Original Research Articles

NGX-4010, a High-Concentration Capsaicin Patch, for the Treatment of Postherpetic Neuralgia: A Randomized, Double-Blind, Controlled Study with an Open-Label Extension

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Abstract

Objectives. To assess the efficacy, tolerability, and safety of NGX-4010, a high-concentration capsaicin dermal patch (capsaicin 640 μg/cm², 8%) in patients with postherpetic neuralgia (PHN).

Methods. Patients were randomized to receive NGX-4010 or control patch in a 4-week, double-blind study. This was followed by an open-label extension phase (up to 48 weeks total) where patients could receive up to three additional treatments no sooner than 12 weeks after initial treatment. The primary efficacy variable was mean change from baseline in mean morning and evening numerical pain rating scale (NPRS) scores.

Results. During days 8–28 after the double-blind treatment, NGX-4010 patients had a mean change in NPRS scores from baseline of −32.7% compared with −4.4% for control patients (P = 0.003). Mean NPRS scores decreased from baseline during week 1 in both treatment groups, remained relatively stable through week 12 in NGX-4010 patients, but returned to near baseline during weeks 2–4 in controls. Mean change in NPRS scores from baseline during weeks 2–12 was −33.8% for NGX-4010 and +4.9% for control recipients. A similar decrease in NPRS scores from baseline was maintained with subsequent NGX-4010 treatments, regardless of the number of treatments received. Transient increases in application site pain were adequately managed with analgesics. No increases in application site reactions or adverse events were observed with repeated treatments. No patients discontinued the study due to an adverse event.

Conclusion. NGX-4010 is a promising topical treatment for PHN patients, which appears to be tolerable, generally safe, and effective.

Key Words. Neuropathic Pain; Postherpetic Neuralgia; Capsaicin

Introduction

Postherpetic neuralgia (PHN) is a chronic pain disorder resulting from reactivation of the varicella zoster virus that initially causes chickenpox [1–4]. After chickenpox has healed, herpes zoster remains dormant in the peripheral nervous system. A second outbreak of herpes zoster (known as shingles) can occur years later. The definition of PHN varies, but it is typically defined as the presence of pain more than 1–6 months after the clearing of skin lesions caused by shingles.

PHN occurs in about 8–19% of patients with herpes zoster, although the likelihood of developing PHN after shingles increases with age [2,3,5]. Other risk factors for developing PHN include severity of pain in the acute phase, severity of rash, and a painful prodrome [6].
High-Concentration Capsaicin Patch for Postherpetic Neuralgia

Though the use of antiviral therapy has been shown to reduce the incidence of PHN [7], the effect of antiviral therapy on the prevalence of PHN depends on several factors including the proportion of zoster patients using antiviral medication, patient compliance to antiviral medication, and the growth rate of the elderly population [7].

Systemic agents used to treat PHN include tricyclic antidepressants, anticonvulsants, and opioids [8,9]. In general, these agents only partially reduce pain [8,10,11] and their benefits may be compromised by tolerability and safety issues (especially in elderly patients), potential drug interactions, a slow onset of action, the need for dose titration, and the administration of multiple daily doses [8,12]. These limitations have prompted interest in the use of localized, nonsystemic therapies, including a topical lidocaine patch [13,14], and topically applied capsaicin [15–17].

Capsaicin, the pungent active ingredient in chili peppers (Capsicum annuum) [18], is an agonist of the transient receptor potential vanilloid 1 (TRPV1) receptor, a ligand-gated cation channel preferentially expressed in nociceptive sensory nerves [18]. Activation of the TRPV1 receptor by capsaicin depolarizes sensory nerve endings and generates electrical excitation, initiating signal transmission to the spinal cord. However, continuous TRPV1 receptor activation by capsaicin leads to the release of high levels of intracellular calcium and related enzymatic and osmotic changes [18]. The net effect of these processes is functionalization, the impairment of nociceptor function for extended periods [18].

