8.1.1.4.2 Efficacy endpoint outcomes

The Sponsor analyzed the trial data using a two-way analysis of variance controlling for treatment and investigational site for the following study efficacy variables: VAS pain reduction (Sessions 1 and 2), pain relief (Sessions 1, 2 and 3), VAS pain reduction during home use (days 1 to 21), and allodynia testing (sessions 1 and 2). The Sponsor also looked at data from the 7-day washout period collected from patients who opted to participate in the open-label continuous use extension. The results of the Sponsor's analysis is presented in Table 4. (See Table 4 below.)

Although VAS pain scores and pain relief were not found to be significantly affected by treatment with the Lidoderm™ Patch during the first 2 treatment sessions, there was a trend by Session 2 in the intergroup differences for both of these parameters (p=0.1075 and 0.1669, respectively), which developed into a statistically significant difference in pain relief (23.8%) for the Lidoderm™ Patch treatment group (2.6 vs 2.1, p=0227) as compared to the placebo patch after the 21-28 day period of home usage. No significant difference in VAS pain scores were noted for the Lidoderm™ Patch and placebo patch-treated patients during the home-use phase of the study (21-day average: 44.9 vs 47.1, p=05364), nor were there any differences seen at the end of the home-use phase (Session 3: 37.7 vs 40.8, p=0.3708). However, both treatment groups did experience a substantial reduction in VAS pain relief over the course of the study relative to the pretreatment scores collected over the 5 days prior to Session 1 (Lidoderm™ Patch: 40.3% from 63.1 to 37.7, p=0.0001; placebo patch: 33.4% from 61.3 to 40.8, p=0.0001). (See Table 4, following below.) This shows that there was a tremendous placebo effect elicited in the control group. The significance of this placebo effect is diminished by the following finding: after discontinuing the Lidoderm™ Patch for 1 week during the washout period prior to the open-label continuous use extension, it was noted that there was a rapid increase in VAS pain reported by patients off treatment (45.9% from 37.7 to 55.0, p=0.0001). This phenomena, which directly supports the efficacy of this agent in the treatment of PHN was also noted in the placebo group (21.3% from 40.8 to 49.5), but it was not as quite as impressive in the Lidoderm™ Patch treated patients where it achieved statistical significance. These findings were supported in turn by the results of a multivariate analysis in which all of the efficacy outcome parameters included in the model were found to be highly significant (p=0.0053) in the absence of a treatment by center interaction effect. (See Table 4, following below.)

The most impressive finding amongst the efficacy parameters examined was that the patients treated with the Lidoderm™ Patch experienced a statistically significant reduction in allodynia as compared to those treated with the placebo patch during the first 2 treatment sessions. Patients treated with the Lidoderm™ Patch experienced a decrease in allodynia of 28.6% at Session 1, and 20.3% at Session 2 as compared to a 3.8% and a 6.0% decrease respectively for the placebo control treated patients (p=0.0001 and p=0.0195, respectively).

Table 4 - Results of the Statistical Analysis of the Phase 3 Lidoderm™ Patch PHN Trial

