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Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy

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ABSTRACT

Background: HIV-associated distal sensory polyneuropathy (HIV-DSP) is a painful condition with limited effective treatment. Capsaicin desensitizes cutaneous nociceptors resulting in reduced pain. We report a placebo-controlled study of a high-concentration capsaicin dermal patch (NGX-4010) for the treatment of painful HIV-DSP.

Methods: This double-blind multicenter study randomized 307 patients with painful HIV-DSP to receive NGX-4010 or control, a low-concentration capsaicin patch. After application of a topical anesthetic, NGX-4010 or control was applied once for 30, 60, or 90 minutes to painful areas on the feet. The primary efficacy endpoint was percent change in Numeric Pain Rating Scale (NPRS) from baseline in mean "average pain for past 24 hours" scores from weeks 2 to 12.

Results: A single NGX-4010 application resulted in a mean pain reduction of 22.8% during weeks 2 to 12 as compared to a 10.7% reduction for controls ($p = 0.0026$). Following a transient treatment-related pain increase, pain was reduced; significant improvement was apparent by week 2 and continued throughout the controlled 12-week observation period. Mean pain reductions in the NGX-4010 30-, 60- and 90-minute groups were 27.7%, 15.9%, and 24.7% ($p = 0.0007$, 0.287, and 0.0046 vs control). One third of NGX-4010-treated patients reported ≥30% pain decrease from baseline as compared to 18% of controls ($p = 0.0092$). Self-limited, mild-to-moderate local skin reactions were commonly observed.

Conclusions: A single NGX-4010 application was safe and provided at least 12 weeks of pain reduction in patients with HIV-associated distal sensory polyneuropathy. These results suggest that NGX-4010 could provide a promising new treatment for painful HIV neuropathy.

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GLOSSARY

AEs = adverse events; **ARV** = antiretroviral; **BPI** = Brief Pain Inventory; **CGIC** = Clinician Global Impression of Change; **HIV-DSP** = HIV-associated distal sensory polyneuropathy; **NPRS** = Numeric Pain Rating Scale; **PGIC** = Patient Global Impression of Change.

HIV-associated distal sensory polyneuropathy (HIV-DSP) is the most common neurologic complication of HIV infection, affecting 29% to 62% of patients with HIV and AIDS.[1-5] Symptoms occur predominantly in the feet and include paresthesias and pain.[4,5] Therapeutic options consist primarily of local or systemic symptomatic treatments with inconsistent benefit.[6-9]

Capsaicin {6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl- (6E)} acts as a highly selective agonist for transient receptor potential vanilloid 1 receptor (TRPV1), a ligand-gated, nonselective cation channel, preferentially expressed on small-diameter afferent neurons specialized for the detection of noxious sensations.[10] By activating the TRPV1-expressing nociceptors, capsaicin initially produces a burning

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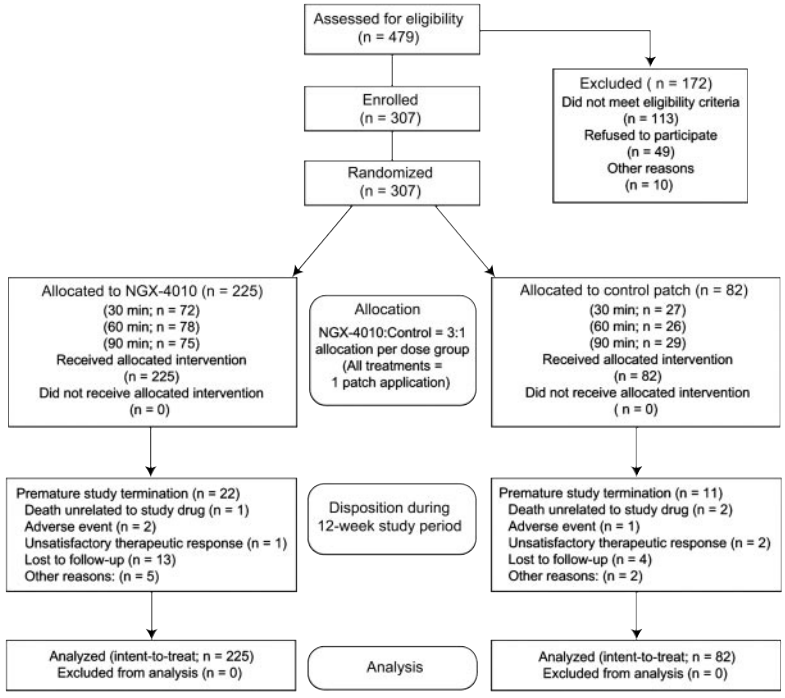
Figure 1 Subject flow through the trial



