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A Randomized, Double-Blind, Controlled Study of NGX-4010, a Capsaicin 8% Dermal Patch, for the Treatment of Painful HIV-associated Distal Sensory Polyneuropathy

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Abstract

Introduction: Effective treatment of HIV-associated distal sensory polyneuropathy (HIV-DSP) remains a significant unmet therapeutic need.

Methods: In this randomized, double-blind, controlled study, patients with pain due to HIV-DSP received a single 30- or 60-minute application of NGX-4010 – a capsaicin 8% patch (n=332) – or a low-dose capsaicin (0.04%) control patch (n=162). The primary endpoint was the mean percent change from baseline in Numeric Pain Rating Scale (NPRS) score to weeks 2-12. Secondary endpoints included Patient Global Impression of Change (PGIC) at week 12.

Results: Pain reduction was not significantly different between the total NGX-4010 group (-29.5%) and the total control group (-24.5%; p=0.097). Greater pain reduction in the 60-minute (-30.0%) vs. the 30-minute control group (-19.1%) prevented intended pooling of the control groups to test individual NGX-4010 treatment groups. No significant pain reduction was observed for the 30-minute NGX-4010 group compared with 30-minute control (-26.2% vs. -19.1%, respectively, p=0.103). Pain reductions in the 60-minute NGX-4010 and control groups were comparable (-32.8% vs. -30.0%, respectively; p=0.488). Posthoc non-parametric testing demonstrated significant differences favoring the total (p=0.044) and 30-minute NGX-4010 groups (p=0.035). Significantly more patients in the total and 30-minute NGX-4010 group felt improved on the PGIC vs. control (67% vs. 55%, p=0.011 and 65% vs. 45%, p=0.006, respectively). Mild to moderate, transient application site pain and erythema were the most common adverse events.

Conclusions: While the primary endpoint analyses were not significant, trends toward pain improvement were observed following a single 30-minute NGX-4010 treatment.

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Key Words: HIV-associated distal sensory polyneuropathy, neuropathic pain, capsaicin, NGX-4010

Introduction

Peripheral neuropathy is the most frequent neurologic complication associated with HIV infection.[1,2] The majority of HIV-associated peripheral neuropathies can be attributed to distal sensory polyneuropathy (HIV-DSP) which affects up to 60% of HIV patients.[2–8] Patients with HIV-DSP predominantly report symptoms in their feet, including paresthesias, pain, and numbness,[2,7,9] and almost 40% report neuropathic pain.[8]

Systemic treatments such as anticonvulsants, opioids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors that are frequently used for this condition are limited by poor tolerability, the need for titration, administration of multiple daily doses and have yielded disappointing results in large randomized controlled studies[10–16]. A recent review concluded that evidence of efficacy exists only for capsaicin 8% (NGX-4010), smoked cannabis and rhNGF.[17]

Altered expression of the transient receptor potential vanilloid 1 (TRPV1) on nociceptors may play a role in neuropathic pain in post-herpetic neuralgia (PHN)[18,19] and painful diabetic neuropathy (PDN)[20,21] making this receptor a logical target for treating neuropathic pain. Capsaicin is a highly selective TRPV1 agonist and produces an initial burning sensation by activating the TRPV1-expressing nociceptors.[18] However, repeated exposure to capsaicin at low concentrations or a single exposure to high concentrations defunctionalizes these nociceptors, inhibiting pain.[22,23]

NGX-4010 is a capsaicin 8% patch that rapidly delivers high concentration capsaicin locally into the skin.[22,24] Pain reduction has been observed in patients with painful HIV-DSP

following single and repeated NGX-4010 applications in phase 2 and 3 studies.[25–27] The current 12-week phase 3 study sought to confirm the results of the previous phase 3 study.

Methods

Patients

Patients ≥18 years old with HIV-DSP for ≥2 months and an average baseline Numeric Pain Rating Scale (NPRS)[28] score of 3–9 were eligible. Patients taking chronic pain medications, such as anticonvulsants, non-selective serotonin reuptake inhibitor (non-SSRI) antidepressants, opioids, nonsteroidal anti-inflammatory drugs or salicylates had to be on a stable dose ≥21 days before patch application and throughout the study.

Key exclusion criteria included prior use of NGX-4010, topically applied pain medication, initiation or cessation of treatment with neurotoxic antiretroviral agents, use of parenteral opioids, evidence of another contributing cause for peripheral neuropathy, or any implanted medical device for the treatment of neuropathic pain. Patients using concomitant oral or transdermal opioid medication were required to be on doses ≤80 mg/day morphine equivalent.