Variable	Placebo Patch†		Lidocaine Patch†
Session 1 (First Treatment)			
VAS (Average Reduction)	8.3 ± 12.0 (50)		9.6 ± 17.7 (100)
§p=	(T = 0.6586;	C=0.8150;	I = 0.0795)
Allodynia (Reduction)	0.1 ± 0.6 (50)		0.6 ± 0.7 (100)
p=	(T = 0.0001;	C=0.6069;	I = 0.1981)
Pain Relief (Average)	1.8 ± 0.8 (50)		2.0 ± 0.9 (100)
p=	(T = 0.3166;	C=0.6131;	I = 0.2037)
Session 2 (Second Treatment)			
VAS (Average Reduction)	7.8 ± 9.9 (50)		12.0 ± 16.5 (100)
p=	(T = 0.1075;	C=0.8526;	I = 0.6320)
Allodynia (Reduction)	0.1 ± 0.6 (50)		0.4 ± 0.6 (100)
p=	(T = 0.0195;	C=0.0390;	I = 0.5517)
Pain Relief (Average)	1.9 ± 0.9 (50)		2.2 ± 1.0 (100)
p=	(T = 0.1669;	C=0.3715;	I = 0.9061)
Session 3 ((After 21-28 days of Home Treatment)			
VAS	40.8 ± 19.9 (50)		37.7 ± 19.9 (100)
p=	(T = 0.3708;	C=0.1381;	I = 0.7679)
Pain Relief	2.1 ± 1.0 (50)		2.6 ± 1.3 (100)
p=	(T = 0.0227;	C=0.0728;	I = 0.2946)
Home-Use Session VAS (Avg.)	47.1 ± 21.2 (50)		44.9 ± 20.8 (100)
p=	(T = 0.5364;	C=0.1826;	I = 0.9288)
Washout Session VAS (Avg.)	49.5 ± 24.2 (49)		55.0 ± 20.7 (92)
p=	(T = 0.1616;	C=0.0821;	I = 0.5205)
Multiple p=	(T = 0.0053;	C=0.1637;	I = 0.4524)

* If a particular variable was evaluated for each patient more than once after treatment in any given session, only the average value (derived by averaging the mean scores for all patients) is provided.

† Least square mean (in mm for VAS, no units for other variables) ± one s.d. provided, with n in parenthesis. Some values were derived by subtracting posttreatment scores from those obtained immediately prior to treatment (reduction), while all others are raw scores.

§ P values for most variables were derived from a two-way ANOV with treatment (T) and center (C) as factors in the model along with treatment by center interaction (I). For session 3 VAS data, session 1 and 2 pretreatment scores (combined average) were included in the model as a covariate. For the multiple variable, a multivariate analysis was completed in which the following dependent variables were included in the model: average pain relief from sessions 1, 2 and 3; VAS pain reduction scores for sessions 1 and 2; VAS pain scores for session 3; average VAS pain scores at home-use; and allodynia reduction at sessions 1 and 2. P values less than 0.05 are highlighted in bold.

8.1.1.4.3 Safety outcomes

There were 3 measures of safety: monitoring of systemic lidocaine blood levels, skin examinations of the area treated, and patient's self-reporting of symptoms via a side-effects check list.

Systemic lidocaine levels were measured in plasma samples via gas chromatography technique with a quantitation limit of 10 ng/ml. Monitoring of lidocaine blood levels during the trial showed that very low steady state levels of lidocaine were obtained by patients even after 3-4 weeks of patch use. The following table, Table 5, summarizes the lidocaine blood levels obtained during the trial.

Table 5 - Intra-Trial Lidocaine Blood Levels (ng/ml) as Measured by Gas Chromatography Technique.

	Mean	Standard Deviation	Number
Placebo Patch:			
Pre-application	5.2 ng/ml	11.7	48
6 Hours Post-Application	4.0 ng/ml	10.8	48
After 3 Weeks Home Use	5.2 ng/ml	9.4	48
Active Patch:			
Pre-application	6.4 ng/ml	5.7	97
6 Hours Post-Application	33.9 ng/ml	27.4	97
After 3 Weeks Home Use	41.0 ng/ml	36.6	97

Overall, systemic lidocaine levels ranged from non-detectable to 205 ng/ml. Pre-application and placebo application means were all below quantitation limits of the assay. The data shown in Table 5 (see above) excludes the 6 hour level for Patient 397 and the pre-application level for Patient 384. Both of these samples had higher than expected levels (431 ng/ml and 207 ng/ml respectively) and were thought to have been mixed-up or contaminated during the assay procedure. Another patient, Patient 203, who was randomized to the placebo patch, had elevated levels of lidocaine ranging from 50-78 ng/ml at all sampling times. The Sponsor speculated that this patient may have had an endogenous substance that interfered with the lidocaine assay. *(See pharmacokinetic review for further discussion re: systemic lidocaine levels.)*