sensation, allodynia, hyperalgesia, and erythema.[10] After exposure to capsaicin, TRPV1-containing sensory axons are desensitized and pain lessens.[11]

Low-concentration (up to 0.1% by weight [w/w]) topical capsaicin may reduce neuropathic pain,[12,13] although one trial failed to show efficacy in HIV-DSP.[14] Higher concentrations of capsaicin may desensitize the cutaneous nociceptors[15] and provide prolonged analgesia.[16] NGX-4010, a high-concentration capsaicin proprietary matrix-formulated dermal patch (8% w/w capsaicin), rapidly delivers a therapeutic dose of capsaicin into the skin in a single, short treatment. In an open-label study in HIV-DSP, a single NGX-4010 application reduced pain.[17] The current controlled study evaluates the efficacy and safety of NGX-4010 in painful HIV-DSP.

METHODS

This was a randomized, controlled, double-blind, multicenter study of the efficacy, safety, and tolerability of a single application of NGX-4010 for the treatment of pain associated with HIV-DSP.

Eligibility and enrollment. Eligible subjects had ≥2 months of moderate to severe neuropathic pain in both feet secondary to HIV-DSP or neurotoxic antiretroviral (ARV) drug exposure, with an average Numeric Pain Rating Scale (NPRS) score during screening of 3 to 9 (inclusive). A study neurologist diagnosed HIV-DSP based on pain, burning, or dysesthetic discomfort in both feet, diminished ankle reflexes, and diminution of vibration, pain, or temperature sensation in the distal legs. Patients receiving neurotoxic ARV (didanosine [ddI], zalcitabine [ddC], stavudine [d4T]) must have been on stable doses for ≥8 weeks. Doses of other pain medications (anticonvulsants, nonselective serotonin reuptake inhibitor antidepressants, opioids) had to be stable for ≥21 days before treatment and throughout the study. Patients were excluded if they were using topical analgesics; had pain other than painful HIV-associated neuropathy; had another cause for neuropathy (e.g., diabetes mellitus, B12 deficiency, alcoholism); had abnormalities in cardiac, renal, hepatic, or pulmonary function; or had hypersensitivity to capsaicin or opioids. Subjects receiving ≥60 mg morphine equivalent were excluded based on experience from a previous high-concentration capsaicin patch study[17] during which use of high-dose opioids limited responsiveness to opioid rescue medications.

The study was conducted in accordance with the ethics principles of the Declaration of Helsinki, was consistent with Good Clinical Practice guidelines, and was approved by Institutional Review Boards. Written informed consent was obtained from all participating patients.

Randomization scheme and treatment. Patients were stratified by current neurotoxic ARV use and randomized to NGX-4010, an experimental high-concentration capsaicin patch (NeurogesX, Inc., San Mateo, CA) or a low-concentration capsaicin control patch in a 3:1 allocation for each of the 30-, 60-, and 90-minute groups (figure 1). Treatment areas were identified by a line drawn around the dorsal, lateral, plantar, and medial aspects of the foot that enclosed the most proximal level of painful symptoms and all distal areas of the foot, including the outer surfaces of the toes, on each foot. Study patches were wrapped around the affected area and could be cut to conform to the treatment area.