Procedures

The study included a ≥14-day baseline screening period, a treatment day (day 0) and clinic visits at weeks 4, 8, and 12. Eligible patients were randomly assigned to NGX-4010 (capsaicin 640 μg/cm^2, 8% w/w; NeurogesX, Inc., San Mateo, CA, USA) or a low-concentration capsaicin (3.2 μg/cm^2, 0.04% w/w) control patch, for 30 or 60 minutes to both feet (up to 1120 cm^2), according to a 2:2:1:1 allocation scheme prepared by Fisher Clinical Services (Allentown,

PA, USA). Low-dose capsaicin control patches were used instead of placebo to provide effective blinding, as topical capsaicin can produce application site erythema and pain.

Patients were pre-treated with a topical local anesthetic cream (LMX4 lidocaine 4%; Ferndale Laboratories, Inc., Ferndale, MI, USA) for 60 minutes before patch application. After patch removal, the area was cleansed with a cleansing gel developed to remove residual capsaicin (NeurogesX, Inc., San Mateo, CA, USA). A rapid-onset opioid-based oral pain medication (e.g. oxycodone hydrochloride oral solution, 1 mg/ml) could be administered at the onset of treatment-associated discomfort and as needed while in the clinic. Following patch removal, local cooling could also be used. After discharge, patients could take an opioid-based oral pain medication (e.g. hydrocodone bitartrate/acetaminophen 5 mg/500 mg) as needed for treatment-associated discomfort for up to 5 days. Patients were allowed to take acetaminophen up to 3 g/day as needed.

Efficacy Analyses

The primary efficacy endpoint was the percent change in NPRS scores from baseline during weeks 2 through 12. NPRS scores for 'average pain for the past 24 hours' were captured daily at approximately 9PM in a written diary. The NPRS is an 11-point scale with 0 indicating no pain and 10 indicating the worst possible pain.[28] Baseline NPRS scores were the average of all NPRS scores from day -14 through day -1. To avoid the potentially confounding effect of opioid medications allowed during days 0–5, week 1 NPRS scores were not included in the primary endpoint analysis. Other efficacy measures included the percentage of responders (mean percent decrease of ≥30%), the percentage of patients improved on the PGIC and CGIC[29],

changes from screening in SFMPQ[30] and SF-36v2[31,32] scores and responses to the Self Assessment of response to Treatment (SAT) questionnaire developed by NeurogesX, Inc.[33]

Changes in NPRS scores from baseline to weeks 2–12 were analyzed using a gender-stratified analysis of covariance (ANCOVA) model with baseline pain score as the covariate. The null hypothesis was that there is no difference between the total control and total NGX-4010 groups in the percent change in the 'average pain for the past 24 hours' NPRS scores from baseline to weeks 2–12. If the null hypothesis was rejected, comparison of each NGX-4010 dose group vs. the total control group was to be performed provided the control groups were poolable. The poolability of the 30- and 60-minute control groups was assessed by the 90% confidence interval (CI) approach proposed by Westlake.[34] If the 90% CI fell within the equivalence margin, determined by the 80–125% ratio of the means of the 60- and 30-minute groups using the approach outlined in the Center for Drug Evaluation and Research guidance for bioequivalence,[35] then the results from the two control groups were to be pooled. If not, then each individual NGX-4010 group was to be compared with the respective control group. Posthoc Shapiro–Wilk tests for normality were performed and non-parametric stratified Wilcoxon rank sum/Van Elteren[36] tests (stratified by patch duration and/or gender) were used to compare the percent change in NPRS score from baseline to weeks 2–12 between each NGX-4010 and the respective control group. Pre-topical anesthetic (pre-LMX4) pain score, percent change in pain score after topical anesthetic (LMX4) treatment, age, use of concomitant neuropathic pain medications (defined as use of anticonvulsants, non-SSRI antidepressants or opioids the day before treatment and for ≥7 consecutive days), baseline viral load, baseline CD4 cell count, race, use of neurotoxic antiretrovirals (defined as didanosine, zalcitabine or stavudine use ≥8 weeks

prior to screening) and duration of HIV-DSP were explored as covariates using stepwise model selection with a cutoff p-value of 0.10.

Missing post-treatment NPRS scores were imputed using a modified last observation carried forward approach as previously described.[37] The proportion of responders was compared between groups using logistic regression with baseline pain score and gender as covariates. Weekly percent change from baseline in average pain was analyzed using mixed-effect repeated-measures ANCOVA without imputing missing pain scores.

Improvements in PGIC/CGIC were compared using Fisher's exact test. Changes from screening in SFMPQ and SF-36v2 scores were compared using a gender-stratified ANCOVA with screening score as the covariate. SAT responses were compared using a Cochran–Mantel–Haenszel test.