Only one patient out of the 161 patients that were exposed to test articles had to withdraw from the study due to a skin reaction. This patient, Patient 414, had a prior history of novocaine allergy and was dropped from the study after she developed erythema following patch application. *(See section 10.1.2 of the safety review for further discussion.)*

The change in scores on the Side Effects Check List from the baseline values as compared to those from Session 3 show that there was a slight decrease after the 3-weeks of home use (see Table 6 below.) This was substantiated by a reduction in the scores for the Side Effects Check List during the test period recorded at Session 2 (see

Tables 6 below).

Table 6 - Results of the Statistical Analysis of the Side-Effects Checklist from the Phase 3 Lidoderm™ Patch PHN Trial

Variable*	Placebo Patch†		Lidocaine Patch†
Session 1 (First Treatment)			
Side Effects			
Pretreatment	6.6 ± 4.4 (52)		7.1 ± 6.8 (108)
§p=	(T = 0.6132;	C=0.3270;	I = 0.2410)
Posttreatment Average	3.7 ± 3.0 (52)		3.7 ± 4.3 (108)
p=	(T = 0.9349;	C=0.1245;	I = 0.1228)
Session 2 (Second Treatment)			
Side Effects			
Pretreatment	4.0 ± 3.6 (51)		4.7 ± 4.9 (107)
p=	(T = 0.3937;	C=0.1709;	I = 0.4262)
Posttreatment Average	3.8 ± 3.2 (51)		3.5 ± 4.2 (105)
p=	(T = 0.4284;	C=0.6526;	I = 0.0100)
Session 3 (After 21-28 days of Home Treatment)			
Side Effects			
Pretreatment	5.3 ± 3.6 (52)		5.9 ± 5.5 (108)
Posttreatment	4.2 ± 3.4 (51)		4.1 ± 3.4 (101)
p=	(T = 0.7966;	C=0.7904;	I = 0.9294)

* For the first and second treatment sessions, the side effects checklist was completed by the patients at 2, 6, and 10 hours after applying the test article. Only the average posttreatment value (derived by averaging the mean scores for all patients) is provided for these sessions.

† Least square mean (except pretreatment session 3) ± one s.d. provided, with n in parenthesis. Pretreatment scores were obtained immediately prior to patch application in sessions 1 and 2, while the session 3 pretreatment score is the average of sessions 1 and 2 as the patients were wearing a patch at the time of the session 3 visit.

§ P values were derived from a two-way ANOV with treatment (T) and center (C) as factors in the model along with treatment by center interaction (I), plus a covariate (pretreatment scores) for the posttreatment analyses.

8.1.1.5 Conclusions Regarding Efficacy Data

This placebo-controlled trial demonstrates that the Lidoderm™ Patch is a safe and effective treatment for the reduction of painful allodynia and the chronic pain experienced by patients with post-herpetic neuralgia despite the large placebo response associated with the use of the control patch.

8.1.2 Reviewer's Trial #2

Title: A Protocol for a Randomized, Double-Blind, Four Session Study of the Analgesic Efficacy of Topical Lidocaine Patches in Patients with Post-Herpetic Neuralgia.

8.1.2.1 Objective/Rationale

The objectives of this trial were to evaluate the efficacy and safety of Lidoderm™ Patch in the treatment of pain from PHN.

8.1.2.2 Design

This was a single-site, double-blind, randomized, placebo-controlled 4-session, Phase 2 trial of cross-over design in patients with PHN of the lower cervical, thoracic, or lumbar region. Each of the 4 sessions lasted 12 hours with assignment to any one treatment occurring randomly. Patients spent the first 6 hours of each session in the clinical lab, and the second 6 hours at home. Each patient had their painfully affected PHN area treated twice with the Lidoderm™ Patch, once with the placebo patch, or was observed once without treatment to provide control data for a total of 4 sessions.