Before patch application, a topical local anesthetic (L.M.X.4 lidocaine 4% cream, Ferndale Laboratories, Inc., Ferndale, MI) was applied for 60 minutes and then removed with soap and water. NGX-4010 (capsaicin 640 mcg/cm^2, 8% w/w) or the control patch (3.2 mcg/cm^2, 0.04% w/w) was applied for 30, 60, or 90 minutes. Up to 4 patches (each 14 × 20 cm) could be applied to an estimated total surface area of 1,000 cm^2 (both feet). After patch removal, the treatment area was washed with a cleansing gel formulated to remove residual capsaicin. Oxycodone hydrochloride oral solution (1 mg/mL) or equivalent could be administered at the onset of treatment-associated discomfort and as required. Patients were monitored for 2 hours after patch removal. Patients could take hydrocodone bitartrate/acetaminophen 5 mg/500 mg for up to 7 days. During the 12-week study, patients continued their stable chronic pain medication regimens.

The study included a baseline screening period, treatment day (day 0), and a 12-week blinded observation period. Patient self-recorded baseline NPRS scores for "average pain for the past 24 hours," present pain intensity ("pain now"), and "worst pain in the past 24 hours" were collected for 5 to 7 days before study treatment (baseline) and for the duration of the study. The Gracely Pain Scale,[18] Short-Form McGill Pain Questionnaire,[19] Brief Pain Inventory (BPI),[20] Patient Global Impression of Change (PGIC), and Clinician Global Impression of Change (CGIC) were completed during office visits at various time points. Patients who completed week-12 study evaluations could enter a 40-week open-label

extension period with 60-minute NGX-4010 treatments (data not presented).

Assessments. The primary efficacy measure was the percent change in the "average pain for the past 24 hours" NPRS score, from baseline to weeks 2 to 12. To avoid bias from rescue opioid medications, week 1 scores were not used for the primary efficacy evaluations. Secondary efficacy variables included percent change from baseline in the "average pain for the past 24 hours" NPRS score for weeks 2 to 4 and 2 to 8; proportion of patients with a ≥30% mean decrease from baseline in "average pain for the past 24 hours" NPRS scores during weeks 2 to 12 (responders); and percent change from baseline in the "worst pain for the past 24 hours" and "pain now" NPRS scores. The percent change from baseline and the proportion of patients with a ≥30% mean decrease from baseline were also calculated for each study week. Change from baseline to week 12 was used to assess the Gracely Pain Scale, Short-Form McGill Pain Questionnaire, and BPI. Both PGIC and CGIC were assessed at week 12.

Safety assessments included adverse events (AEs), dermal assessment scores (severity scale of 0 to 7 points[21]), clinical laboratory tests, vital signs, physical examination, electrocardiograms, and use of concomitant medications. Neurologic evaluations (sharp, warm, and vibratory sensation and deep tendon reflexes) were performed at screening and weeks 4 and 12. Quantitative sensory testing using a CASE-IV System Computer Aided Sensory Evaluator (WR Medical Electronics Co., Stillwater, MN) to measure heat pain detection (0.5 and 5.0), cool thermal detection, and vibration perception thresholds was performed at selected study sites at screening and weeks 4 and 12. Tolerability was assessed by evaluating the duration of patch application, "pain now" NPRS scores the evening following treatment, and rescue medication use on days 0 through 5.

Statistical analysis. The study was designed to provide 90% power to detect a 15% difference in the mean percent NPRS change from baseline between all NGX-4010-treated subjects and controls at an alpha level of 0.05. All efficacy and safety measures were assessed for all patients who received a study patch based on the intention-to-treat principal. For the primary efficacy endpoint, a gender stratified analysis of covariance model was used for treatment comparisons, with baseline pain score, pain score immediately before topical lidocaine application, and pain reduction (percent change) following topical lidocaine application as covariates. The last observation carried forward method was used to impute missing NPRS scores. Adjusted means (least squares means, adjusted for the three covariates) were calculated. The initial efficacy assessment compared all NGX-4010 subjects to all controls. If the initial null hypothesis was rejected, the 90-, 60-, and 30-minute NGX-4010 groups were compared to the combined control group. The same method was used to analyze the secondary endpoints: percent change from baseline in the "average pain for the past 24 hours" NPRS score during weeks 2 to 4 and during weeks 2 to 8 and the percent change from baseline in the "worst pain for the past 24 hours" and "pain now" NPRS scores (baseline compared to weeks 2 to 12).