To achieve 90% power at the 0.05 significance level with a standard deviation of 31%, 160 patients per treatment arm (total of 480) were required to detect a difference of 10% in change from baseline in NPRS scores between the total NGX-4010 and total control group. This sample size also allowed for 80% power for comparisons between each NGX-4010 group and the pooled control group.

Safety Analyses

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (Version 9.0). Medication for treatment-related discomfort use from days 0–5, the proportion of patients completing the intended patch duration, demographics, and baseline characteristics were compared with Fisher's exact test or t-test, as appropriate. The maximum level of dermal

response[38] was summarized for each patient and proportions of patients reporting each level compared using a Cochran–Mantel–Haenszel test. Maximum change in "Pain Now" NPRS score during and after patch application from the pre-topical anesthetic time point were summarized and compared using a Wilcoxon rank sum test. Other safety assessments included clinical laboratory tests, vital signs and physical examination.

Results

Patients

A total of 494 patients were enrolled and received double-blind treatment (Figure 1): 332 patients in the NGX-4010 groups and 162 patients in the control groups.

Two patients inadvertently enrolled twice. One patient first received NGX-4010 for 60 minutes and was re-treated 2 months later with NGX-4010 for 30 minutes. The other first received NGX-4010 for 30 minutes and was re-treated 1 month later with control for 60 minutes. For these patients, only their first enrollment is included in Figure 1 and only data collected before the date of the second treatment were included in the safety and efficacy analyses. One patient, in the control group, randomized to receive a 30-minute treatment actually received a 60-minute treatment and was analyzed as randomized for the efficacy analyses and as treated for the safety analyses.

The proportion of patients terminating prematurely was 7% for the total NGX-4010 group and 6% for the total control group. Only 2 patients (1 in the 60-minute NGX-4010 group and 1 in the 60-minute control group) withdrew from the study due to non-fatal AEs, both of

which were judged to be unrelated to study medication. One patient in the 60-minute NGX-4010 group died of pre-existing arteriosclerotic cardiovascular disease that was not considered to be treatment-related.

Demographics and baseline characteristics were similar between treatment groups (Table 1).

Efficacy

The mean percent change in NPRS score from baseline to weeks 2–12 in the total NGX-4010 group was -29.5% compared with -24.5% for the total control group (Table 2; p=0.097). A large difference in mean percent change in NPRS score from baseline to weeks 2–12 was observed between the 30- and 60-minute control groups (-19.1% versus -30.0%, respectively) and the ratio of means between the 60- and 30-minute control groups [1.57 (90% CI: 1.12, 2.35)] was greater than the pre-specified equivalence margin ratio. As a result, the control groups could not be pooled for testing of each individual treatment group and comparisons were performed between the 30- and 60-minute NGX-4010 groups and their respective control group. The mean percent change in NPRS score from baseline to weeks 2–12 in the 30-minute NGX-4010 group was -26.2% compared with -19.1% for the respective control group (Table 2; p=0.103). Patients in the 60-minute treatment groups experienced similar decreases in NPRS scores (-32.8% vs. -30.0%, for NGX-4010 and control, respectively; p=0.488). Results of the Shapiro–Wilk tests demonstrated a non-normal distribution of the residuals from the primary endpoint analyses ($p<0.0001$ for all treatment groups). Results of posthoc non-parametric tests showed the differences in reduction of NPRS scores to be significant compared with the respective control group for the total (p=0.044) and 30-minute NGX-4010 group (p=0.035; Table 2).

Covariate analysis found the effect of concomitant neuropathic pain medication use, age, pre-LMX4 pain, and percent decrease in pain during LMX4 application to be significant. Primary endpoint analyses that included these covariates demonstrated that the difference in pain reduction was significant in the total NGX-4010 group compared with the total control group (-31.2% vs. -25.3%, respectively; p=0.038). This was mostly driven by the difference between the 30-minute NGX-4010 and control group (-28.0% vs. -20.5%; p=0.072). The difference between the 60 minute NGX-4010 and control group was small and not significant (-34.3% vs. -30.0%; p=0.265).

The proportion of patients in the total and 30-minute NGX-4010 groups reporting a ≥30% decrease in NPRS scores compared with control trended to be greater, but differences were not statistically significant (p=0.066 and p=0.055, respectively; Table 2). Beginning at week 2 and continuing through week 12, the 30-minute NGX-4010 group reported greater reductions in NPRS scores compared with the 30-minute control group; the NPRS scores for the 60-minute NGX-4010 and control group were generally similar (Figure 2).

Analysis of PGIC data (Table 2) demonstrated that, compared with the respective control groups, significantly more NGX-4010 recipients in the total and 30-minute groups considered themselves to have improved (slightly, much, or very much) at week 12 (67% vs. 55%, p=0.011 and 65% vs. 45%, p=0.006 for total and 30-minute treatment groups, respectively). Results of the CGIC generally mirrored those of the PGIC. No significant differences in PGIC or CGIC results were noted between the 60-minute NGX-4010 and 60-minute control group.