Although low-concentration capsaicin creams (0.025 and 0.075%) have demonstrated favorable results in clinical trials, these agents must be applied multiple times daily, cause burning pain each time they are applied during the early phase of treatment, and provide only modest pain relief [15–17]. To counteract these limitations, while retaining the benefits of capsaicin therapy, NGX-4010 has been developed. NGX-4010 is a high-concentration capsaicin dermal patch (capsaicin, 8%) that delivers a therapeutic dose of capsaicin during a single 60-minute application. This article describes the first study that evaluated the efficacy, safety, and tolerability of NGX-4010 in patients with PHN and reports on the findings of an initial 4-week double-blind, randomized controlled study followed by an extension during which patients could receive three additional open-label treatments for a total duration of 48 weeks.

Methods

Patients

Patients 18 years of age or older with a diagnosis of PHN and an average Numeric Pain Rating Scale (NPRS) [19] score of 3–8 (inclusive) were eligible for the 4-week study if at least 6 months had elapsed since shingles vesicle crusting and if the patients had painful areas located below the neck (maximum of two sites) with a combined surface area between 100 cm² and 1,000 cm². Patients taking concomitant pain medications were required to maintain a stable dose from at least 21 days before study patch application and to continue the same dose throughout the study. Females were of nonchildbearing potential (defined by absence of menses for a minimum of 3 months or surgically sterile) and males agreed to use adequate contraception for 60 days after receiving study medication. Exclusion criteria included diffusely distributed neuropathic pain or significant pain outside the target areas; an implanted medical device for the treatment of neuropathic pain; use within the past 21 days of topicaly applied agents including capsaicin-containing products, a 5% lidocaine patch or similar products, nonsteroidal anti-inflammatory drugs or aspirin, local anesthetics, or steroids; opioid use within the past 21 days; current use of any class 1 anti-arrhythmic drug; and opioid tolerance.

Patients were eligible for the open-label extension study if they completed the 4-week double-blind study and continued to meet inclusion and exclusion criteria for that study.

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

Study Design and Procedures

To assess the implementation and the tolerability of the treatment procedure, six patients received an initial single 60-minute open-label patch application of NGX-4010 (capsaicin 640 mg/cm², 8%; NeurogesX, Inc., San Mateo, CA). This was followed by the double-blind phase in which 38 patients were randomized to receive either NGX-4010 (N = 26) or a low-concentration capsicain (3.2 mg/cm², 0.04%) control patch (N = 12). To provide adequate study blinding, a low-concentration capsaicin patch was utilized for the control. It was expected that the low-concentration capsaicin control patch would produce local erythema and burning, but not have a significant analgesic effect. After a single 60-minute application, patients were followed for 4 weeks.

During the double-blind period, treatment assigned to individual patients was determined by a randomization scheme prepared by Cardinal Health (Morrisville, NC). Numbers were assigned only once, and no patient was randomized into the study more than once. The NGX-4010 and control patches were identical in appearance, as were the blinded study drug kits.
Patients who completed the 4-week controlled study and met the entry criteria were eligible to enroll in the open-label extension phase (Figure 1). During the extension phase, patients could receive up to three additional open-label treatments with NGX-4010. Each treatment was considered a cycle. Cycle 0 refers to the first treatment and cycles 1–3 refer to each of the possible re-treatments. The first re-treatment could not be administered until at least 12 weeks after the initial treatment, and the interval between additional treatments was to be at least 6 weeks, based on pain recurrence. No treatment could be performed beyond 40 weeks after the initial double-blind treatment. Patients were followed for a maximum of 48 weeks after the initial double-blind treatment.

Study Treatments

Patients were pretreated with a topical local anesthetic cream (ELA-Max®, lidocaine 4%; Ferndale Laboratories, Inc., Ferndale, MI) for 60 minutes before application of the study patch. Following removal of the topical anesthetic, NGX-4010 or the control patch was applied for 60 minutes to the painful area(s), up to a maximum area of 1,000 cm². Local cooling as well as oxycodone hydrochloride oral solution (1 mg/mL) could be administered as required for discomfort during treatment application. Following patch application, patients could take opioid rescue medication (hydrocodone bitartrate/acetaminophen 5 mg/500 mg) for up to 5 days as needed.
scores from baseline during weeks 2–12 after initial treat-

