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A Multicenter, Randomized, Double-Blind, Controlled Dose Finding Study of NGX-4010, a High-Concentration Capsaicin Patch, for the Treatment of Postherpetic Neuralgia

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Abstract: **Postherpetic neuralgia (PHN) is a painful complication of acute herpes zoster. This multicenter, double-blind, controlled study randomized 299 PHN patients to receive either NGX-4010, a high-concentration capsaicin (8%) patch, or a low-concentration capsaicin (0.04%) control patch for 30, 60, or 90 minutes. The mean percent reductions in NPRS score from baseline to weeks 2 through 8 were significantly greater in the total NGX-4010 group (26.5%, *P* = .0286) and the 90-minute NGX-4010 group (27.8%, *P* = .0438) compared to the pooled control group (17.3%). After review of the data suggested a difference between genders in reporting of pain scores and a higher proportion of males (61%) in the 60-minute NGX-4010 group, post hoc gender-stratified analyses were performed and showed that the 60-minute NGX-4010 group also had a significantly larger mean percent reduction in average pain scores (28.0%, *P* = .0331). Pain reduction in the 30-minute NGX-4010 group, although similar in magnitude to the other doses, was not significantly different from control in either of these analyses. Similar results were observed during weeks 2 through 12. Most treatment-emergent adverse events were application-site specific, transient and mostly mild to moderate in severity.**

Perspective: ***This article reports the safety and efficacy of NGX-4010 applied for 3 different durations (30, 60, or 90 minutes) in patients with PHN. The results identified the 60-minute duration as the dose to be evaluated in subsequent studies and identified a gender effect on reported changes in pain.***

Key words: *Neuropathic pain, postherpetic neuralgia, capsaicin.*

Postherpetic neuralgia (PHN) is a painful disorder that represents a complication of acute herpes zoster. Herpes zoster (shingles) is caused by reactivation of the varicella zoster virus usually contracted in childhood. The disorder is often very painful, either before the rash, during, or after the inflammatory response appears. Usually this pain subsides, but if it persists with healing, it is referred to as PHN. Transition from acute herpes zoster to PHN occurs when the pain in the affected area persists after crusting of the skin lesions, and definitions of PHN vary from as short as 1 month to as long as 6 months after lesion crusting.[26] The prevalence of PHN increases with age. It is estimated that between 25% and 50% of patients with herpes zoster older than 50 years of age, and up to 75% of patients with herpes zoster over 70 years of age, develop PHN.[19,27,34]

PHN is a chronic pain syndrome and its treatment often requires the use of more than 1 neuropathic pain medication.[2,15,16] Treatment options include anticonvulsants such as pregabalin and gabapentin, topical lidocaine, opioids, tricyclic antidepressants, and selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). However, most of these treatments only provide partial

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relief[4,11,18,29] and their use is often limited by poor tolerability, the need for titration, and administration of multiple daily doses.

Sensitization of peripheral nociceptors that express transient receptor potential vanilloid 1 receptor (TRPV1), a ligand-gated nonselective cation channel, is thought to play a role in pain in PHN.[24,26] Therefore, treatment strategies directly targeting TRPV1 have been developed. Capsaicin is a highly selective activating ligand for TRPV1, and causes depolarization, action potential initiation, and the transmission of pain signals to the spinal cord resulting in a burning sensation, hyperalgesia, allodynia, and erythema.[8] Following continued capsaicin exposure, the TRPV1 receptor is activated allowing calcium to flow into the cell and inducing calcium release from the endoplasmic reticulum which also express TRPV1.[6,30] High levels of intracellular calcium induce enzymatic and osmotic changes leading to the reversible defunctionalization of TRPV1-containing sensory axons and inhibition of the initiation of pain transmission for a sustained period of time.[6,30] Although low-concentration capsaicin creams (.025% and .075%) have demonstrated efficacy in the treatment of PHN,[5,23,34] they require continued multiple daily applications over several weeks before therapeutic effects are observed, and cause a burning sensation at the application site, both of which may lead to a lack of compliance. In contrast, NGX-4010 is a high-concentration capsaicin patch (capsaicin, 8%) that has been developed to locally deliver a dose of capsaicin that is tolerable and sufficient to induce rapid defunctionalization following a single administration.

Previously, NGX-4010 applied for 60 minutes has been reported to reduce pain for up to 12 weeks in controlled clinical trials in patients with PHN.[1,3] We report the results of a multicenter, double-blind, controlled, dose-finding study which evaluated the safety and efficacy of NGX-4010 applied for 3 different application durations (30, 60, or 90 minutes) in patients with PHN. Since the delivery of capsaicin from NGX-4010 into the skin is related to the duration of patch application, the dose of capsaicin delivered was varied by varying the time of exposure.

Methods

Patients

Patients 18 years or older with a diagnosis of PHN and an average Numeric Pain Rating Scale (NPRS)[12] score of 3 to 9 (inclusive) were eligible if at least 6 months had elapsed since shingles-vesicle crusting. Patients taking chronic pain medications (opioids, antidepressants, anticonvulsants and other) had to be on a stable dose for at least 21 days before the treatment day and throughout the study period. Women of childbearing age were required to have a negative pregnancy test and be willing to use an effective method of contraception for 30 days after exposure to study medication.

