

Novel High-Concentration Capsaicin Patch for the Treatment of Painful HIV-Associated Distal Symmetrical Polyneuropathy: Results of an Open Label Trial

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ABSTRACT

This open-label multi-center study evaluated the efficacy, safety and tolerability of high-concentration capsaicin patches (640 µg/cm²) in the treatment of HIV-DSP. Twelve patients at 3 centers in the U.S. were treated once and followed for 12 weeks. Treatment consisted of a topical anesthetic application for 1 hour, followed by a 1-hour patch application to the most painful areas of the feet, up to 1000 cm². Patients recorded their pain intensity daily on an 11-point numerical scale. The primary efficacy endpoint was % change from baseline in the “average pain for the past 24 hours” numerical pain score (i.e., average of scores during Weeks 2–12, compared to baseline). Average pain decreased to a mean of 3.2 from a pre-treatment mean of 5.6, corresponding to a decrease of 40% (p=0.003). Sixty-seven percent of patients experienced a pain decrease of 30% or more, while 33% experienced pain decreases of at least 50%. Pain decrease was noted during the first week after treatment and remained stable throughout the 12-week observation period. Despite expected, self-limited pain increases during and shortly following treatment, overall tolerability was good. Other treatment-related adverse events were usually mild and transient. Treatment with high-concentration capsaicin patch resulted in substantial pain reduction in patients with HIV-DSP over 12 weeks after a single 1-hour application. Tolerability was good and no significant safety issues were noted. These promising findings warrant further evaluation in a larger, randomized, controlled study.

INTRODUCTION

Activation by capsaicin of vanilloid receptors (TRPV1) expressed in dermal and epidermal nociceptive sensory nerve fibers results in burning pain sensations followed by functional inactivation of these nociceptors. Low-concentration capsaicin creams are used to treat various neuropathic pain conditions, but are limited by pain and patient non-compliance. In a prior controlled study, a novel high-concentration capsaicin patch (NGX-4010) resulted in 4 weeks of pain relief after a single 1-hour administration in patients with postherpetic neuralgia, without systemic capsaicin exposure.

We report here the results of a pilot study evaluating this new investigational treatment in painful HIV-associated distal symmetrical neuropathy (HIV-DSP).

METHODS

Study C109 was an open-label evaluation of NGX-4010 (Capsaicin Dermal Patch, 640 µg/cm²) at 3 U.S. sites. Twelve subjects with HIV-DSP due to HIV disease and/or antiretroviral toxic neuropathy with moderate to severe pain in both feet were enrolled. Painful areas up to a total surface area of 1000 cm² were treated. **Key eligibility criteria** included:

- Unbroken skin over the treatment areas
- Stable systemic pain medications, if any, from 21 days before study start
- No concomitant use of topical pain medications
- No significant pain of other etiology

Subjects were treated once and followed for 12 weeks.

Efficacy was assessed by daily pain intensity scores on an 11-point scale (0=no pain, 10=worst possible pain), as documented in patient diaries. Subjects were asked to rate each evening:

- Current pain
- Average pain during the past 24 h
- Worst pain during the past 24 h

These assessments were performed starting 7 to 10 days before treatment through the end of the study. The primary efficacy endpoint was defined as the % change in **average pain** (mean of days 8-84), compared to baseline.

TREATMENT PROCEDURES Treatment consisted of a topical anesthetic (lidocaine 4% cream) applied for 1 hour, followed by 1 hour application of NGX-4010 patches. Upon patch removal, cleansing gel was applied for 1 minute and removed, followed by washing the treated areas with soap then water [Fig. 1].



A. Application of topical anesthetic
B. Application of NGX-4010 patches
C. Application / removal of cleansing gel

Figure 1: Demonstration of Treatment Procedures

RESULTS

PATIENT DISPOSITION All subjects were evaluable for safety and efficacy, and analyses were performed using data from the entire study population. One subject discontinued participation early for personal reasons, and another subject was lost to follow-up after week 5. Baseline characteristics are shown in Table 1.

BASELINE CHARACTERISTICS Subjects with a range of HIV-DSP duration (0.5 to > 10 years), baseline average pain levels (3.6 to 8.2, on 0-10 scale), and concomitant pain medication use were enrolled. Mean treatment area size was 493 cm² (range 45-880 cm²). Four of 12 subjects were taking one or more of the potentially neurotoxic dideoxynucleoside antiretroviral agents at entry.

| Age [yr] | | Duration of HIV-DSP [yr] | |
|------------------|---------|------------------------------|------------|
| Mean | 44 | Mean | 3.6 |
| Min - Max | 32 - 52 | Range | 0.5 - 10.1 |
| Gender | | Baseline Avg. Pain Level | |
| Female | 3 (25%) | Mean (SD) | 5.6 ± 1.4 |
| Male | 9 (75%) | Range | 3.6 - 8.2 |
| Race | | Concomitant Pain Medications | |
| African American | 6 (50%) | Anticonvulsants | 7 (58%) |
| White | 6 (50%) | Antidepressants | 0 (0%) |
| | | Opioids | 7 (58%) |
| | | Any of above | 8 (67%) |

Table 1: Summary of Baseline Characteristics

EFFICACY The mean percent change in average pain was -40% (95% confidence interval -60.7% to -18.7%, p = 0.003). Pain decreases were noted as early as the first week after treatment and remained stable throughout the 12-week observation period. Average pain reductions stably exceeded 40% during weeks 2–10 [Fig. 2].