Efficacy Assessments and Analyses

Efficacy was assessed using the NPRS [19], the Brief Pain Inventory (BPI) Short Form [20], and a self-assessment of response to treatment (SAT) questionnaire. The NPRS is an 11-point scale (0–10) in which 0 indicates no pain and 10 indicates the worst possible pain [19]. On the treatment day, scores were recorded immediately before treatment, at 15-minute intervals during the treatment period (anesthetic and patch), immediately after patch removal, and every 15 minutes until 1 hour after treatment. On all subsequent study days through study completion, patients used the NPRS to rate “pain level now” in the morning and the evening as part of a diary record. The BPI is an index of pain severity, pain relief, and the effects of pain on the patient’s ability to function [20,21]. The SAT is a questionnaire developed by NeurogesX that includes the following five questions: 1) How do you assess the pain relief you achieved by the treatment in this study; 2) how do you assess the change in activity you achieved by the treatment in this study; 3) how has your quality of life improved; 4) would you repeat this treatment again; and 5) how do you compare the treatment you received during the study to previous medication or therapies for your pain?

Four-Week Randomized Study

In the 4-week double-blind study, the primary efficacy variable was the change from baseline in the mean morning and evening NPRS scores during days 8–28. Baseline NPRS scores were recorded from days −10 to −1 prior to treatment. For missing morning and evening NPRS scores on days 2–28, the most recent prior morning NPRS score was carried forward. To avoid the potential confounding effect of allowed opioid rescue medications during days 0–5, week 1 NPRS scores were not included in the primary analysis. Efficacy analyses were based on the intent-to-treat population, defined as all patients who were randomly assigned and received study medication. Secondary efficacy variables were change in weekly mean of morning and evening average NPRS scores, change in BPI from screening to termination, and SAT at termination. All efficacy measures were summarized with descriptive statistics. The Wilcoxon Rank Sum test was used to test for differences between treatment groups for all variables except change in weekly NPRS scores and SAT responses. Changes in weekly NPRS scores were not compared between treatment groups, and SAT responses were compared using the Cochran-Mantel-Haenszel (CMH) Row Mean Scores test with modified ridit scores.

Extension Study

In the extension phase, the primary efficacy variables were: 1) change in mean morning and evening NPRS scores from baseline to termination of the extension study; and 3) change in mean morning and evening NPRS scores from baseline during cycle 0; 2) the change in BPI scores from extension study entry to termination; and 3) SAT at termination.

Safety and Tolerability Assessments and Analyses

Four-Week Randomized Study

Safety and tolerability assessments during the 4-week study included adverse events, dermal assessment (0–7-point severity score) [22], concomitant medication use, electrocardiogram, clinical laboratory tests, vital signs, physical examination, treatment pain rating, and use of rescue medication. For the treatment pain rating, patients evaluated their pain during and immediately after treatment as worse, better, or unchanged. In addition, NPRS scores were recorded after treatment at 15, 30, 45, and 60 minutes, day 1 morning and evening, and day 2 morning to evaluate treatment-related pain. Differences between the treatment groups were compared using the t-test for continuous variables and the Fisher exact test for categorical variables. The CMH Row Mean Score test was used to compare the maximum level of dermal response and the proportion of patients reporting a pain increase on the NPRS during the first 48 hours after patch application. The Fisher exact test was used to compare between-group differences in the proportion of patients using rescue medication (oxycodone and/or hydrocodone bitartrate/acetaminophen) after patch application.

Extension Study

In addition to assessments used in the 4-week study, the extension study included a sensory assessment, which determined whether sharp and dull stimuli produced similar sensations in the treatment area and a contralateral area. Percentage of allodynia in the treatment area was also determined. Sensory assessments were performed at study entry, treatment, follow-up weeks 12, 24, and 36, and termination visit. During treatment visits, sensory assessment was performed prior to anesthetic application and after anesthetic removal. Determination of the area of allodynia (%) was performed prior to anesthetic application only. Treatment-emergent adverse events and the proportions of patients reporting a pain increase during, immediately after, and in the first 48 hours after treatment were reported separately for each treatment cycle.
Results