Exclusion criteria were as follows: use of any topically applied pain medication on the painful area within 21 days before the treatment day; current use of any investigational drug or class 1 anti-arrhythmic drug; uncontrolled diabetes mellitus or uncontrolled hypertension; significant pain of an etiology other than PHN; painful PHN areas located only on the face, above the scalp hairline, or near mucous membranes; and hypersensitivity to capsaicin, local anesthetics, oxycodone hydrochloride, hydrocodone, or adhesives. As prior use of high-dose opioids could limit the responsiveness to the optional oral opioid analgesics used during the treatment procedure, patients using concomitant opioid medication that were not orally or transdermally administered or exceeded a total dose of 60 mg/day morphine equivalent were excluded.

The study was approved by Institutional Review Boards at all participating sites, and conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. Written informed consent was obtained from all participating patients before initiating study-related procedures.

Procedures

A baseline screening period was followed by a treatment day (day 0) and a 12-week posttreatment assessment period with clinic visits at weeks 4, 8, and 12. Eligible patients were randomized 3:3:3:1:1:1 to receive either NGX-4010 (capsaicin 640 μg/cm^2, 8%; NeurogesX Inc., San Mateo, CA) or identically appearing control (capsaicin 3.2 μg/cm^2, 0.04%) patches for 30, 60, or 90 minutes according to a randomization scheme prepared by Cardinal Health (Morrisville, NC). The low-concentration capsaicin control patches were used in place of placebo patches to provide effective blinding in the study since topical capsaicin can produce local erythema and a burning sensation. All patients were pretreated with a topical local anesthetic cream (ELA-Max,® lidocaine 4%; Ferndale Laboratories, Inc., Ferndale, MI) for 60 minutes before the application of the study or control patch(es), which were applied directly to the painful area(s) (up to 1,000 cm^2). After patch removal, the area was cleansed with a proprietary cleansing gel formulated to remove residual capsaicin. Patients were monitored for 2 hours after patch removal. Local cooling as well as oxycodone hydrochloride oral solution (1 mg/mL) or equivalent could be administered at the onset of treatment-associated discomfort and as needed. Patients could take opioid medication (hydrocodone bitartrate/acetaminophen 5mg/500mg) every 8 hours for up to 3 days after patch application for treatment-associated discomfort as needed. Topical pain medications were not permitted during the 12-week study period. Patients were allowed to take acetaminophen up to 2 g/day as needed for aches and pains. Patients who completed the week-12 study evaluations could enter a 40-week open-label extension period with up to 3 open-label, 60-minute NGX-4010 treatments at least 12 weeks apart (data not presented).

Measures and Data Analysis

Efficacy

Efficacy was evaluated with daily Numeric Pain Rating Scale (NPRS) scores throughout the 12-week study period. The NPRS is an 11-point scale (0–10) with 0 indicating no pain and 10 indicating the worst possible pain.[12] Patients recorded NPRS scores for "worst pain for the past 24 hours," "average pain for the past 24 hours," and "pain now" in a take-home diary beginning on the evening of the treatment day (day 0) through the evening before the week-12 visit. Patient Global Impression of Change (PGIC) where patients described how they felt compared to baseline on a scale of −3 indicating "very much worse" to +3 indicating "very much improved" with 0 being "no change," and investigator-rated Clinical Global Impression of Change (CGIC)[28] were evaluated at weeks 4, 8, and 12. The modified Brief Pain Inventory (BPI)[7] was collected at screening and weeks 4, 8, and 12. The Short-Form McGill Pain Questionnaire (SFMPQ)[21] was collected at screening and weeks 4, 8, and 12.

The primary efficacy endpoint was the percentage change in "average pain for the past 24 hours" NPRS scores from baseline to weeks 2 through 8. To avoid the potential confounding effect of allowed opioid medications for treatment-related pain during days 0 to 3, week 1 NPRS scores were not included in the primary analysis. Other efficacy measures included: percentage change in NPRS scores from baseline to weeks 2 to 4 and 2 to 12; the percentage of patients with a ≥30% and ≥50% reduction in NPRS score from baseline to weeks 2 to 4, 2 to 8, and 2 to 12; the percentage of patients considered improved (slightly, much, or very much) on the PGIC and CGIC at weeks 4, 8, and 12; changes from screening in the BPI questionnaire collected at weeks 4, 8, and 12; and changes from screening in the SFMPQ questionnaire collected at weeks 4, 8, and 12. Weekly changes in NPRS scores were also evaluated.

Efficacy analyses were based on the intent-to-treat population that consisted of all patients who received any study treatment and had at least 3 days of available NPRS scores during the baseline period. Initially, all treatment groups as well as the total NGX-4010 group were compared to the pooled control group using an ANCOVA model with baseline pain as the only covariate. After review of the data suggested a gender-related difference in pain response, with male patients in both the NGX-4010 and control groups reporting smaller reductions in average pain scores from baseline to weeks 2 to 8 compared to female patients, differences between the NGX-4010 groups and the pooled control group in NPRS scores for weeks 2 to 8 were also compared using a gender-stratified ANCOVA model with baseline pain score as a covariate. The same method was used to analyze the differences between the NGX-4010 groups and the pooled control group in NPRS scores for weeks 2 to 4 and 2 to 12. Logistic regression with gender (post hoc) and baseline pain score as covariates tested the difference in the proportion of patients with a ≥30% and a ≥50% mean decrease from baseline in NPRS scores during weeks 2 to 4, 2 to 8, and 2 to 12. For the SFMPQ and BPI, a t-test was used to test for differences in change from screening to week 8 between treatment groups. For PGIC and CGIC, a Wilcoxon rank sum test was used to test for differences between treatment groups.