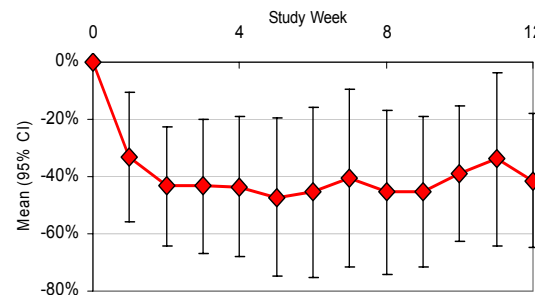


Figure 2: Percent Change from Baseline for Average Pain by Week

| Baseline (Day -10 to Day -1) | |
|------------------------------|----------------|
| Mean | 5.6 |
| Min - Max | 3.6 - 8.2 |
| Days 8 to 84 | |
| Mean | 3.2 |
| Min - Max | 0.9 - 6.7 |
| Change from Baseline | |
| Mean | -2.4 |
| 95% CI | (-3.9, -0.8) |
| Min - Max | -7.0 - 1.0 |
| p-value vs. baseline | 0.01 |
| Percent Change from Baseline | |
| Mean | -40 |
| 95% CI | (-60.7, -18.7) |
| Min - Max | -85.7 - 17.3 |
| p-value vs. baseline | 0.003 |

Table 2: Average in Past 24 Hours Pain Score

Individual patient change in average pain between days 8 to 84 compared to subjects' pre-treatment values is shown in Figure 3. With the exception of a subject whose pain remained unchanged and another whose pain slightly increased after treatment, the remaining subjects reported pain reductions of -17% to -85%.

Two-thirds of patients were considered responders, based on a threshold of at least 30% pain reduction.

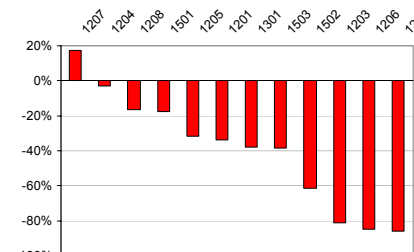


Figure 3: Percent Change from Baseline for Average Pain by Subject

Similar results were obtained for “worst pain during the past 24 hours” and “pain now” scores that were also recorded each evening [Fig. 4].

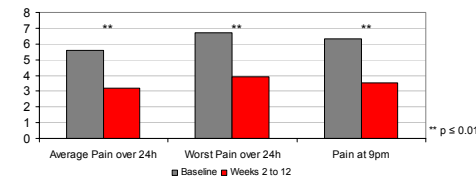


Figure 4: Mean Pain Intensity Scores during Baseline and after Treatment

TOLERABILITY Overall, good tolerability was observed with 100% of subjects able to complete treatment. Consistent with observations from earlier studies, exposure to high-concentration capsaicin patches led to some pain increase. Two-thirds of subjects noted at least one pain score more than 30% above their baseline level during the first 48 hours after patch application. Fifty-eight percent of subjects required Roxicodeone rescue medication on the day of treatment, and 25% reported using Vicodin during the first 5 days after treatment.

SAFETY Seven subjects reported at least one adverse event during the study. At least one adverse event for five of these subjects was considered by the investigator to be possibly or probably study drug-related. A serious adverse of “severe pain and paraesthesia” judged as definitely related to investigational drug was reported in a 48-year-old male. This subject's ongoing use of fentanyl patch 200 mcg per hour and oxycodone 80 mg BID likely precluded the ability to relieve treatment-associated discomfort with orally administered narcotics, such as Roxicodeone.

CONCLUSIONS

The study showed substantial and statistically significant pain decreases over 12 weeks after a single 1-hour treatment. The mean decrease in average pain was 40%, and 67% of subjects were responders (pain decrease of at least 30%). Similar results were seen using worst pain during the past 24 hours and pain now scores. Pain decreases were observed as early as the first day and remained stable throughout the 12-week follow-up period. Importantly, further pain relief was seen even for subjects already using other neuropathic treatment regimens, including opioid and anticonvulsant medications. These results suggest that high-concentration capsaicin patches could be a very effective and safe treatment alternative for patients suffering from painful HIV-DSP. Efficacy and safety is being confirmed in a larger randomized, controlled study.