Logistic regression with the same covariates tested the difference in the proportion of patients with a ≥30% mean decrease from baseline in "average pain for the past 24 hours" NPRS scores during weeks 2 to 12. For the Gracely Pain Scale, Short-Form McGill Pain Questionnaire, BPI, PGIC, and CGIC, a Wilcoxon rank sum test was used for categorical data and analysis of variance was used for the total score. Baseline scores or "no improvement" were imputed for missing values.

RESULTS

Patient characteristics. A total of 307 patients were randomized and treated at 30 centers from August 2003 to December 2005 (225 NGX-4010, 82 controls; figure 1). Treatment groups were balanced for baseline NPRS score (mean 5.9, both groups; range 2.5–9.6), neuropathy duration, analgesic treatment, and neurotoxic ARV treatment (table 1). Overall, 274 patients (89%) completed the 12-week study; 22 NGX-4010 subjects (10%) and 11 control subjects (13%) terminated early.

Efficacy. Patients receiving NGX-4010 demonstrated greater pain reduction during the 12-week period than patients receiving the low-concentration control. During weeks 2 to 12, the mean reduction from baseline in NPRS scores was 22.8% in NGX-4010 subjects and 10.7% in controls ($p = 0.0026$; table 2). Thirty-four percent of NGX-4010 patients experienced a ≥30% mean decrease in pain during weeks 2 to 12, compared to 18% of controls ($p = 0.0092$; table 2). Similar results were observed for weeks 2 to 4 and weeks 2 to 8 and for the "pain now" and "worst pain for past 24 hours" NPRS assessments (data not shown). Pain reduction was greater with NGX-4010 during week 2 and throughout the 12-week evaluation period (figure 2). During week 12, 31% of NGX-4010 patients experienced a ≥30% mean decrease in pain compared to 14% of controls ($p = 0.007$).

NGX-4010 reduced pain in patients using other neuropathic pain treatments (22.2%, $p = 0.0119$) and in patients not using other treatments (27.7%, $p = 0.0215$). Similar pain reduction was also observed in NGX-4010 patients using neurotoxic ARV therapy (27.9%) and not using neurotoxic ARV (21.7%).

No dose response was apparent. Pain decrease from baseline during weeks 2 to 12 for the NGX-4010 30-, 60-, and 90-minute groups were 27.7%, 15.8%, and 24.7% ($p = 0.0007$, 0.287, and 0.0046 vs control); 42%, 24%, and 36% of NGX-4010 subjects in the 30-, 60-, and 90-minute groups had a ≥30% mean reduction in pain ($p = 0.0015$, $p = 0.39$, and $p = 0.0092$ vs control). At week 12, improvements in the Gracely Pain Scale, Short-Form McGill Pain Questionnaire, BPI composite score, and PGIC and CGIC scores were greater overall, and in all three NGX-4010 dose groups; most differences were significant (table 2).