Missing posttreatment NPRS scores were imputed using a modified last-observation-carried-forward approach. If the NPRS score was missing on days 0 to 8, the baseline score was imputed for that day. If the NPRS score was missing for any day past day 8, then the latest available nonmissing score collected before that day was imputed for that missing value. If NPRS scores were missing for all posttreatment study days (including day 0), then the baseline score was imputed for all missing scores. No imputation was used for the calculation of weekly scores. For the calculation of NPRS baseline scores, all available screening scores which were not biased by pain-medication changes were used.

It was estimated that to achieve 90% power at the .05 significance level with a standard deviation of 31%, a total of 300 patients were required to detect a difference of 15% in change from baseline in NPRS scores between the NGX-4010 and control groups.

Safety

Safety was assessed by continuous monitoring of adverse events and periodic assessments of clinical laboratory parameters, vital signs, physical examinations, dermal assessments (0- to 7-point severity score),[32] pain experienced during and after the patch application using NPRS scores on the day of treatment (prior to topical local anesthetic application, 5 minutes prior to patch application, 5 minutes prior to patch removal, and 1 hour after patch removal), medication for treatment-related pain use on days 0 to 5, and concomitant medication use. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 7.0). Treatment-associated erythema, discomfort, and pain on the day of treatment were not captured as adverse events but were reported as dermal-assessment scores or NPRS scores, respectively. Standardized neurological and sensory examinations (allodynia, light brush, pinprick, warmth, and vibration) were performed at screening, week 8, and week 12. Changes in neurological and sensory assessments from screening to each assessment time point were categorized using prespecified algorithms. On the day of treatment, the proportions of patients reporting each level of dermal response, pain score, and the change in pain score from the pre-local-anesthetic time point were summarized. In addition, vital signs (systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate) and change in vital signs from the pre-local-anesthetic time point and the number and proportion of patients who had shorter patch-application times (< 90% of intended patch-application duration) were summarized.

Patient demographics, baseline clinical characteristics, the use of medication for treatment-related pain on days

0 to 5, and the number of patients completing the intended patch duration were compared using Fisher's exact tests or *t*-tests, as appropriate. The results of the allodynia assessments at each visit were compared using a t-test while the rest of the neurologic sensory exams were compared using a Cochran-Mantel-Haenszel test for trend.

Results

Patients

A total of 299 patients were enrolled into the study and received double-blind treatment: 222 patients received NGX-4010 and 77 patients received control (Fig 1). A total of 273 (91%) patients completed the 12-week study: 200 (90%) patients in the total NGX-4010 group and 73 (95%) patients in the pooled control group. The most common reasons for premature termination included loss to follow-up (7 [3%] NGX-4010 patients and 1 [1%] control patient) and "other" reasons (5 [2%] NGX-4010 patients and 1 [1%] control patient) such as withdrawal of consent and patients moving away. Two (0.9%) NGX-4010 patients discontinued prematurely due to an adverse event, ie, an increase in PHN pain; both events were considered treatment related. No patients in the control group discontinued due to an adverse event. One patient, a 91-year-old male who received control for 90 minutes, died of multi-organ failure on day 108 that was not considered related to study drug.

Demographics, baseline pain scores, duration of PHN, the size of the painful area, the size of the treated area, and use of baseline concomitant pain medications (opioids, antidepressants, anticonvulsants, and others) were generally similar between treatment groups (Table 1). However, there was a higher proportion of male patients in the 60-minute NGX-4010 group (61%), compared to the other NGX-4010 groups (43% and 47%) and the pooled control group (49%).

Efficacy

The total NGX-4010 group demonstrated a mean reduction in "average pain for the past 24 hours" from baseline to weeks 2 to 8 of 26.5% compared with 17.3% in the pooled control group (Table 2; $P = .0286$). Patients treated for 90, 60, or 30 minutes reported similar mean reductions in pain of 27.8%, 25.6%,and 26.2%, respectively. However, only the 90-minute dose group was significantly different from control ($P = .0438$). During weeks 2 to 12, the total NGX-4010 group demonstrated a mean reduction in "average pain for the past 24 hours" from baseline of 25.0% compared with 14.7% in the pooled control group ($P = .0120$). Patients treated for 90, 60, or 30 minutes reported similar mean reductions in pain of 26.1%, 24.4%, and 24.4%, respectively. The 90-minute as well as the 60-minute dose groups were