Patient Disposition

Forty-four patients received study drug; six in the open-label, and 38 in the double-blind study phases (Figure 1). One NGX-4010 recipient in the double-blind phase withdrew prematurely due to an adverse event not related to the study drug. Patient demographic and clinical characteristics are shown in Table 1. The control group had a greater proportion of males than the NGX-4010 group (75% vs 23%) and a longer mean duration of PHN (4.4 vs 3.5 years). Twenty-four patients were subsequently enrolled in the extension study; 15 from the NGX-4010 group, and nine from the control group (Figure 1). Twenty-one patients (88%) received NGX-4010 during the extension phase; three patients chose not to receive treatment. Of the 21 patients who were treated, six received one treatment, six received two treatments, and nine received three treatments. Two patients terminated the study prematurely after one re-treatment because of unsatisfactory therapeutic response.

Efficacy

Four-Week Randomized Study

Baseline mean morning and evening NPRS scores were similar between patients randomized to receive either NGX-4010 (5.8 ± 1.3) or control (6.0 ± 0.8; Table 2). Patients treated with NGX-4010 had a mean 32.7% decrease from baseline in mean morning and evening NPRS scores during days 8–28, compared with a 4.4% decrease for the control group (P = 0.003). The greatest decrease from baseline in NPRS scores occurred during the first week after treatment, and was evident in both treatment groups (Figure 2). The decrease in NPRS scores remained relatively stable throughout the 4-week study period in the NGX-4010 group, but returned to near baseline levels during weeks 2–4 in the control group.

BPI results demonstrated statistically significant differences between the NGX-4010 and control groups, for “pain at its worst in the last 24 hours” (mean change

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics and clinical characteristics of 38 patients included in the 4-week randomized double-blind study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGX-4010 (n = 26)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>74.4 (7.4)</td>
</tr>
<tr>
<td>Male, %</td>
<td>23%*</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25 (96)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Duration of PHN, mean (SD), y</td>
<td>3.5 (2.5)</td>
</tr>
<tr>
<td>Baseline pain level, mean (SD)†</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>Size of treatment area, mean (SD), cm²</td>
<td>352.8 (181.4)</td>
</tr>
</tbody>
</table>

* P = 0.004 vs control.
† Baseline pain level was defined as the mean of the day −10 to day −1 morning and evening average NPRS scores.
SD = standard deviation; PHN = postherpetic neuralgia; NPRS = Numeric Pain Rating Scale.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical efficacy of NGX-4010 vs control in patients with PRN included in the randomized 4-week study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGX-4010 (n = 26)*</td>
</tr>
<tr>
<td>NPRS scores</td>
<td></td>
</tr>
<tr>
<td>Baseline,† mean (SD)</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>Change from baseline during days 8–28, mean (SD)</td>
<td>−1.8 (1.8)</td>
</tr>
<tr>
<td>Percentage change from baseline during days 8–28, mean (SD)</td>
<td>−32.7 (29.6)</td>
</tr>
<tr>
<td>BPI scores</td>
<td></td>
</tr>
<tr>
<td>Pain at its worst (last 24 hours), mean (SD)</td>
<td>6.7 (1.7)</td>
</tr>
<tr>
<td>Change from baseline to day 28/termination</td>
<td>−1.7 (2.0)</td>
</tr>
<tr>
<td>Average pain, mean (SD)</td>
<td>5.4 (1.2)</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
</tr>
<tr>
<td>Change from baseline to day 28/termination</td>
<td>−1.3 (1.7)</td>
</tr>
</tbody>
</table>

* One patient discontinued the study prematurely and did not complete the BPI.
† Baseline pain level was defined as the mean of the day −10 to day −1 morning and evening average NPRS scores.
PHN = postherpetic neuralgia; NPRS = Numeric Pain Rating Scale; SD = standard deviation; BPI = Brief Pain Inventory.
from baseline −1.7 vs +0.3 for NGX-4010 and control groups, respectively; \( P = 0.014 \) and “average pain” (−1.3 vs +0.4; \( P = 0.032 \), respectively) (Table 2). For the remaining items, no difference was observed between the NGX-4010 and control groups. Responses to each SAT question were not different between the double-blind treatment groups.

