[redacted]	[redacted]

Duration of Treatment:

The duration of study treatment was a single dose on Day 1.

Criteria for Evaluation

Efficacy:

Efficacy was not assessed in this study.

Pharmacokinetic:

Samples for pharmacokinetic analysis were collected prior to dose and for the 4 hours following oral administration of study drug. Values for the pharmacokinetic parameters of ABT-639 and lidocaine including the maximum observed plasma concentration (C_{max}), time to the C_{max} (T_{max}) and area under the plasma concentration-time curve from time zero to the last measured concentration (AUC_t) were determined using noncompartmental methods.

Pharmacodynamic:

The following were determined for 10 minute intervals after the oral dose for each C-fiber for which microneurography recording was done. Note that recording may have been done for a subject on more than one C-fiber.

- Number of Significant Latency Increases (SLI): Number of times the unit latency departs from baseline due to spontaneous activity per minute. SLI was defined as any departure > 300 µs from baseline latency.
- Maximum Percentage Increase (% baseline): Maximum Percentage Increase was the largest individual SLI expressed as a percentage of baseline latency.
- Total Increase (TI, % baseline): Sum of all the SLI. Total increase was defined by the sum of individual SLI increases with an increase measured as percentage of baseline latency.

Subjects recorded their assessment of pain associated with diabetic neuropathy on an 11-point NRS prior to oral dosing and at 1, 2 and 3 hours after oral dosing.

Safety:

Adverse events, physical examinations, laboratory data, ECG, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

This study was not designed to assess efficacy and no efficacy data was collected.

Pharmacokinetic:

Plasma concentrations of ABT-639 and lidocaine, and pharmacokinetic parameter values were tabulated for each subject and each regimen. Summary statistics were computed for each sampling time and each parameter.

Pharmacodynamic:

For each of the microneurogaraphy variables, descriptive statistics were provided by regimen and time interval (baseline and each 10-minute interval after oral dosing and initiation of infusion). For a post dose time interval, the descriptive statistics were provided for the time interval itself and for the change from baseline.

For each microneurography variable, three analyses were performed to compare the effects of ABT-639 and placebo, and one analysis was performed to compare the effect of lidocaine to that of placebo.

- For the comparison of ABT-639 to placebo, one analysis was performed for the first 30 minutes post-dose (three 10-minute intervals). For this analysis the data of subjects randomized to lidocaine were included as responses to placebo since lidocaine infusion did not begin until 30 minutes after oral dosing.
- A second analysis to compare ABT-639 to placebo was performed on the data from 30 minutes to 90 minutes post-dose, for which only the data of subjects randomized to ABT-639 and placebo were included.
- The third analysis was performed on the data of the first 90 minutes post-dose, using only data of subjects randomized to ABT-639 and placebo.
- The analysis to compare lidocaine to placebo was performed on data for the 40 minutes following the beginning of the lidocaine/placebo infusion (four 10-minute intervals), for which only data of subjects randomized to lidocaine and placebo were included.

In order to avoid substantial skewness in the probability distributions, the fifth root and tenth root transformation was used for total increase and maximum increase, respectively, but no transformation was necessary for the number of significant latency increases. For all these analyses, a linear mixed effects model was employed. The model included classification of observations by regimen, time interval and the interaction of regimen and time interval. The effects defined by these classifications were fixed. The baseline value was also included as a covariate. The subjects were viewed as a random sample. For a subject from whom there were data for more than one fiber, the fibers were considered a random sample from the subject. The model had a random effect for subject. A second part of the random effects component of the model was a repeated measures structure for the measurements from the same fiber of a subject, with the structure being compound symmetry or first order autoregressive.

For NRS for pain, a repeated measures analysis was performed with effects for the baseline value, time of measurement, regimen, the interaction of regimen and time of measurement. Within the framework of this model, each of ABT-639 and lidocaine was compared to placebo.

Safety:

Adverse events were coded by Medical Dictionary for Regulatory Affairs (MedDRA) version 15.1. The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by MedDRA Preferred Term and System Organ Class with a breakdown by regimen. Laboratory test values, measurements of vital signs, and electrocardiogram (ECG) measurements that were potentially clinically significant, according to predefined criteria, were identified.

Summary/Conclusions

Pharmacokinetic Results:

The mean ± SD pharmacokinetic parameters of ABT-639 and lidocaine are presented in the following table.

		Regimen	
Pharmacokinetic Parameters	**Units**	**A: 100 mg ABT-639 (N = 16)**	**B: 3 mg/kg Lidocaine IV (N = 10)**
C_{max}	(ng/mL)	4280 ± 1620	1940 ± 630
T_{max}	(h)	1.72 ± 1.19	1.00 ± 0.00
AUC_t	(ng•h/mL)	12000 ± 4400	2870 ± 600

Pharmacodynamic Results:

Lidocaine and ABT-639 both failed to generate statistically significant improvements in number of significant latency increases, maximum percentage increases, or total increases compared to placebo. ABT-639 was statistically significantly worse than placebo with respect to number of significant latency increases during the first 30 minutes following oral drug administration, specifically during the 20 – 30 minute interval. Similarly, neither lidocaine nor ABT-639 resulted in statistically significant changes in pain score compared to placebo.

Safety Results:

Overall, 6 out of 39 subjects (6/39, 15%) reported at least one treatment-emergent adverse event during the study. The proportion of subjects reporting at least one treatment-emergent adverse event was 5% for subjects who received 100 mg ABT-639, 30% for subjects who received 3 mg/kg lidocaine and 20% for subjects who received placebo. The most common treatment-emergent adverse event reported by two or more subjects in any treatment group was dizziness.

One treatment-emergent adverse event was considered by the investigator to be moderate in severity, while all remaining treatment-emergent adverse events were considered by the investigator to be mild in severity. The treatment-emergent adverse events were considered by the investigator as either probably not related or possibly related to study drug. No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study.

No consistent changes in individual vital signs or laboratory measurements were observed during the study. No potentially clinically significant vital sign values were reported and no clinically significant abnormal ECG findings were obtained during the course of the study.

Conclusions:

Subjects receiving oral doses of 100 mg ABT-639 reached a mean C_{max} of 4280 ng/mL approximately 1.7 hours after dosing. Subjects receiving an IV infusion of 3 mg/kg lidocaine reached a C_{max} of 1940 ng/mL at 1.0 hours after the beginning of the oral dose, coinciding with the end of the infusion.

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