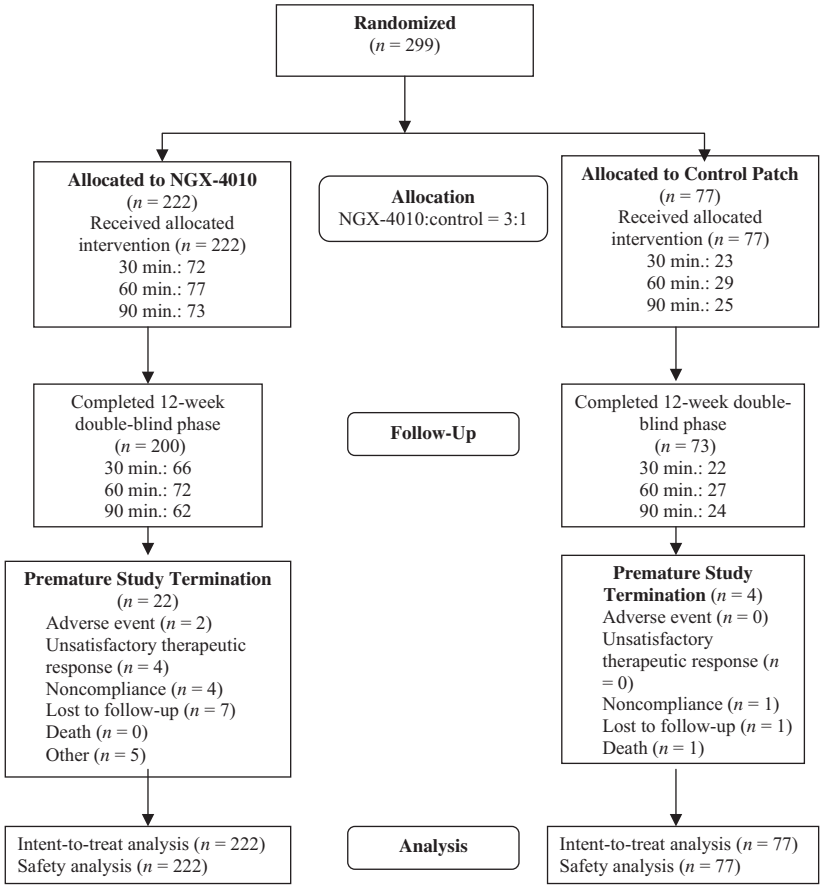

Figure 1. Study randomization and disposition.

Table 1. Patient Demographics and Clinical Characteristics

	NGX-4010				Control
	Total (N = 222)	90 min (N = 73)	60 min (N = 77)	30 min (N = 72)	Total (N = 77)
Demographics					
Age (yr), mean ± SD	71.6 ± 10.27	70.9 ± 11.55	73.5 ± 8.46	70.2 ± 10.49	71.1 ± 10.44
Male, n (%)	112 (50%)	34 (47%)	47 (61%)	31 (43%)	38 (49%)
Race, n (%)					
Asian	3 (1%)	3 (4%)	0 (0%)	0 (0%)	1 (1%)
African American	2 (<1%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
White	208 (94%)	68 (93%)	75 (97%)	65 (90%)	68 (88%)
Other	9 (4%)	2 (3%)	1 (1%)	6 (8%)	7 (9%)
Clinical Characteristics					
Duration of pain (yr), mean ± SD	3.8 ± 4.80	3.6 ± 4.90	3.9 ± 4.34	4.0 ± 5.20	3.8 ± 4.47
Baseline* "average pain for the past 24 hours," mean ± SD	5.6 ± 1.63	5.6 ± 1.44	5.4 ± 1.73	5.8 ± 1.70	5.3 ± 1.45
On concomitant pain medication,† n (%)	179 (81%)	61 (84%)	64 (83%)	54 (75%)	61 (79%)
Opioids	61 (27%)	19 (26%)	18 (23%)	24 (33%)	14 (18%)
Anticonvulsants	78 (35%)	28 (38%)	26 (34%)	24 (33%)	19 (25%)
Antidepressants	32 (14%)	12 (16%)	11 (14%)	9 (13%)	10 (13%)
Other	128 (58%)	38 (52%)	48 (62%)	42 (58%)	49 (64%)
Size of painful area at screening (cm^2), mean ± SD	364.8 ± 260.68	354.9 ± 293.78	394.5 ± 273.49	343.1 ± 205.92	326.5 ± 241.56

*Baseline pain level was defined as the mean of all available nonbiased Screening NPRS scores.
†A patient was defined as being on concomitant pain medication if pain medication started prior to day of treatment, continued on the day of treatment, and was taken for at least 7 days.

significantly different from control (P = .0240 and .0491, respectively). The results of the analyses for change in "worst pain for the past 24 hours" and "pain now" scores from baseline to weeks 2 to 8 and 2 to 12 were comparable to the results for change in "average pain for the past 24 hours" though statistical significance was not always reached (data not shown).