8.1.2.3 Protocol

Eligibility criteria for the study were as follows: age 21 years or older (female not of child bearing potential) in stable general health, suffering from PHN (diagnosed on physical exam and review of medical records) affecting the lower cervical, thoracic or lumbar regions, of moderate severity defined as a self-rated scale of average pain level of 25 mm on a 100 mm visual analog scale (VAS). Excluded from the study were subjects with active herpes zoster (HZ) lesions or dermatitis of any origin, spinal cord or brain injury, pain problems of another origin, subjects who had neurological ablation by block or neurosurgical intervention for control of pain, or who continue to use topically applied analgesic compounds.

After signing an informed consent, patients were assigned a subject number in the order of recruitment. The patients underwent a pre-evaluation for clinical pain assessment, and a neurological exam to exclude conditions such as neuropathy, memory loss and local skin infiltration due to coagulopathy or infectious dermatitis. All 4 test sessions followed the same 12-hour format, and both the investigators and the subjects were blinded to which test session occurred on any one of the 4 test days. The test days were scheduled every 3-7 days and had to be completed within a 28 day period. If a patient experienced prolonged pain relief, the next test session could be postponed until pain intensity had returned to baseline, and the study period could than be extended to a maximum of 42 days.

Each test session for patch application lasted 6 hours in the pain clinic lab and was organized as follows:

Baseline Measures: Pain measured by 100 mm VAS (15 minutes apart)
Symptom Checklist
Sensory Examination of Area of Pain

Inspection of Affected Skin
Blood Lidocaine Level

Up to 3 patches were applied to the area of maximum pain. Subsequent to patch application (Time 0), measures were collected at the following time points:

30 minutes: Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist

1 hour: Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist and Blood Lidocaine Level

2 hours: (+/-15 min) Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist

4 hours: (+/-30 min) Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist and Blood Lidocaine Level

6 hours (+/-30 min) Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist, Blood Lidocaine Level, Sensory Examination of Area of Pain, and Inspection of Affected Skin.

If the skin was abnormal at the 6 hour exam, the patch(es) were be left off and the patient returned the next day for follow-up. If the skin was still abnormal, the patient returned weekly until the abnormality had resolved. If the skin was normal at the 6 hour exam, the patch(es) were replaced on the test area and the patient returned home to complete the remaining 6 hours of the test session.

At home the patient completed the last 2 efficacy time point ratings as follows:

9 hours (+/-60 min) Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist.

12 hours (+/-60 min) Global Pain via VAS, Pain Relief via Categorical Scales, and Symptom Checklist.

The patients removed the test patches after performing the 12 hour rating and returned the used patches to the investigators. If skin irritation was noted, the patients were to call the study nurse and return the following day for follow-up. The observational session was conducted just like the 3 other sessions except that no lidocaine blood levels were drawn.

8.1.2.3.1 Population

A total of 40 patients were enrolled into the trial at the site where the trial was conducted. (See Table 7 below.)

Table 7 - Investigator Site and Number of Patients Entered and Evaluable for the Cross-Over, Double-Blind, Randomized Trial

Investigator/Site	Total Enrolled	Total Evaluable
Michael Rowbotham, MD Pain Center Research Clinic University of California 2233 Post Street, Suite 104 San Francisco, CA 94115	40	35

The following table, Table 8, gives the background demographic characteristics of the people entered in this trial. (See Table 8 below.)

Table 8 - Demographic and Subject Characteristics of Patients Entered in the Cross-Over, Double-Blind, Randomized Trial

Characteristic	Active Patch
Number Entered	40
Age: (years)	
Mean	74.28
SD	8.97
Range	50.0-90.0
Sex: (%)	
Male	2(55%)
Female	18(45%)
Race:	
Caucasian	37(91%)
Black	1(1%)
Hispanic	1(1%)
Asian	1(7%)
Weight: (lbs)	
Mean±SD	149.03±34.41
Range	95.0-240.0
Duration of Disease:	
Mean±SD(yrs.)	3.97±5.74
Range	0.0-26.0
Pain from PHN Every Day?	
Yes	38(100%)
No	0(0%)
Not Reported	2

Table 8 - Demographic and Subject Characteristics of Patients Entered in the Cross-Over, Double-Blind, Randomized Trial (Cont.)