Table 1 Demographic and baseline characteristics

	Control (n = 82)	NGX-4010 (n = 225)	NGX-4010 30 min (n = 72)	NGX-4010 60 min (n = 78)	NGX-4010 90 min (n = 75)
Age, y					
Mean ± SD	48.4 ± 7.6	47.7 ± 8.4	47.2 ± 8.6	48.3 ± 7.8	46.9 ± 8.3
Range	33–70	29–74	29–66	33–74	30–69
Gender, n (%)					
Female	3 (4)	18 (8)	9 (13)	5 (6)	4 (5)
Male	79 (96)	207 (92)	63 (88)	73 (94)	71 (95)
Race, n (%)					
Caucasian	50 (61)	136 (60)	42 (58)	46 (59)	48 (64)
African American	18 (22)	63 (28)	24 (33)	22 (28)	17 (23)
Other	14 (17)	26 (12)	6 (8)	10 (13)	10 (13)
Baseline pain level					
Mean ± SD	5.9 ± 1.6	5.9 ± 1.6	5.9 ± 1.6	5.8 ± 1.7	6.1 ± 1.6
Range	2.6–9.6	2.5–9.6	2.9–9.0	2.5–9.6	3.0–9.6
Concomitant pain medications, n (%)					
Anticonvulsants	32 (39)	131 (43)	38 (53)	35 (45)	26 (35)
Antidepressants	31 (38)	108 (35)	29 (40)	27 (35)	21 (28)
Opioids	15 (18)	77 (25)	21 (29)	20 (26)	21 (28)
Any of the above	53 (65)	209 (68)	56 (78)	53 (68)	47 (63)
Duration of HIV- or ARV-painful neuropathy, y					
Mean ± SD	5.1 ± 3.4	4.7 ± 3.3	4.2 ± 3.0	5.4 ± 3.7	4.4 ± 3.1
Range	0.1–14.2	0.1–15.8	0.1–10.7	0.2–15.8	0.2–13.3
$CD4^+$ count (cells/mm^3)					
Mean ± SD	434 ± 280	437 ± 235	415 ± 269	396 ± 236	497 ± 285
Median	406	388	382	368	419
Range	12–1,373	7–1,478	7–1,227	9–1,172	9–1,478
HIV-1 RNA (log_{10} copies/mL)*					
Mean ± SD	3.32 ± 0.91	3.28 ± 0.86	3.27 ± 0.79	3.42 ± 0.99	3.14 ± 0.75
Median	3.01	3.01	3.01	3.08	2.82
Range	2.60–5.82	2.60–6.74	2.60–5.79	2.60–6.74	2.60–5.84
d-drug ARV, n (%)					
Not taking	67 (82)	184 (82)	58 (81)	65 (83)	61 (81)
Taking	15 (18)	41 (18)	14 (19)	13 (17)	14 (19)

*Values reported as <400 are set to 400 copies/mL.

Safety and tolerability. NGX-4010 treatment was generally well tolerated. Application site pain necessitated early patch removal (<90% of scheduled application time) in two patients (0.9%), both in the 90-minute NGX-4010 group. Treatment was followed by a ≥30% pain increase in 79 (36%) NGX-4010 patients and 10 (13%) control patients. Pain scores in the NGX-4010 group increased over baseline on day 0 (mean percent change D0: NGX-4010 +27%, control −7.5%) and day 1 (mean percent change D1: NGX-4010 +13.7%, control −10.1%). By day 2, mean pain scores in the NGX-4010 group fell to 0.9% below baseline and remained below baseline for the remainder of the study. Treatment-related pain was manageable in most patients with local cooling or short-acting oral opioids. On day 0, 44% of NGX-4010 patients and 11% of controls received oxycodone (mean doses, 14.1 mg and 8.9 mg). During days 0 to 5, 55% of NGX-4010 patients and 23% of controls received hydrocodone/acetaminophen.

Pain reductions during weeks 2 to 12 were similar for NGX-4010 patients who used (21.9%) or did not use (23.7%) rescue medication. Slightly fewer NGX-4010 patients in the 30-minute group

Table 2 Differences between NGX-4010 groups and controls in change from baseline at 12 weeks after treatment, as measured by non-diary questionnaires and global assessments