Upon examination of the study data it was found that, in general, male patients reported smaller changes in pain scores than female patients. This was noted in both the NGX-4010 (−21.5% for males vs. −32.7% for females) and control groups (12.9% for males vs. −21.7% for females) so that the resulting differences between the NGX-4010 and the control groups were similar for males and females. Given the difference in response between males and females and the fact that the 60-minute NGX-4010 group had a higher proportion of male patients (61%), post hoc analyses using a gender-stratified ANCOVA model were performed to investigate whether this gender imbalance had influenced the results. The results of the gender-stratified analysis (Table 3) differed slightly from the primary analysis presented in Table 2. There were significantly larger mean reductions in percent change from baseline to weeks 2 to 8 in the total NGX-4010, and 90- and 60-minute NGX-4010 groups (−27.1%, P = .0173; −27.7%, P = .0402; and −28.0%, P = .0331, respectively) compared to the pooled control group (−17.2%). Patients treated for 30 minutes reported a similar mean reduction in pain of 25.6%, but this was not significantly different from control (P = 0.104). Using logistic regression with gender, gender-by-treatment, and baseline pain as covariates, the proportion of patients reporting a ≥30% decrease in "average pain for the past 24 hours" score from baseline to weeks 2 to 8 was higher in each of the NGX-4010 groups (35–40%) compared to the pooled control group (29%), but the differences were not significant (all P > .05). However, the proportion of patients reporting a ≥50% decrease in "average pain for the past 24 hours" score from baseline to weeks 2 to 8 was significantly higher in each of the NGX-4010 groups (23–27%) compared to the pooled control group (10%; all $P \leq .05$).

Differences between the NGX-4010 patients and controls were observed regardless of concomitant pain-medication use, although greater differences between NGX-4010 patients and controls were observed in patients receiving concomitant pain medications compared to those not receiving concomitant pain medication. In patients using concomitant pain medications, differences in mean percent change in average pain score from baseline to weeks 2 to 8 were significant in all NGX-4010 dose groups (all $P \leq 0.05$) compared to control. The differences in patients not using concomitant pain medications were not significant in any of the NGX-4010 groups compared to the pooled control group.

During week 1, the total NGX-4010 group had a 27.3% mean reduction in "average pain for the past 24 hours"

Table 2. Summary of Change in ''Average Pain for the Past 24 Hours'' NPRS Scores from Baseline

	NGX-4010				Control
NPRS Scores	Total (N = 222)	90 min (N = 73)	60 min (N = 77)	30 min (N = 72)	Total (N = 77)
Baseline Scores					
Mean ± SE	5.6 ± 0.11	5.6 ± 0.17	5.4 ± 0.20	5.8 ± 0.20	5.3 ± 0.17
Weeks 2–8					
Change from baseline					
LS Mean* ± SE	−1.4 ± 0.11	−1.4 ± 0.20	−1.3 ± 0.19	−1.40 ± 0.20	−1.0 ± 0.19
P-value*	0.071	0.096	0.217	0.132	
% Change from baseline					
LS Mean* ± SE	−26.5 ± 2.11	−27.8 ± 3.68	−25.6 ± 3.58	−26.2 ± 3.71	−17.3 ± 3.61
P-value*	0.0286	0.0438	0.104	0.088	
Weeks 2–12					
Change from baseline					
LS Mean* ± SE	−1.3 ± 0.11	−1.3 ± 0.19	−1.2 ± 0.18	−1.3 ± 0.19	−0.8 ± 0.19
P-value*	0.0333	0.061	0.101	0.092	
% Change from baseline, LS Mean* ± SE	−25.0 ± 2.05	−26.1 ± 3.58	−24.4 ± 3.49	−24.4 ± 3.61	−14.7 ± 3.51
p-value[a]	0.0120	0.0240	0.0491	0.055	

Abbreviation: SE, Standard error.
*LS Mean and p-value were computed using ANCOVA to test for difference between the NGX-4010 and pooled control groups with baseline pain as a covariate.

scores compared to baseline (Fig 2). The pain reduction remained relatively constant over the first 7 weeks of the study and gradually decreased to a 19.7% reduction at week 12. The percent changes from baseline in "average pain for the past 24 hours" scores showed greater pain reduction in the total and each individual NGX-4010 dose compared to the pooled control group from weeks 2 through 12.

PGIC results demonstrated that more patients in the total NGX-4010 group reported improvement (slightly, much or very much) at week 4 (56%), week 8 (55%), and week 12 (55%) compared to the pooled control group (42%, 45%, and 41% for weeks 4, 8, and 12, respectively). The results of the CGIC were comparable to the results of the PGIC. More patients in the total NGX-4010 group were judged by the study investigators to have been improved (slightly, much, or very much) at week 4 (59%), week 8 (55%), and week 12 (52%) compared to the pooled control group (42%, 45% and 42% for weeks 4, 8 and 12, respectively). There were

Table 3. Summary of Efficacy (Post hoc Analyses)

	NGX-4010				Control
	Total (N = 222)	90 min (N = 73)	60 min (N = 77)	30 min (N = 72)	Total (N = 77)
Baseline scores, mean ± SE	5.6 ± 0.11	5.6 ± 0.17	5.4 ± 0.20	5.8 ± 0.20	5.3 ± 0.17
Weeks 2–8					
% Change from baseline, LS mean* ± SE	−27.1 ± 2.09	−27.7 ± 3.61	−28.0 ± 3.59	−25.6 ± 3.67	−17.2 ± 3.53
P-value*	0.0173	0.0402	0.0331	0.104	
Number (%) of patients with ≥ 30% decrease	83 (37%)	29 (40%)	27 (35%)	27 (38%)	22 (29%)
P-value†	0.054	0.067	0.162	0.108	
Number (%) of patients with ≥ 50% decrease	55 (25%)	17 (23%)	21 (27%)	17 (24%)	8 (10%)
P-value†	0.0049	0.0186	0.0050	0.0161	

Abbreviation: SE, Standard error.
*LS Mean and p-value were computed using a gender-stratified ANCOVA model to test for difference between NGX-4010 treatment and pooled control groups, with baseline pain score as covariate.
†P-value was computed using logistic regression to test for differences between NGX-4010 and pooled Control groups, with gender, gender-by-treatment, and baseline pain as covariates.