Characteristic	Active Patch
Number Entered	40
Ave. Daily PHN Pain	
Faint	0(0%)
Mild	1(3%)
Moderate	6(16%)
Strong	20(53%)
Intense	11(29%)
Not Reported	2
Surface of Skin Painfully Sensitive?	
Yes	32(94%)
No	2(6%)
Not Reported	6

8.1.2.3.2 Endpoints

Efficacy parameters were assessed at each of the 4 study sessions, and are as follows: magnitude of pain via a 100 mm visual analogue scale (VAS), pain relief via a categorical scales, and qualitative and quantitative sensory testing.

Safety was evaluated via the following: lidocaine blood levels, monitoring of local and systemic adverse drug effects via a symptom check list, and examination of the skin following patch application.

8.1.2.3.3 Statistical considerations

The Sponsor did not perform any sample size, nor power calculations while designing this trial protocol.

8.1.2.4 Results

8.1.2.4.1 Populations enrolled/analyzed

Five Thirty-five (35) out of the 40 patients enrolled in the trial were discontinued prematurely. The primary reasons for these 5 patients not to have completed the trial are as follows: 1 patient failed to meet study criteria, 3 patients withdrew consent, and 1 complained of depression and other medical illnesses. Only 1 out of these 5 patients failed to participate in the first treatment session, the remaining 4 withdrew from the trial during or after completing the first treatment session.

8.1.2.4.2 Efficacy endpoint outcomes

The Sponsor calculated the decrease in pain as compared to baseline for each treatment (Lidoderm™ Patch, placebo patch, observation) and time interval, and performed a statistical analysis of the data using an analysis of variance (ANOV) for a

4-way crossover design and contrast analysis. The results of the reduction in pain as measured by the VAS are shown in the following table, Table 9 (see below).

Table 9 - Results of the Statistical Analysis of Reduction in Pain in the Phase 2, Crossover Trial of Lidoderm™ Patch in the Treatment of PHN

Time†	(1) Lidocaine Patch	(2) Placebo Patch	(3) Observation	p Values
30 min	8.95 ± 15.95 (69)	7.26 ± 10.28 (35)	1.52 ± 14.73 (34)	1vs2 = 0.528 1vs3 = 0.007 2vs3 = 0.067
1 hr¶	9.00 ± 13.85 (68)	5.93 ± 13.61 (35)	3.59 ± 15.96 (33)	1vs2 = 0.176 1vs3 = 0.021 2vs3 = 0.376
2 hr	9.56 ± 15.75 (70)	9.39 ± 13.70 (34)	1.22 ± 18.15 (34)	1vs2 = 0.954 1vs3 = 0.005 2vs3 = 0.016
4 hr	12.27 ± 15.46 (70)	5.83 ± 16.62 (35)	2.74 ± 18.19 (35)	1vs2 = 0.038 1vs3 = 0.002 2vs3 = 0.383
6 hr	11.63 ± 14.99 (70)	4.71 ± 15.59 (34)	-1.83 ± 15.44 (34)	1vs2 = 0.012 1vs3 < 0.001 2vs3 = 0.041
9 hr	10.83 ± 21.12 (69)	0.82 ± 15.33 (35)	-1.05 ± 19.60 (34)	1vs2 = 0.009 1vs3 = 0.002 2vs3 = 0.669
12 hr	9.14 ± 19.89 (68)	-3.12 ± 16.68 (35)	-4.74 ± 19.95 (34)	1vs2 = 0.001 1vs3 < 0.001 2vs3 = 0.690
Overall Pain Reduction§ (30 min-12 hr)	10.22 ± 13.39 (70)	4.23 ± 9.77 (35)	0.24 ± 15.04 (35)	1vs2 = 0.008 1vs3 < 0.001 2vs3 = 0.122

* Least square mean (in mm) ± one s.d. provided, with n in parenthesis. Values derived by subtracting posttreatment scores from baseline.