The 30-minute NGX-4010 group showed greater improvements in mean SF-36v2 scores compared with the 30-minute control group in all categories; statistical significance was

demonstrated for mean physical functioning (9.0 vs. -1.7, respectively; p<0.0001), role physical (11.5 vs. 3.5, respectively; p=0.019), and social functioning (11.0 vs. 1.3, respectively; p=0.002). The differences between the 60-minute NGX-4010 and control groups were minimal.

Changes in the SFMPQ scores favored the NGX-4010 groups compared with their respective control groups but the differences were generally not significant. On the SAT questionnaire completed at study termination, a significantly greater proportion of patients in the 30-minute NGX-4010 group compared with the 30-minute control group indicated an improvement ('somewhat/much better') in pain level (62% vs. 41%, respectively), activity level (44% vs. 26%, respectively), and quality of life (50% vs. 30%, respectively) (p<0.01 for all three comparisons). The differences between the 60-minute NGX-4010 and control groups were minimal.

Safety

NGX-4010 was generally well tolerated. Ninety-seven percent of patients in the NGX-4010 group and all control patients completed at least 90% of the intended patch application duration.

During days 0–5, medication for the relief of treatment-associated discomfort was used by more patients in the total NGX-4010 group compared with the total control group (74% vs. 33%; p<0.0001). Medication use occurred predominantly on the treatment day (day 0) and declined rapidly, with 38% of NGX-4010 and 11% of control patients using medication on day 1 and 8% of NGX-4010 and 4% of control patients using medication by day 5.

The proportion of patients with ≥1 AE was 93% in the NGX-4010 group and 83% in the control group (Table 3). This difference was primarily due to expected, capsaicin-related application site events, the most common ones being application site erythema and pain, reported by 90% of NGX-4010 and 62% of control patients. The incidence of AEs and application site AEs was higher in the 60-minute NGX-4010 group compared with the 30-minute NGX-4010 group but similar between the control groups. Most events were mild or moderate; more patients treated with NGX-4010 than control experienced a severe application site event (19% vs. 2%, respectively) and the incidence of severe application site events was higher in the 60-minute NGX-4010 group compared with the 30-minute NGX-4010 group (14% vs. 24%, respectively). The incidence of serious AEs, mostly classified as "infections and infestations", was similar (6%) for the total NGX-4010 and control group and none were treatment related.

The mean maximum change in NPRS score during and after patch application on the day of treatment was +0.5 for the total NGX-4010 group and -0.8 for the total control group ($p<0.0001$), and was higher for the 60-minute NGX-4010 group (+1.1) compared with the 30-minute NGX-4010 group, which on average showed no pain increase. On the evening of the treatment day, mean NPRS score changes from baseline were +1.3 for the total NGX-4010 group and -0.9 for the total control group ($p<0.0001$), and were again higher for the 60-minute NGX-4010 group (+1.6) compared with the 30-minute NGX-4010 group (+0.9). By the evening of the third day, mean NPRS scores had returned to near-baseline levels. Dermal irritation was generally mild and transient. Only 4% of patients in the total NGX-4010 group had maximum dermal assessment scores over two (definite erythema or minimal edema or minimal papular response). There was more dermal irritation in the 60-minute NGX-4010 group compared with

the 30-minute NGX-4010 group. Pain and dermal irritation were comparable between the two control groups.

No clinically important changes in vital signs, physical examinations or laboratory parameters were noted during the study.

Discussion

While the differences observed using the prespecified primary endpoint analyses were not statistically significant, the results of this study were confounded by a large pain reduction in the 60-minute control group (-30.0%), which was significantly greater than the change observed in the 30-minute control group (-19.1%), and prevented pooling of the control groups according to pre-specified criteria. As a result, comparisons were performed between each NGX-4010 group and the respective control groups, reducing the power to detect a treatment difference of 10% from 82% to 65%. In addition to the confounding effect resulting from large difference in pain reduction between the two control groups, the validity of the prespecified parametric ANCOVA is also questioned by the finding that the residuals from the primary ANCOVA analysis were not normally distributed. The ANCOVA validity depends on several assumptions, including normality of error terms, an assumption which was not met, as evidenced by the results of the Shapiro–Wilk test. Posthoc non-parametric analyses, which do not depend on this assumption, and therefore may have been more appropriate, showed a statistically significant difference between the total and the 30-minute NGX-4010 groups and their respective control groups.