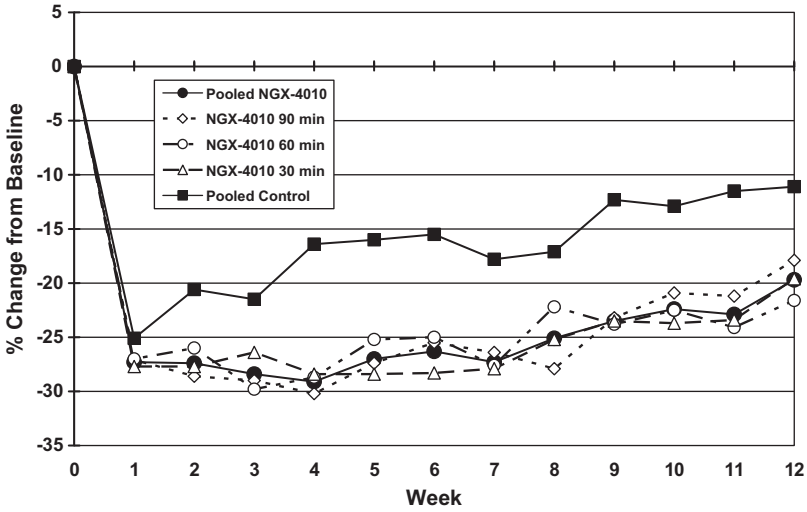

Figure 2. Mean Numeric Pain Rating Scale (NPRS) scores for 12 weeks after patch application in treated and control patients. NGX-4010 showed greater improvement in pain scores at all assessment times from week 2 to week 12.

significant differences in the 90-minute NGX-4010 group, compared to the control, in CGIC at weeks 4 ($P = .0168$) and 8 ($P = .0154$). No other treatment groups showed significant differences from control in PGIC or CGIC.

The total NGX-4010 group and the 60-minute NGX-4010 group reported significant ($P < .05$) improvements from screening to week 8 compared to the pooled control group in each BPI category except the "pain has interfered" categories. Patients treated with NGX-4010 for 30 minutes reported significant improvements from screening to week 8 compared to the control group in each BPI category except "pain at its least" and "pain has interfered." In the 90-minute NGX-4010 group, the only significant improvement from screening to week 8 compared to the pooled control group was in "pain has interfered with mood in the last 24 hours." The results of the SFMPQ frequently demonstrated larger improvements in the NGX-4010 groups compared to the pooled control group; however, the differences were not statistically significant (all $P > .05$).

Safety

NGX-4010 was generally well tolerated in the majority of patients. All but 3 of 222 patients (99%) completed at least 90% of the intended patch application. Two patients in the 90-minute NGX-4010 group and 1 patient in the 60-minute NGX-4010 group requested early removal of their patches due to application-site pain.

On the day of treatment, NPRS scores decreased following topical anesthetic application in all treatment arms. NPRS scores subsequently increased following patch application. Patients receiving 90-minute NGX-4010 treatments reported larger increases compared to patients receiving 60- or 30-minute NGX-4010 treatments. Mean maximum increases in NPRS score from pretreatment levels were 2.5, 1.7, and .5 for patients treated with NGX-4010 for 90, 60, and 30 minutes, respectively. In contrast, control patch application did not result in an increase in NPRS score above pretreatment levels. After patch removal, NPRS scores decreased to below pretreatment levels at 85 minutes after patch removal for patients receiving 90- and 60-minute NGX-4010 treatment, and at 55 minutes after patch removal for patients receiving 30-minute NGX-4010 treatments. On the evening of the day of treatment, all treatment groups had reductions in "pain now" NPRS scores compared to baseline.

Treatment-related pain was manageable in most patients with the use of local cooling or short-acting oral opioids. Overall, 51% of NGX-4010 and 4% of control patients received oxycodone on the day of treatment ($P < .0001$). The percentage of NGX-4010 patients using oxycodone increased with duration of patch application, from 40% of patients treated for 30 minutes to 66% in patients treated for 90 minutes. Few patients used hydrocodone/acetaminophen for treatment-related pain from days 0 to 5: 6% of NGX-4010 patients and 4% of controls.

Dermal irritation was generally mild and transient. At patch removal, 68% of NGX-4010 patients and 13% of control patients had dermal scores of 2 (definite erythema, readily visible, minimal edema, or minimal papular response) or more. More patients in the 90- and 60-minute NGX-4010 groups had a dermal score of ≥ 2 (84% and 78%, respectively) than patients in the 30-minute group (43%). Two hours after removal of the patch, 39% of NGX-4010 patients had dermal scores of ≥ 2 compared to 6% of controls. Six NGX-4010 patients (3%) and no control patients had dermal assessment scores >3 (erythema and papules). By week 4, the majority of patients in both the total NGX-4010 (88%) and pooled control (94%) groups had no evidence of dermal irritation (score = 0).