† Time is measured relative to beginning of treatment (patch application or observation).

¶ At one hour, the F-test for overall treatment effect was of borderline significance (p = 0.058).

§ Calculated by averaging mean pain reduction for each patient/treatment at the seven time periods.

Patients had a significantly greater decrease in pain following the use of the Lidoderm™ Patch as compared to the placebo patch starting at 4 hours post-treatment which continued to the end of the test session when the patches were finally removed, and over the entire 12-hour active treatment session when compared to the observational session (no treatment). The Sponsor attributes the improvement in pain experienced during the first 2 hours of the treatment sessions with both the Lidoderm™ Patch and the placebo patch due to placebo effect. This is supported by the greater overall decrease in pain during the 12-hour treatment sessions experienced following treatment with the Lidoderm™ Patch (average of 10.22 mm, or 20.7% decrease from baseline), versus treatment with the placebo patch (average of 4.23 mm, or 8.7%

decrease from baseline) as compared to the observation or no treatment session (average of 0.24 mm, or 0.5% decrease from baseline). Only the Lidoderm™ Patch vs control comparisons achieved statistical significance for the overall reductions in pain at the various time points measured. (See Table 9 above.)

Patients also reported increased pain relief as measured via a 5-point categorical scale, following treatment with the Lidoderm™ Patch as compared to the placebo patch or no treatment. (See Table 10, below.) Although the Lidoderm™ Patch vs placebo patch treatment comparison was not statistically significant at any of the time points measured (see Table 10 below) overall pain relief was significantly greater following treatment with the Lidoderm™ Patch as compared to the placebo patch (2.17 vs 1.85 respectively, p=0.033). This was particularly true in patients with slight to moderate relief while patients with none to slight relief had experienced smaller magnitudes of pain relief. Again, a significant placebo effect was experienced by patients when treated with the placebo patch vs no treatment (p=0.001) in terms of pain relief. (See Table 10, below.)

Table 10 - Results of the Statistical Analysis of Pain Relief in the Phase 2, Crossover Trial of Lidoderm™ Patch in the Treatment of PHN

Time†	Treatment * (1) Lidocaine Patch	(2) Placebo Patch	(3) Observation	p Values¶
30 min	1.91 ± 1.10 (69)	1.85 ± 0.94 (35)	1.07 ± 0.75 (34)	1vs2 = 0.753 1vs3 < 0.001 2vs3 = 0.001
1 hr	2.04 ± 1.09 (69)	1.72 ± 0.96 (34)	1.41 ± 0.82 (34)	1vs2 = 0.076 1vs3 = 0.001 2vs3 = 0.128
2 hr	2.28 ± 1.07 (70)	2.09 ± 0.98 (34)	1.35 ± 1.10 (34)	1vs2 = 0.310 1vs3 < 0.001 2vs3 = 0.001
4 hr	2.44 ± 1.11 (70)	2.20 ± 1.00 (35)	1.43 ± 1.01 (35)	1vs2 = 0.182 1vs3 < 0.001 2vs3 < 0.001
6 hr	2.35 ± 1.17 (70)	1.96 ± 1.03 (33)	1.17 ± 1.18 (34)	1vs2 = 0.057 1vs3 < 0.001 2vs3 = 0.001
9 hr	2.09 ± 1.37 (68)	1.66 ± 1.18 (35)	1.14 ± 0.95 (34)	1vs2 = 0.078 1vs3 < 0.001 2vs3 = 0.070
12 hr	2.03 ± 1.31 (67)	1.63 ± 1.26 (35)	1.27 ± 0.87 (33)	1vs2 = 0.067 1vs3 = 0.001 2vs3 = 0.158
Overall Pain Relief§ (30 min-12 hr)	2.17 ± 0.97 (70)	1.85 ± 0.72 (35)	1.26 ± 0.75 (35)	1vs2 = 0.033 1vs3 < 0.001 2vs3 = 0.001