	Control (n = 82)	NGX-4010 (n = 225)	NGX-4010 30 min (n = 72)	NGX-4010 60 min (n = 78)	NGX-4010 90 min (n = 75)
Percent change from baseline*					
Baseline to week 2–12, least squares mean (SD)	−10.7 (30.8)	−22.8† (30.6)	−27.7‡ (30.9)	−15.8 (30.4)	−24.7† (30.6)
≥30% Response*					
Baseline to week 2–12, n (%)	15 (18)	76 (34)†	30 (42)†	19 (24)	27 (36)†
Gracely Pain Scale					
Change from baseline to week 12, mean (SD)	−0.04 (0.31)	−0.21† (0.47)	−0.22§ (0.55)	−0.24† (0.45)	−0.17§ (0.41)
SF-MPQ–Sensory					
Change from baseline to week 12, mean (SD)	−2.07 (6.82)	−6.24† (7.31)	−6.70† (7.02)	−7.20† (7.54)	−4.78§ (7.25)
SF-MPQ–Total					
Change from baseline to week 12, mean (SD)	−3.20 (8.77)	−8.33† (9.66)	−9.02† (9.43)	−9.65† (9.65)	−6.29 (9.75)
BPI–Composite score					
Change from baseline to week 12, mean (SD)	−0.99 (2.51)	−1.61 (2.39)	−2.03§ (2.46)	−1.65 (2.29)	−1.14 (2.38)
PGIC, n (%)¶	65	187	61	64	62
Total improved	20 (31)	125 (67)‡	40 (66)‡	45 (70)‡	40 (65)§
Very much	5 (8)	22 (12)	10 (16)	7 (11)	5 (8)
Much	4 (6)	39 (21)	13 (21)	11 (17)	15 (24)
Slight	11 (17)	64 (34)	17 (28)	27 (42)	20 (32)
CGIC, n (%)¶	65	186	62	63	61
Total Improved, n (%)	24 (37)	123 (66)†	40 (65)†	40 (63)§	43 (70)†
Very much	3 (5)	15 (8)	5 (8)	3 (5)	7 (11)
Much	6 (9)	30 (16)	13 (21)	10 (16)	7 (11)
Slight	15 (28)	78 (42)	22 (35)	27 (43)	29 (48)

*NPRS average pain for the past 24 hours.
†$p < 0.01$ versus control.
‡$p < 0.001$ versus control.
§$p < 0.05$ versus control.
¶p Value calculated from the Wilcoxon rank sum test for all seven potential responses.
SF-MPQ = Short-Form McGill Pain Questionnaire; BPI = Brief Pain Inventory; PGIC = Patient Global Impression of Change; CGIC = Clinician Global Impression of Change.

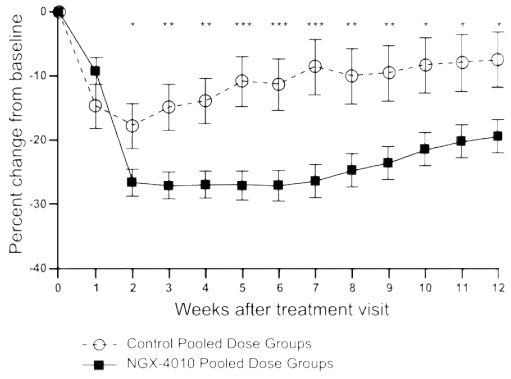
received rescue medication (D0 to D5 hydrocodone/acetaminophen use: NGX-4010 90-minute [56%], 60-minute [60%], and 30-minute [49%]). Changes in pain after treatment were also less in the 30-minute group compared to the 60- and 90-minute groups. The greatest mean change within 2 hours of treatment was −0.2 for the 30-minute group compared to +0.5 for the 60-minute and +0.7 for the 90-minute groups.

A total of 161 NGX-4010 patients (72%) and 45 (55%) control patients reported AEs. The most frequent were application site reactions, which were more common in NGX-4010 patients (table 3). Three subjects (1%) died: one due to sepsis (NGX-4010), one presumed drug overdose (control), and one due to coma (control). No deaths were considered related to treatment.

Before treatment, 3% of NGX-4010 and 10% of controls had dermal assessment scores >0 (i.e., minimal erythema or greater). At patch removal, 52% of NGX-4010 and 32% of controls had scores >0; 2 hours after patch removal, 41% of NGX-4010 and 28% of controls had scores >0. At 1 week after treatment, only 6% of NGX-4010 and 8% of controls had scores >0. Only two NGX-4010 subjects and no control subjects had dermal assessment scores >3 (erythema and papules).