The results of the covariate analysis demonstrated concomitant neuropathic pain medication use, age, pre-LMX4 pain, and percent decrease in pain during LMX4 application to be additional significant covariates. Although included in the prespecified analyses of the previous phase 3 HIV-DSP study[26], pre-LMX4 pain and percent change in pain during LMX4 application were not included in the prespecified analyses of the current study because in the phase 3 NGX-4010 PHN studies[37,39], they were not found to be significant. These covariates were previously included because lidocaine and capsaicin target hyperactive peripheral nociceptors and a substantial response to topical lidocaine was thought to indicate a large peripheral contribution to a patient's pain, thus predicting a response to capsaicin. The fact that these covariates were found to be important in this study suggests that, at least in HIV-DSP, the acute response to topical lidocaine may be predictive. Subjects not using any concomitant neuropathic pain medication had greater improvements in pain scores and treatment differences were larger compared with subjects using concomitant neuropathic pain medication (data not shown). Subjects in the total and 30-minute NGX-4010 groups not using any concomitant neuropathic pain medications had significantly greater decreases in NPRS scores from baseline during weeks 2–12 compared with their respective control groups (-37.7% vs. -25.8% and -37.5% vs. -19.6%, p=0.031 and 0.041, respectively). The fact that two thirds of patients were using concomitant neuropathic pain medication at study entry and during the study (Table1) may therefore have decreased the chance of observing a significant treatment effect.

Consistent trends favoring the 30-minute NGX-4010 group were observed for the responder analyses and other assessments of treatment response, such as PGIC and CGIC. The PGIC provides a global assessment of patient improvement and is determined independent of NPRS scores. Its use is recommended in chronic pain trials by IMMPACT[40] and has been shown

to be more sensitive to treatment effects than pain intensity measurements[41]. Other assessments, such as the SF-36v2 and SAT questionnaires, also appear to be supportive of efficacy of the 30-minute NGX-4010 group.

The large pain reduction in the control groups was greater than the control response observed in the previous NGX-4010 phase 3 study in HIV-DSP (-10.7%) which had demonstrated statistically significant pain reduction.[26] The differences between the two control groups could not be explained by baseline differences. Capsaicin related application site reactions in the control groups, treated with a low-dose capsaicin patch, could have enhanced the "placebo" response, particularly in the 60-minute control group, which displayed more dermal irritation and treatment-related pain. It is also possible that the expectation that increased treatment duration results in increased pain relief, could have contributed to the elevated "placebo" response observed in the 60-minute control group since patch application duration cannot be blinded. In the previous study, the control group had only a 10.7% pain reduction and two-thirds of those patients received the control patch for 60 or 90 minutes.[25] Although a therapeutic effect from the 60 minute patch cannot be entirely ruled out, it is highly unlikely that the effect would be sufficient to explain the magnitude of the reduction observed in this study.

NGX-4010 treatment was generally safe and well tolerated. Treatment-related AEs were application site specific, reported on the day of treatment or shortly thereafter, were mostly mild to moderate and could be adequately managed by local cooling or, if needed, by short-acting oral opioid analgesics. On average, treatment-associated pain peaked on the evening of the treatment day and returned to near-baseline levels by the evening of the third day. No potential safety concerns were identified based on vital signs, physical findings or laboratory values as NGX-4010 is applied locally and associated with only low transient systemic exposure to capsaicin.[42]

In conclusion, this study failed to demonstrate significant pain reduction associated with the application of NGX-4010 for 30 or 60 minutes by the pre-specified analysis. Interpretation of the study was complicated by the use of concomitant medications with real or potential analgesic benefit, and by the skin irritation and strong placebo effects caused by the application of long duration placebo patches. Nonetheless, it may be taken as encouraging that differences between the NGX-4010 and control groups were greater in the 30-minute than in the 60-minute groups with PGIC, CGIC, SF-36v2, SAT questionnaires and posthoc non-parametric testing results all suggesting a significant benefit associated with the 30-minute NGX-4010 dose. Treatment with NGX-4010 was safe and generally well tolerated, with the majority of adverse findings being brief expected capsaicin-related application-site reactions. Given these results, its unique mode of action and efficacy in other neuropathic pain syndromes, further evaluation of NGX-4010 as a non-narcotic treatment modality to address HIV-associated peripheral neuropathy should be considered.

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REFERENCES

1. Ferrari S, Vento S, Monaco S, et al. Human immunodeficiency virus-associated peripheral neuropathies. *Mayo Clin Proc*. 2006;81:213–219.

2. Verma A. Epidemiology and clinical features of HIV-1 associated neuropathies. *J Peripher Nerv Syst*. 2001;6:8–13.

3. Simpson DM, Kitch D, Evans SR, et al. HIV neuropathy natural history cohort study: Assessment measures and risk factors. *Neurology*. 2006;66:1679–1687.