* Least square mean ± one s.d. provided, with n in parenthesis.
† Time is measured relative to beginning of treatment (patch application or observation).
¶ Values derived from ANOV/contrast analysis.
§ Calculated by averaging mean pain relief scores for each patient/treatment at the seven time periods.

In terms of quantitative sensory testing, no significant differences were seen in either the perception of warm/cool temperatures or heat/cold-induced pain by normal skin but the PHN skin was less sensitive to warm temperatures after a 6-hour treatment with the Lidoderm™ Patch as compared to the placebo patch or no treatment (p=0.077 and p=0.036, respectively). (See Table 11, below.) PHN skin was also found to be less sensitive to cool temperatures or cold-induced pain following treatment with the Lidoderm™ Patch (mean of 7.91°C and 4.88°C respectively) but were unchanged following treatment with the placebo patch or no treatment (increased by 0.05°C/decreased by 0.95°C and decreased 0.04°C/decreased 0.55°C respectively). (See Table11, below.) The data from the semiquantitive sensory testing only showed trends on analysis which corroborated the quantitative thermal sensory testing, and therefore was not subjected by the Sponsor to formal statistical analysis.

Table 11 - Results of the Statistical Analysis of the Quantitative Sensory Testing in the Phase 2, Crossover Trial of Lidoderm™ Patch in the Treatment of PHN

Test Parameter	Treatment* (1) Lidocaine Patch	(2) Placebo Patch	(3) Observation
Quantitative			
Warm Stimulus - Normal Skin	-0.46 ± 2.23 (69)	0.26 ± 2.64 (32)	0.29 ± 2.61 (35)
†p=	(1 vs 2 = 0.154;	1 vs 3 = 0.126	2 vs 3 = 0.966)
- PHN Skin	-1.19 ± 4.67 (69)	0.61 ± 6.46 (34)	0.92 ± 2.44 (35)
p=	(1 vs 2 = 0.077	1 vs 3 = 0.036¶	2 vs 3 = 0.786)
Heat/Pain Stimulus - Normal Skin	0.18 ± 3.26 (69)	-0.11 ± 3.72 (32)	0.13 ± 2.78 (35)
p=	(1 vs 2 = 0.686;	1 vs 3 = 0.946	2 vs 3 = 0.767)
- PHN Skin	-0.42 ± 3.58 (69)	-0.56 ± 2.87 (34)	0.02 ± 3.14 (35)
p=	(1 vs 2 = 0.836	1 vs 3 = 0.500	2 vs 3 = 0.447)
Cool Stimulus - Normal Skin	0.23 ± 2.36 (69)	0.69 ± 2.82 (32)	0.04 ± 1.44 (35)
p=	(1 vs 2 = 0.358;	1 vs 3 = 0.684	2 vs 3 = 0.252)
- PHN Skin	7.91 ± 7.21 (68)	-0.05 ± 6.39 (34)	0.04 ± 3.92 (35)
p=	(1 vs 2 < 0.001	1 vs 3 < 0.001	2 vs 3 = 0.953)
Cold/Pain Stimulus - Normal Skin	-0.44 ± 6.10 (69)	-1.51 ± 6.10 (32)	-1.85 ± 6.84 (35)
p=	(1 vs 2 = 0.449;	1 vs 3 = 0.302	2 vs 3 = 0.835)
- PHN Skin	4.88 ± 7.08 (67)	0.95 ± 6.14 (34)	0.55 ± 5.27 (35)
p=	(1 vs 2 = 0.002	1 vs 3 < 0.001	2 vs 3 = 0.773)

* Least square mean (in °C for quantitative variables, no units for semiquantitative) ± one s.d. provided, with n in parenthesis. Please note that normal skin was not actually treated with lidocaine or placebo patch, but was included as a contralateral comparison site. Values derived by subtracting posttreatment scores from baseline.