NGX-4010 did not result in detectable changes in warm, sharp, or vibratory sensation, or deep tendon reflexes. In a subset of 39 subjects, no significant differences between NGX-4010 and controls were observed in just noticeable differences for vibratory, cooling detection, and heat pain detection

Figure 2 Mean Numeric Pain Rating Scale (NPRS) scores for the "average pain level in past 24 hours"; the least-squares mean and standard error of the weekly average percent change from baseline



*$p < 0.05$ for pooled NGX-4010 dose groups compared with control. **$p \leq 0.01$ for pooled NGX-4010 dose groups compared with control. ***$p \leq 0.001$ for pooled NGX-4010 dose groups compared with control. Baseline pain level was defined as the mean of all evaluable screening "average pain level in past 24 hours" NPRS scores. Missing scores during days 1 to 84 were not imputed.

thresholds obtained by quantitative sensory testing at 4 and 12 weeks following treatment (data not shown).

DISCUSSION This randomized, double-blind, controlled study demonstrated that a single application of a high-concentration capsaicin dermal patch produced a sustained reduction in pain over 12 weeks in patients with painful HIV-DSP. NGX-4010 was well-tolerated; transient increases in pain and local erythema were manageable.

Peripheral neuropathy is the most common neurologic complication of HIV infection.[22] Whereas optimized ARV therapy with reduction in HIV plasma viral load is associated with improvement in quantitative thermal thresholds,[23] no data associate HIV virologic control with clinical improvement in HIV neuropathy. Highly active ARV therapy-era studies have not shown an association with plasma HIV viral load.[1,2,24] Neuropathy is a dose-limiting effect of dideoxynucleoside analogues[3] and may also be associated with protease inhibitor exposure.[25]

Studies of restorative treatments for HIV-DSP have yielded disappointing results.[26-28] Although the primary management approach remains pain reduction, clinical trials evaluating amitriptyline, mexiletine, acupuncture, memantine, topical lidocaine gel, lamotrigine, gabapentin, and opioids have yielded negative, inconsistent, or poorly generalizable results.[24,29-33] Cannabinoids may have a role in the treatment of painful HIV-DSP.[34]

Oral compounds with proven efficacy in painful neuropathy may cause systemic AEs and risk compromise to ARV compliance through the added pill burden.[35] A topically administered treatment with sustained analgesia, such as NGX-4010, could substantially benefit this population.

Limitations of this study include the difficulty of blinding topical high-concentration capsaicin. To prevent unblinding from the localized skin reaction of the active treatment, the control patch contained a low concentration of capsaicin. Increased pain, localized erythema, and use of rescue medication were observed in both NGX-4010 and control subjects, suggesting that the control patch provided study blinding. While there was a higher rate of localized application site side effects and an increase in pain in the 2 days following NGX-4010 application compared to control, similar changes in pain during week 1 and the substantial difference in analgesia beginning at week 2 provide further evidence of successful blinding without interference with the primary outcome measure. An analgesic effect of the low-concentration capsaicin control cannot be completely excluded; therefore the efficacy of NGX-4010 may have been underestimated. The allowed use of rescue medications did not influence the overall study results as patients who required rescue opioid medications responded similarly to those who did not.

A second limitation relates to the lack of a dose response for NGX-4010. Significant improvements in the primary efficacy measure were observed in the 30- and 90-minute NGX-4010 groups, but not the 60-minute group. Differences in baseline characteristics or postrandomization factors could not account for this result. Secondary measures of pain response (the Gracely Pain Scale, Short-Form McGill Questionnaire, and PGIC) suggest that the 60-minute NGX-4010 dose has efficacy comparable to the 30- and 90-minute doses. Random variability within relatively small groups evaluated over a shallow portion of the dose-response curve appears to be the most likely explanation.