4. Hewitt DJ, McDonald M, Portenoy RK, et al. Pain syndromes and etiologies in ambulatory AIDS patients. *Pain*. 1997;70:117–123.

5. Morgello S, Estanislao L, Simpson D, et al. HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: the Manhattan HIV Brain Bank. *Arch Neurol*. 2004;61:546–551.

6. Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;9:153–161.

7. Keswani SC, Pardo CA, Cherry CL, et al. HIV-associated sensory neuropathies. *AIDS*. 2002;16:2105–2117.

8. Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. *Arch Neurol*. 2010;67:552–558.

9. Vogl D, Rosenfeld B, Breitbart W, et al. Symptom prevalence, characteristics, and distress in AIDS outpatients. *J Pain Symptom Manage*. 1999;18:253–262.

10. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol*. 2007;14:952–970.

11. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2009 revision. *Eur J Neurol*. 2010 17(9):1113-e88.

12. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237–251.

13. Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain: consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage*. 2007;12:13–21.

14. Jackson KC 2nd. Pharmacotherapy for neuropathic pain. *Pain Pract*. 2006;6:27–33.

15. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain*. 1999;83:389–400.

16. Simpson DM, Schifitto G, Clifford DB, et al. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. *Neurology*. 2010;74:413–420.

17. Phillips TJ, Cherry CL, Cox S, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010;5:e14433.

18. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1. An update. *Eur J Biochem*. 2004;271:1814–1819.

19. Petersen KL, Fields HL, Brennum J, et al. Capsaicin evoked pain and allodynia in post-herpetic neuralgia. *Pain*. 2000;88:125–133.

20. Facer P, Casula MA, Smith GD, et al. Differential expression of the capsaicin receptor TRPV1 and related novel receptors TRPV3, TRPV4 and TRPM8 in normal human tissues and changes in traumatic and diabetic neuropathy. *BMC Neurol*. 2007;7:11.

21. Wilder-Smith EP, Ong WY, Guo Y, et al. Epidermal transient receptor potential vanilloid 1 in idiopathic small nerve fibre disease, diabetic neuropathy and healthy human subjects. *Histopathology*. 2007;51:674–680.

22. McCormack PL. Capsaicin dermal patch: in non-diabetic peripheral neuropathic pain. Drugs. 2010 Oct 1;70(14):1831-42..

23. Bley KR. TRPV1 agonist approaches for pain management. In: Arthur Gomtsyan & Connie R. Faltynek, eds. Vanniloid Receptor TRPV1 in Drug Discovery. John Wiley & Sons, Inc., 2010;325-347. ..

24. Noto C, Pappagallo M, Szallasi A. NGX-4010, a high-concentration capsaicin dermal patch for lasting relief of peripheral neuropathic pain. *Curr Opin Investig Drugs*. 2009;10:702–710.

25. Simpson DM, Estanislao L, Brown SJ, et al. An open-label pilot study of high-concentration capsaicin patch in painful HIV neuropathy. *J Pain Symptom Manage*. 2008;35:299–306.

26. Simpson DM, Brown S, Tobias J. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*. 2008;70:2305–2313.

27. Simpson DM, Gazda S, Brown S, et al. Long-term safety of NGX-4010, a high-concentration capsaicin patch, in patients with peripheral neuropathic pain. *J Pain Symptom Manage*. 2010; 39:1053–1064.

28. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

29. Schneider LS, Clark CM, Doody R, et al. ADCS prevention instrument project: ADCS-clinicians' global impression of change scales (ADCS-CGIC), self-rated and study partner-rated versions. *Alzheimer Dis Assoc Disord*. 2006;20(4 Suppl 3):S124–S138.

30. Melzack R. The short-form McGill Pain Questionnaire. *Pain*. 1987;30:191–197.

31. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473–483.

32. Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36® health survey (standard and acute forms). Lincoln, RI: QualityMetric, 2000.

33. Backonja MM, Malan TP, Vanhove GF, Tobias JK; C102/106 Study Group. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. *Pain Med.* 2010;11:600-8. Epub 2010 Jan 22.

34. Westlake WJ. Symmetrical confidence intervals for bioequivalence trials. *Biometrics*. 1976;32:741–744.

35. US Food and Drug Administration Center for Drug Evaluation and Research: Guidance for industry: statistical approaches to establishing bioequivalence. Washington, DC: US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, 2001. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf. Accessed May 11, 2010.

36. Van Elteren, P H. On the combination of independent two-sample tests of Wilcoxon. Bulletin of the International Statistical Institute. 1960;37:351-361.

37. Irving GA., Backonja M, Dunteman E et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Medicine* 2011; 12: 99-109. Epub 2010 Nov 18.2010.