† Derived from ANOV/contrast analysis.

¶ The F-test was of borderline significance for warm stimulus PHN skin (P = 0.059)

8.1.2.4.3 Safety outcomes

There were no significant drug-related adverse events reported following the use of either the active or placebo patch in this study. Three patients did develop minor skin problems related to treatment with the study patches. Two patients experienced transient skin erythema following removal of the study patch; 1 following the use of the placebo patch and 1 following use of the active patch. The third patient developed minor bruising with severe pain following removal of the placebo patch. This patient had been chronically treated with steroids which was thought to have contributed to this adverse event.

The analysis of the 27-item Symptom Checklist which covered items common to PHN (ex. Itching, burning), local anesthetic effects due to high-dose intravenous medications, and adverse events associated with the use of tricyclic antidepressants used off-label to treat PHN failed to show any significant differences between treatment groups. (See Table 12, below.)

Table 12 - Results of the Statistical Analysis of the Symptom Checklist in the Phase 2, Crossover Trial of Lidoderm™ Patch in the Treatment of PHN

Time†	Treatment* (1) Lidocaine Patch	(2) Placebo Patch	(3) Observation	p Values¶
30 min	1.57 ± 2.64 (68)	1.12 ± 1.48 (35)	0.73 ± 1.70 (36)	1vs2 = 0.262 1vs3 = 0.041 2vs3 = 0.406
1 hr	1.72 ± 2.96 (70)	1.13 ± 1.44 (35)	1.01 ± 1.56 (36)	1vs2 = 0.162 1vs3 = 0.099 2vs3 = 0.813
2 hr	1.54 ± 2.89 (71)	1.41 ± 1.88 (34)	0.99 ± 1.63 (37)	1vs2 = 0.790 1vs3 = 0.237 2vs3 = 0.434
4 hr	1.16 ± 2.09 (71)	1.24 ± 2.63 (35)	0.78 ± 1.72 (38)	1vs2 = 0.845 1vs3 = 0.375 2vs3 = 0.350
6 hr	1.50 ± 2.80 (71)	1.59 ± 2.09 (34)	1.01 ± 1.94 (37)	1vs2 = 0.838 1vs3 = 0.304 2vs3 = 0.291
9 hr	1.44 ± 2.97 (68)	0.91 ± 1.62 (33)	0.35 ± 4.22 (35)	1vs2 = 0.409 1vs3 = 0.084 2vs3 = 0.432
12 hr	1.25 ± 3.41 (67)	0.62 ± 1.67 (30)	0.55 ± 3.52 (31)	1vs2 = 0.321 1vs3 = 0.259 2vs3 = 0.921
Overall SCS Reduction§ (30 min-12 hr)	1.42 ± 2.49 (71)	1.17 ± 1.39 (35)	0.79 ± 1.98 (38)	1vs2 = 0.530 1vs3 = 0.120 2vs3 = 0.425

* Least square mean ± one s.d. provided, with n in parenthesis. Values derived by subtracting posttreatment scores from baseline.
† Time is measured relative to beginning of treatment (patch application or observation).
¶ Values derived from ANOV/contrast analysis.
§ Calculated by averaging mean symptom checklist scores (SCS) for each patient/treatment at the seven time periods.

8.1.2.5 Conclusions Regarding Efficacy Data

This small, cross-over, placebo-controlled trial demonstrates that the Lidoderm™ Patch is a safe and effective treatment in producing topical analgesia of pain associated with PHN as measured by the reduction in pain and increase in overall pain relief over a 12-hour period time in spite of the large placebo effect associated with the use of the placebo patch by the same treatment population.