Another limitation relates to the modest pain reduction with NGX-4010 in this study compared with analgesics in other neuropathic pain states, such as diabetic polyneuropathy and postherpetic neuralgia. However, the majority of trials in HIV neuropathy have yielded negative results. Even agents proven effective in other neuropathic pain disorders, such as amitriptyline in diabetic neu-

Table 3 Most frequent adverse events (AEs)

Common AEs (>2%): Body system and MeDDRA preferred terms*	NGX-4010 (n = 225)	Control (n = 82)
No. of subjects reporting one or more AEs	161 (72)	45 (55)
Gastrointestinal disorders		
Diarrhea	6 (3)	3 (4)
Gastritis	0	2 (2)
Nausea	5 (2)	1 (1)
Vomiting	1 (<1)	2 (2)
General disorders and administration site conditions		
Application site burning	18 (8)	2 (2)
Application site desquamation	2 (1)	2 (2)
Application site dryness	33 (15)	4 (5)
Application site pain	47 (21)	7 (9)
Application site papules	11 (5)	1 (1)
Application site pruritus	39 (17)	5 (6)
Application site swelling	29 (13)	7 (9)
Application site urticaria	5 (2)	1 (1)
Application site vesicles	11 (5)	0
Fatigue	4 (2)	2 (2)
Pain exacerbated	4 (2)	0
Pyrexia	6 (3)	0
Infections and infestations		
Bronchitis	2 (1)	2 (2)
Gastroenteritis	0	2 (2)
Influenza	4 (2)	2 (2)
Upper respiratory tract infection	17 (8)	5 (6)
Investigations		
Weight decreased	1 (<1)	3 (4)
Musculoskeletal and connective tissue disorders		
Arthralgia	7 (3)	1 (1)
Back pain	3 (1)	2 (2)
Muscle cramp	2 (1)	2 (2)
Myalgia	4 (2)	2 (2)
Nervous system disorders		
Dizziness	5 (2)	0
Headache	9 (4)	1 (1)
Psychiatric disorders		
Anxiety	4 (2)	1 (1)
Depression	7 (3)	1 (1)
Insomnia	6 (3)	1 (1)
Respiratory, thoracic, and mediastinal disorders		
Cough	5 (2)	1 (1)
Pharyngolaryngeal pain	1 (<1)	2 (2)
Skin and subcutaneous tissue disorders		
Rash	4 (2)	1 (1)

Values are n (%).
*Counts indicate the numbers of subjects reporting one or more AEs that map to the MedDRA (version 7.0) system organ class. At each level of summarization, subjects were only counted once.

ropathy, have failed in HIV neuropathy.[29] The clinical significance of the reduction in absolute pain in the current study is supported by improvement in other secondary measures, including global improvement scores. Finally, the pain reduction with a topical agent such as NGX-4010 does not cause systemic AEs and treatment is needed no more than once every 3 months.

In the current study, there was no reduction in sensory function following NGX-4010 administration in patients with preexisting sensory neuropathy, suggesting that capsaicin treatment can lead to meaningful, prolonged pain reduction without clinically evident changes in protective sensation. Quantitative sensory testing supported these clinical observations, although these studies were performed in a relatively small subset. A longer term, 52-week, open-label extension study, with repeated applications of NGX-4010 in the treatment of painful HIV neuropathy, supports the safety data reported in the current trial.[36] When used as a topical analgesic, capsaicin's mechanism of action is thought to selectively and reversibly defunctionalize cutaneous sensory nerve endings expressing TRPV1; large myelinated sensory fibers are unaffected, preserving the integrity of protective touch, vibratory, and thermal sensations.[37,38]

It is common to use multiple analgesic agents for the treatment of pain, a concept termed rational polypharmacy.[39] A recent study demonstrated the superiority of the combination of gabapentin and morphine sulfate in the treatment of neuropathic pain.[40] Data from the current study support the use of NGX-4010 both in combination with systemically acting analgesics and as monotherapy.

APPENDIX

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