38. US Food and Drug Administration Center for Drug Evaluation and Research: Guidance for industry: skin irritation and sensitization testing of generic transdermal drug products. Washington, DC: US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, 1999. Available at: http://www.fda.gov/ohrms/dockets/98fr/990236Gd.pdf#search=%22HillTop%20Research%2C%20Inc.%20dermal%20irritation%22. Accessed January 27, 2009.

39. Backonja M, Wallace MS, Blonsky ER et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol* 2008; 7: 1106-1112. Erratum in: *Lancet Neurol.* 2009; 8: 31.

40. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

41. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ, Rice AS, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment.Pain. 2011 Jan;152(1):14-27. Epub 2010 Sep 19.

42. Babbar S, Marier JF, Mouksassi MS et al. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. *Ther Drug Monit*. 2009;31: 502-10.

FIGURE LEGENDS

FIGURE 1. Patient disposition.

FIGURE 2. Pain scores over 12 weeks. Mean and standard error of the mean (SEM) values are shown. *$P < 0.05$ for 60-minute NGX-4010 vs. 60-minute control.

TABLE 1. Demographics and baseline characteristics

	NGX-4010			Control		
	Total (n = 332)	**60 minutes (n = 165)**	**30 minutes (n = 167)**	**Total (n = 162)**	**60 minutes (n = 90)**	**30 minutes (n = 72)**
Mean age ± SD (years)	49.7 ± 8.5	49.0 ± 8.5	50.5 ± 8.3	49.7 ± 8.7	50.1 ± 9.3	49.3 ± 7.8
Male, n (%)	290 (87)	148 (90)	142 (85)	142 (88)	79 (88)	63 (88)
Race, n (%)						
Black/African American	83 (25)	43 (26)	40 (24)	39 (24)	23 (26)	16 (22)
White	227 (68)	113 (69)	114 (68)	107 (66)	57 (63)	50 (69)
Other	22 (7)	9 (5)	13 (8)	16 (10)	10 (11)	6 (8)
Baseline exposure to neurotoxic antiretrovirals[*]	25 (8)	14 (9)	11 (7)	8 (5)	7 (8)	1 (1)
Mean CD4 count ± SD ($\times 10^6$/l)	424 ± 237	404 ± 252	443 ± 220	479 ± 329	459 ± 351	504 ± 300
Mean HIV RNA ± SD (copies/ml)[†]	17,746 ± 71,475	25,976 ± 81,525	9,461 ± 58,801	12,373 ± 47,309	16,858 ± 58,932	6,345 ± 23,326

Mean duration of pain ± SD (years),	6.3 ± 4.0	6.4 ± 4.2	6.2 ± 3.8	5.8 ± 4.3	5.4 ± 4.5	6.3 ± 4.1
Mean baseline pain level[‡] for 'average pain for the past 24 hours' ± SD	6.1 ± 1.5	6.2 ± 1.5	6.0 ± 1.6	5.9 ± 1.5	5.9 ± 1.5	5.9 ± 1.5
Concomitant neuropathic pain medication[§], n (%)	230 (69)	106 (64)	124 (74)	107 (66)	54 (60)	53 (74)
Opioids	103 (31)	47 (29)	56 (34)	44 (27)	23 (26)	21 (29)
Anticonvulsants	155 (47)	76 (46)	79 (47)	75 (46)	36 (40)	39 (54)
Antidepressants	92 (28)	39 (24)	53 (32)	50 (31)	24 (27)	26 (36)

CD4 = cluster of differentiation antigen 4; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SD = standard deviation.

[*]Didanosine, zalcitabine, or stavudine.

[†]For HIV RNA, values <400 copies/ml were reported as 400 copies/ml for statistical calculations and values <40 copies/ml were reported as 40 copies/ml for statistical calculations. The median HIV RNA value for all treatment groups was 400 copies/ml.

[‡]Baseline pain level was defined as the mean of all available Numeric Pain Rating Scale scores from day -14 through day -1, inclusive.

[§]A patient was defined as being on concomitant neuropathic pain medication if he or she was on an anticonvulsant, non-selective serotonin reuptake inhibitor antidepressant, or opioid that was used on day -1 and taken for at least 7 consecutive days.