Extension Study

The mean change from baseline in mean morning and evening NPRS scores during weeks 2–12 after the initial double-blind treatment was −33.8% (95% CI: −51.3, −16.4) for 13 NGX-4010 patients vs +4.9% (95% CI: −11.8, 21.6) for eight control patients. Fifty-three per cent of NGX-4010 patients had a ≥33% decrease from baseline in mean morning and evening NPRS scores during weeks 2–4, 56% during weeks 5–8, and 78% during weeks 9–12. None of the control patients had a ≥33% decrease in NPRS score at any time point.

The mean percentage change in NPRS scores from baseline observed in patients treated with NGX-4010 in the double-blind phase was similar to that seen in patients who received subsequent NGX-4010 treatments in the extension phase, and the magnitude of effect remained the same irrespective of the number of treatments: −31.4% (95% CI: −43.5, −19.2) after the first open-label treatment (n = 21); −30.0% (95% CI: −43.1, −16.9) after the second open-label treatment (for 15 patients receiving at least two open-label treatments); and −34.1% (95% CI: −52.7, −15.6) after the third open-label treatment (for nine patients receiving three open-label treatments; Table 3).

Safety and Tolerability

Four-Week Randomized Study

Eighty-eight per cent of NGX-4010 patients and 92% of control patients completed the full 60-minute patch application (28 of 32 NGX-4010 recipients and 11 of 12 controls). Oxycodone use on day 0 was higher in the NGX-4010 group compared with controls (69% vs 33%; \( P = 0.075 \)). Similarly, hydrocodone bitartrate/acetaminophen use on days 0–5 was greater in the NGX-4010 group than in the control group (62% vs 42%, respectively; \( P = 0.307 \)).

Three patients (12%, all in the NGX-4010 group) had a maximum dermal assessment score of 3, all other scores

Table 3 Summary of mean morning and evening NPRS scores during the extension study

<table>
<thead>
<tr>
<th>NPRS Score (Week 2–12)</th>
<th>n</th>
<th>Mean ± SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving at least 1 treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline*</td>
<td>21</td>
<td>5.8 ± 1.1</td>
<td>5.3, 6.3</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1†</td>
<td>−31.4 ± 26.8</td>
<td>−43.5, −19.2</td>
<td></td>
</tr>
<tr>
<td>Patients receiving at least 2 treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline*</td>
<td>15</td>
<td>5.9 ± 1.1</td>
<td>5.3, 6.5</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 2†</td>
<td>−30.0 ± 23.7</td>
<td>−43.1, −16.9</td>
<td></td>
</tr>
<tr>
<td>Patients receiving 3 treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline*</td>
<td>9</td>
<td>6.1 ± 1.3</td>
<td>5.1, 7.1</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 3†</td>
<td>−34.1 ± 24.2</td>
<td>−52.7, −15.6</td>
<td></td>
</tr>
</tbody>
</table>

* Baseline score was defined as the mean of the day −10 to day −1 (i.e., prior to 4-week double-blind study) morning and evening NPRS scores.
† Percentage change from baseline = 100 × ([mean rating at time point] − [mean baseline rating]) ÷ (mean baseline rating). NPRS = Numeric Pain Rating Scale.
were transient increases in NPRS scores of 33% from baseline at 24 and 48 hours after treatment compared with control patients (38% vs 8%, $P = 0.007$ for each time point).

Overall, 42% of NGX-4010 recipients and 17% of controls had at least one adverse event in the double-blind study period. Adverse events that occurred in more than one patient in any treatment group are presented in Table 5. The most common adverse events reported with NGX-4010 were fatigue (12%) and dizziness (12%), each occurring in 3 of 26 NGX-4010 patients, but in none of the control patients. Nausea, pruritus, and hypertension were each reported in two NGX-4010 recipients, pruritus was also reported in one patient in the control group. Nausea, fatigue, and dizziness were considered treatment-related on one occasion, and pruritus was considered treatment related in both NGX-4010 treated patients. One serious adverse event, subarachnoid hemorrhage in an 82-year-old woman with a history of hypertension, resulted in premature study discontinuation, and was considered by the investigator to be remotely or not related to study drug. No deaths occurred during the study.

No clinically significant changes in laboratory values, vital signs, and physical findings were observed during the extension study. Sensory examinations of the treated areas and determination of percentage of allodynia in painful areas were highly variable, with no evident trend over the course of this study that would indicate sensory nerve damage with repeated treatment.