A total of 131 NGX-4010 patients (59%) and 43 control patients (56%) reported adverse events (Table 4). The incidence of treatment-emergent adverse events was similar among the 3 NGX-4010 dose groups (range 56%

to 64%). The most frequently reported adverse events were related to local application-site reactions. These application site reactions occurred more commonly in NGX-4010 patients, were mostly mild or moderate in severity, and transient. Treatment-associated erythema, and discomfort and pain on the day of treatment were not recorded as adverse events but were reported as dermal assessment scores or NPRS scores, respectively. Serious adverse events occurred in 4% and 6% of NGX-4010 and control patients, respectively. No serious adverse event was considered related to treatment.

There were no differences in neurosensory evaluations between the NGX-4010 and control groups. Treatment with NGX-4010 did not result in detectable changes in allodynia, light brush, pinprick, vibration, and warmth sensations.

Small, transient changes in blood pressure were noted during and shortly after the treatment procedure. Blood pressure decreased following topical anesthetic application and increased after patch application in both treatment groups. Increases in blood pressure seen during and after patch application were greater in the NGX-4010 groups than those observed in the control group. These changes paralleled increases in pain as measured by NPRS scores during this period with patients receiving 90- and 60-minute treatments reporting larger increases compared to patients receiving 30-minute treatments. Mean increases in blood pressure at all time points were <10 mm Hg for systolic and <6 mm Hg for diastolic blood pressures. Blood pressure began returning toward pretreatment values within 60 minutes after patch removal.

There was no evidence of an effect of NGX-4010 on any laboratory parameter evaluated. Hematologic and serum chemistry laboratory values showed no trends for any parameter during the 12-week study in either treatment group. No other safety issues were identified.

Discussion

This randomized, double-blind, dose-finding study demonstrates that, in patients with PHN, a single

Table 4. Most Frequently (≥3% of patients) Reported AEs

	NGX-4010 n (%)				*Control n (%)*
*Body System and MedDRA Preferred Terms**	*Total (n = 222)*	*90 min (n = 73)*	*60 min (n = 77)*	*30 min (n = 72)*	*Total (n = 77)*
Number of patients reporting one or more events	131 (59%)	41 (56%)	44 (57%)	46 (64%)	43 (56%)
Endocrine Disorders	**2 (1%)**	**0**	**0**	**2 (3%)**	**0**
Hypothyroidism	2 (1%)	0	0	2 (3%)	0
Gastrointestinal disorders	**32 (14%)**	**11 (15%)**	**12 (16%)**	**9 (13%)**	**13 (17%)**
Abdominal pain	1 (< 1%)	0	1 (1%)	0	3 (4%)
Diarrhea	7 (3%)	1 (1%)	4 (5%)	2 (3%)	3 (4%)
Nausea	13 (6%)	6 (8%)	3 (4%)	4 (6%)	7 (9%)
Vomiting	9 (4%)	4 (5%)	3 (4%)	2 (3%)	1 (1%)
General disorders and administration site conditions	**47 (21%)**	**14 (19%)**	**17 (22%)**	**16 (22%)**	**16 (21%)**
Application site pain	1 (< 1%)	1 (1%)	0	0	2 (3%)
Application site papules	3 (1%)	0	1 (1%)	2 (3%)	2 (3%)
Application site pruritus	17 (8%)	6 (8%)	4 (5%)	7 (10%)	9 (12%)
Application site swelling	3 (1%)	0	1 (1%)	2 (3%)	5 (6%)
Pain exacerbated	7 (3%)	1 (1%)	5 (6%)	1 (1%)	3 (4%)
Infections and infestations	**44 (20%)**	**12 (16%)**	**19 (25%)**	**13 (18%)**	**13 (17%)**
Gastroenteritis viral	3 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (3%)
Nasopharyngitis	15 (7%)	3 (4%)	6 (8%)	6 (8%)	1 (1%)
Pneumonia	3 (1%)	1 (1%)	2 (3%)	0	4 (5%)
Upper respiratory tract infection	4 (2%)	2 (3%)	1 (1%)	1 (1%)	2 (3%)
Musculoskeletal and connective tissue disorders	**16 (7%)**	**5 (7%)**	**8 (10%)**	**3 (4%)**	**6 (8%)**
Arthralgia	1 (< 1%)	0	0	1 (1%)	2 (3%)
Back pain	5 (2%)	3 (4%)	2 (3%)	0	2 (3%)
Nervous system disorders	**20 (9%)**	**7 (10%)**	**7 (9%)**	**6 (8%)**	**6 (8%)**
Dizziness	10 (5%)	5 (7%)	3 (4%)	2 (3%)	2 (3%)
Headache	7 (3%)	2 (3%)	2 (3%)	3 (4%)	2 (3%)
Respiratory, thoracic, and mediastinal disorders	**10 (5%)**	**5 (7%)**	**2 (3%)**	**3 (4%)**	**5 (6%)**
Cough	4 (2%)	1 (1%)	1 (1%)	2 (3%)	3 (4%)