TABLE 2. Clinical efficacy of NGX-4010 in HIV-DSP

		NGX-4010			Control	
Numeric Pain Rating Scale (NPRS) score	**Total (n = 332)**	**60 minutes (n = 165)**	**30 minutes (n = 167)**	**Total (n = 162)**	**60 minutes (n = 89)**	**30 minutes (n = 73)**
Baseline						
Mean (SE)	6.1 (0.1)	6.2 (0.1)	6.0 (0.1)	5.9 (0.1)	5.9 (0.2)	5.9 (0.2)
Weeks 2–12						
LS mean (SE)	4.3 (0.1)	4.1 (0.2)	4.5 (0.1)	4.6 (0.2)	4.2 (0.2)	4.9 (0.2)
P-value*	0.083	0.468	0.090	—	—	—
Change from baseline to weeks 2–12						
LS mean (SE)	-1.8 (0.1)	-2.0 (0.2)	-1.6 (0.1)	-1.4 (0.2)	-1.8 (0.20)	-1.1 (0.2)
P-value*	0.083	0.468	0.090	—	—	—

Percent change from baseline to weeks 2–12						
LS mean (SE)	-29.5 (1.7)	-32.8 (2.4)	-26.2 (2.4)	-24.5 (2.4)	-30.0 (3.3)	-19.1 (3.6)
P-value[*]	0.097	0.488	0.103	—	—	—
P-value[†]	0.044	0. 433	0.035	—	—	—
≥30% decrease from baseline to weeks 2–12						
Proportion, %	43	48	39	36	45	26
P-value[‡]	0.066	0.558	0.055	—	—	—
PGIC at week 12						
Slightly/much/very much improved, %	67	69	65	55	63	45
P-value[#]	0.011	0.384	0.006	—	—	—
CGIC at week 12						
Slightly/much/very much improved, %	66	66	65	52	63	39
P-value[#]	0.006	0.667	0.0003	—	—	—

LS = least squares; SE = standard error; CGIC = Clinical Global Impression of Change; PGIC = Patient Global Impression of Change.

*_P_-value was computed using a gender-stratified analysis of covariance to compare differences between each NGX-4010 group and the respective control group, with baseline pain as the covariate.

[†]*P*-value was computed using a stratified Wilcoxon/Van Elteren test. For comparisons between the total groups, gender and patch duration application were the stratification variables, for all other comparisons gender was the stratification variable.

[‡]*P*-value was computed using logistic regression to compare differences between each NGX-4010 group and the respective control group, with baseline pain and gender as the covariates.

#p-value was computed from Fisher's exact test comparing each NGX-4010 group and the respective control group.

TABLE 3. Treatment-emergent adverse events that occurred in >3% of patients in any group

	NGX-4010			Control		
System organ class preferred term	**Total (n = 332)**	**60 minutes (n = 165)**	**30 minutes (n = 167)**	**Total (n = 162)**	**60 minutes (n = 90)**	**30 minutes (n = 72)**
Patients reporting ≥1 AE, n (%)	309 (93)	160 (97)	149 (89)	134 (83)	73 (81)	61 (85)
Gastrointestinal disorders, %	40 (12)	19 (12)	21 (13)	14 (9)	7 (8)	7 (10)
Diarrhea	13 (4)	7 (4)	6 (4)	2 (1)	1 (1)	1 (1)
Nausea	11 (3)	6 (4)	5 (3)	4 (3)	3 (3)	1 (1)
General disorders and administration-site conditions, %	300 (90)	156 (95)	144 (86)	101 (62)	55 (61)	46 (64)
Application-site erythema	176 (53)	97 (59)	79 (47)	58 (36)	34 (38)	24 (33)
Application-site pain	274 (83)	139 (84)	135 (81)	62 (38)	29 (32)	33 (46)
Application-site papules	12 (4)	7 (4)	5 (3)	0	0	0
Application-site pruritus	12 (4)	4 (2)	8 (5)	2 (1)	2 (2)	0
Edema peripheral	4 (1)	3 (2)	1 (1)	5 (3)	2 (2)	3 (4)

Infections and infestations, %	71 (21)	38 (23)	33 (20)	26 (16)	15 (17)	11 (15)
Upper respiratory tract infection	10 (3)	4 (2)	6 (4)	5 (3)	2 (2)	3 (4)
Musculoskeletal and connective tissue disorders, %	49 (15)	23 (14)	26 (16)	20 (12)	13 (14)	7 (10)
Pain in extremity	20 (6)	10 (6)	10 (6)	6 (4)	4 (4)	2 (3)
Nervous system disorders, %	41 (12)	21 (13)	20 (12)	29 (18)	13 (14)	16 (22)
Peripheral sensory neuropathy	12 (4)	5 (3)	7 (4)	19 (12)	7 (8)	12 (17)
Skin and subcutaneous tissue disorders, %	20 (6)	12 (7)	8 (5)	21 (13)	11 (12)	10 (14)
Erythema	5 (2)	2 (1)	3 (2)	9 (6)	5 (6)	4 (6)

AE = adverse event.

Note: Counts indicate the numbers of patients reporting one or more AEs that map to the *Medical Dictionary for Regulatory Activities* (version 9.0) system organ class. At each level of summarization, patients were only counted once. All AEs with an onset date on or after the treatment administration date and before the week 12/termination cut-off date were included.