Discussion

The results of this first study of NGX-4010 in patients show that the high-concentration capsaicin NGX-4010 patch reduces PHN pain to a significantly greater extent than a low-concentration capsaicin control patch over a 28-day period. Patients treated with NGX-4010 experienced a mean decrease in NPRS score from baseline of approximately 30% that was maintained over the 4-week study period. In contrast, an initial decrease from baseline in mean NPRS scores seen in the control group was short lived, with scores returning to near baseline level during

Table 5  Treatment-emergent adverse events that occurred in $>1$ patient in any treatment group: 4-week double-blind study

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>NGX-4010 (n %)</th>
<th>Control (n %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>11 (42)</td>
<td>2 (17)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pruritus NOS</td>
<td>2 (8)</td>
<td>1 (8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension NOS</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

NOS = not otherwise specified.
weeks 2–4 after patch application. The long-term extension study shows that the reduction in NPRS score seen after NGX-4010 patch application is maintained during weeks 2–12 and during subsequent re-treatment cycles over a 48-week period.

Responses on the BPI were consistent with the NPRS results showing that patients’ pain relief, pain scores, and the effect of pain on daily activities were maintained from entry into the extension to study termination.

NGX-4010 treatment overall appeared to have a good safety profile and to be well tolerated. Study treatment induced an initial, transient increase in pain; however, pain was self-limiting and could be adequately managed with local cooling and short-acting opioids. Nearly all patients were able to complete the 60-minute exposure time. Dermal irritation was generally mild and resolved within a few days. There was no clinical evidence of cumulative toxicity or a detrimental effect on sensory function upon re-treatment over the 48-week study period. No identifiable safety concerns were noted from the adverse events, vital signs, and laboratory data collected.

Limitations of this study include the difficulty of blinding topical high-concentration capsaicin. To prevent unblinding due to local application site reactions, a low-concentration capsaicin control rather than an inert placebo was used in this study. The low-concentration patch delivered an amount of capsaicin that, like NGX-4010, was capable of producing local application site reactions. For example, dermal assessment scores demonstrated that many control patients (58%) experienced at least some level of dermal irritation. Therefore, visual clues, such as application site erythema, were not a reliable indicator of treatment assignment. The treatment procedure induced pain in both NGX-4010 and control patients with 42% of control patients using opioid rescue medications for treatment-related discomfort.

Although no negative trends on sensory function were observed, only sharp and dull sensations were assessed throughout the 48 week study. However, results of a subsequent, 1-year, open-label study of repeated applications of NGX-4010 in patients with PHN or HIV-associated distal sensory polyneuropathy (HIV-DSP) showed no evidence of impaired neurosensory function evaluated by standardized sensory evaluations (deep tendon reflexes, vibration and warmth and sharp sensation for HIV-DSP patients and light brush, pinprick, warmth and vibration for PHN patients) [23].

Other limitations include the small sample size and the variability of response. In addition, the study was limited by imbalances in gender and duration of PHN between the treatment groups. The gender imbalance proves particularly important because subsequent studies showed a smaller response to both NGX-4010 and control treatment in males compared with females, but a similar treatment difference between NGX-4010 and control for both genders (data on file). The high proportion of males in the control group may be one factor contributing to the smaller response seen in the control group in this study compared with the control response seen in a subsequent large, randomized controlled 12-week trial in patients with PHN [24]. Nevertheless, the findings of this study are consistent with this subsequent randomized controlled trial in patients with PHN that evaluated the efficacy of a single 60-minute application of NGX-4010 and showed a significant reduction in pain over a 12-week period [24], as well as with two previously published studies of NGX-4010 in patients with painful HIV-DSP [25,26].

Conclusions

The findings of this 4-week double-blind study and its open-label extension phase suggest that a 1-hour application of NGX-4010 can reduce pain in patients with PHN and that pain reductions can be maintained with repeated administrations over a 1-year period. NGX-4010 may offer a generally safe and effective topical therapy for patients with PHN. Further studies are needed to confirm these findings.

NGX-4010 C102/106 Study Group

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