*Counts indicate the number of patients reporting 1 or more AEs that mapped to the MedDRA (Version 7.0) system organ class. At each level of summarization, patients were only counted once. Treatment-emergent AEs reported in 3% or more of patients in the pooled NGX-4010 group or the pooled control group were included in this table.

application of NGX-4010 can provide pain relief that is maintained for up to 12 weeks following treatment. Pain scores began declining as early as the evening of the day of treatment and were reduced by 27% during week 1. The reduction in pain was sustained, remaining relatively constant over the first 7 weeks of the study and gradually decreasing to a 20% reduction at week 12. During the analysis of the study data, it was noted that males reported smaller reductions in pain scores than females in both the NGX-4010 and control groups. Because of this gender difference and a higher proportion of males in the 60-minute NGX-4010 group, post hoc gender-stratified analyses were also performed. In these post hoc gender-stratified analyses, the difference between the NGX-4010 90- and 60-minute duration group and the pooled control group was found to be statistically significant, with the 90- and 60-minute doses having a small numerical advantage compared to the 30-minute NGX-4010 dose. Given these results, the efficacy of the 60-minute dose was subsequently evaluated and shown to provide sustained pain relief for at least 12 weeks in 2, phase 3 studies in PHN.[1,3] Of note, these phase 3 studies also showed gender-related differences in changes in pain with a smaller percentage of pain reduction reported in males compared to females in both treatment groups (data on file).

Differential responses to pain[14] and pain treatment between genders have been described previously for opioids,[9,10,13,14,22] for nonsteroidal anti-inflammatory agents,[33] and for topical lidocaine,[25] and have been attributed to biological, cultural, social, and psychological differences. However, the study described here is, to our knowledge, the first study that not only demonstrated an effect of gender on reported pain response to NGX-4010 but also to control treatment (resulting in a similar effect size). Similar gender differences have been observed in subsequent studies with NGX-4010 [data on file] and clearly show that the effects of gender should be taken into account when analyzing pain studies.

NGX-4010 provided pain relief when administered alone or with other pain medications. This finding is important given that many patients require treatment with more than 1 pain medication for their neuropathic pain,[2] and a topically administered treatment such as NGX-4010 could provide an additive benefit to the effects of other systemically administered medications without the potential for drug interactions or increased systemic side effects. As previously reported,[3,17] changes in pain reported by patients who were using other pain medications were generally smaller than those in patients who were not receiving pain medications in both the NGX-4010 and control-treated patients. However, in contrast to previous reports,[3,17] the difference between NGX-4010 patients and controls in this study was larger in patients already taking other pain medications.

Treatment with NGX-4010 was well tolerated in the majority of patients, with nearly all patients completing the full duration of treatment. Although an initial increase in pain was evident during and after NGX-4010 patch application, pain returned to near preprocedure levels within 85 minutes after patch removal, and by the evening of the day of treatment, patients had on average less pain compared with baseline. Mild, transient dermal irritation was observed in a majority of patients after patch removal. Capsaicin-related local application-site reactions were the most common adverse events and were transient, mostly mild to moderate, and self-limited. Application-site pain could be adequately managed by pretreatment with a local anesthetic and local cooling or, if needed, short-acting oral opioid analgesics. Small transient increases in systolic and diastolic blood pressure seen during or shortly after treatment were likely due to treatment-associated discomfort. In NGX-4010 patients, pain and blood pressure increases during and after patch application, dermal irritation, the proportion of patients using medication for treatment-related pain, and the mean oxycodone dose on the treatment day, all increased with increased duration of patch application.

No reduction in neurosensory function following NGX-4010 administration was observed, suggesting that capsaicin treatment can lead to pain reduction without clinically relevant changes in protective sensation. Indeed, when used as a topical analgesic, capsaicin's mechanism of action involves the selective and reversible defunctionalization of cutaneous sensory nerve endings expressing TRPV1.[6] However, other skin sensory nerve endings, including those arising from Aβ-fibers, which transduce tactile and proprioceptive stimuli, and nonTRPV1-expressing Aδ-fibers, which are also capable of transducing thermal stimuli, remain intact and functional.[6,20,31]

One of the limitations of this study was the need to address the difficulty in blinding the use of topical high-concentration capsaicin by using a low-concentration capsaicin control instead of an inert placebo. The low-concentration patch delivered an amount of capsaicin that, like NGX-4010, was capable of producing local application-site reactions. However, dermal irritation, NPRS scores on the day of treatment, and use of medication for treatment-related pain were lower in control patients compared to patients treated with NGX-4010. Nevertheless, it may have been sufficiently difficult to break the blind based on an individual patient's initial reaction to treatment. The use of a low-concentration capsaicin control patch may have led to an underestimation of the efficacy of NGX-4010 because of an enhanced response in the control group, due either to application-site reactions resulting from the capsaicin in the control patch or to an intrinsic analgesic effect of the low-concentration capsaicin control patch.

In summary, a single topical application of NGX-4010 provided pain reduction that was maintained for up to 3 months in patients with PHN. A treatment duration of 60 minutes was found to be the lowest effective dose and was generally well tolerated.

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NGX-4010 C108 Study Group

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