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Capsaicin 8% patch repeat treatment in non-diabetic peripheral neuropathic pain: a 52-week, open-label, single-arm, safety study

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Abstract

Objectives: To investigate long-term safety and tolerability of capsaicin 8% patch repeat treatment in non-diabetic patients with peripheral neuropathic pain (NP).

Methods: Prospective, open-label, observational study in patients with post-herpetic neuralgia, post-traumatic or post-surgical nerve injury, HIV-associated distal sensory polyneuropathy, or other peripheral NP, and average daily pain score ≥4, received ≤6 capsaicin 8% patch treatments over 52 weeks according

to clinical need (retreatment at 9–12 week intervals). Sensory testing and analgesic effectiveness were assessed using 'bedside tests' and Brief Pain Inventory (question 5).

Results: Overall, 306 patients received treatment. Treatment-emergent adverse events (TEAE) and drug-related TEAEs were reported by 252 (82.4%) and 207 (67.6%) patients. Application site pain was the most common drug-related TEAE (n=112, 36.6%); no drug-related serious TEAEs were reported. Sensory category shift analyses from baseline to end of study (EoS) in patients attending at least two sensory visits (n=278 for all tests except warm, n=277) found sensory deterioration/loss in at least one modality in 50.4% (n=140); deterioration/loss in one, two, three, four or five modalities occurred in 26.6% (n=74), 14.0% (n=39), 5.8% (n=16), 2.5% (n=7) and 1.4% (n=4). Newly emergent hyperaesthesia or allodynia was apparent in 1.1–3.6% (depending on modality) by EoS. Between 25.2 and 32.0% of patients reported improvement in a sensory modality by EoS. Average daily pain was 6.6 and 4.7 at baseline and Month 12.

Conclusions: Generally, capsaicin 8% patch repeat treatment over 52 weeks was well tolerated, with variable alteration in sensory function and minimal chance of complete sensory loss.

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Introduction

Neuropathic pain (NP) is a common neurological condition with an estimated prevalence of 6.9–8.2% among the general population in Europe, imposing a significant burden on healthcare organisations.[1,2] The condition has been associated with a lower overall health-related quality of life in patients, in particular

impairment of physical, emotional and social functioning as well as sleep quality.[3] In clinical practice the management of NP remains suboptimal and challenging, often resulting in chronic disease. A large proportion of patients with NP still receive inadequate pain relief, despite the availability of a substantial number of treatments.[4,5] Frequently used treatments for NP, such as antidepressant, anticonvulsant and opioid medications, act on the central nervous system and are associated with a number of limitations in routine clinical practice. These include lengthy dose titration, numerous drug-drug interactions, serious adverse events, reduced compliance with treatment due to adverse events, the need for multiple daily dosing, potential for abuse and unclear responder criteria.[5-10]

Capsaicin is a potent, highly selective vanilloid receptor subtype 1 (TRPV1) agonist that causes depolarisation of sensory afferents, inducing short-lived warming, burning, stinging or itching sensations.[11] Exogenous agonists of TRPV1, such as capsaicin, are able to prolong this depolarisation, causing defunctionalisation of hyperactive nociceptors in the skin, leading to pain relief. The capsaicin 8% patch delivers a high concentration of capsaicin directly into the skin to provide both acute and long-lasting pain relief.[11-13] In addition, minimal significant systemic absorption limits the potential for drug-drug interactions or the need for dose adjustment in the elderly or patients with hepatic or renal impairment.[14]

Several prospective, double-blind studies have confirmed the safety and efficacy of the capsaicin 8% patch in post-herpetic neuralgia (PHN) and painful HIV-related neuropathies.[15-18] Results from a large, open-label study in various localised peripheral PNP aetiologies also demonstrated that the capsaicin 8% patch was well tolerated.[19-20] A further study demonstrated non-inferior efficacy versus pregabalin, a first-line treatment for NP.[21] More recently, clinical studies were conducted in patients with painful diabetic peripheral neuropathy,[22,23] which subsequently led to an expansion of the European indication for the capsaicin 8% patch to the treatment of peripheral NP in adults either alone or in combination with other medicinal products for pain.[14]

In healthy subjects, the safety of single and repeated capsaicin 8% patch treatments has been established using neurological examination, quantitative sensory testing and skin punch biopsies.[13] The primary objective of the present prospective study was to investigate for the first time the long-term safety and tolerability of capsaicin 8% patch repeat treatment over 52 weeks in non-diabetic patients with a broad range of peripheral NP aetiologies. Of particular interest in this study was the potential for any clinically relevant deficit in sensory perception or increase in hypersensitivity following repeated application of capsaicin. Analgesic effectiveness was assessed as a secondary outcome. The objective of this study was to mimic capsaicin 8% patch treatment in clinical practice as far as possible.

Methods

Patients

This phase IV, open-label, single-arm, 52-week, observational study (ClinicalTrials.gov Identifier: NCT01252160) was conducted at 63 sites in Europe between October 2010 and September 2013.

Key inclusion criteria included: age between 18 and 90 years with a diagnosis of PHN (pain persisting since shingles vesicle crusting), post-traumatic or post-surgical nerve injury ([PNI]), HIV-associated distal sensory polyneuropathy (HIV-DSPN) (confirmed using the Brief Peripheral Neuropathy Screen), all of a minimum duration of 3 months, or other adequately characterised peripheral NP, including idiopathic small fiber neuropathy (ISFN) (based on clinical criteria or skin biopsy, with loss of pinprick and temperature sensation in both feet); an average daily pain score ≥4 on the question 5 of the Brief Pain Inventory (BPI); intact, non-irritated, dry skin over the painful area to be treated; and in good health as determined by the investigator.

Key exclusion criteria included: any prior use of capsaicin patches; past or current history of type I or type II diabetes mellitus; use of oral or transdermal opioids exceeding a total daily dose of morphine of 80 mg/day, or equivalent, or any parenteral opioids, regardless of dose, within 7 days preceding the first

patch application visit; use of any topical pain medication within 7 days preceding the first patch application visit; unstable or poorly controlled hypertension, or a recent history of a cardiovascular event; clinically significant abnormal electrocardiogram; significant ongoing or untreated abnormalities in cardiac, renal, hepatic or pulmonary function; significant pain of an aetiology other than painful HIV-DSPN, PHN, PNI, ISFN, or other adequately characterised peripheral NP; Complex Regional Pain Syndrome (type I); neuropathic pain areas located only on the face, above the hairline of the scalp, and/or in proximity to mucous membranes.

The study was approved by the institutional review board at each participating site, and was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonization guidelines, and applicable laws and regulations. Written, informed consent was obtained from all patients prior to initiating study-related procedures.

Study treatment

Patients received up to six capsaicin 640 g/cm² (8% weight for weight) patch treatments (QUTENZA™ cutaneous patch (capsaicin 179 mg patch [8% w/w]), supplied by Astellas Pharma Europe Ltd., Chertsey, UK) at 9–12 week intervals over a 52-week period. At each application visit, a maximum of four patches equivalent to an area of up to 1120 cm^2 were applied for 30 minutes to the feet or 60 minutes to other body locations. Prior to patch application, patients received pre-treatment with a topical local anaesthetic, the choice of which was at the investigator's discretion. At screening and each application visit the treatment area was demarcated, which included assessment of the most painful area and the area of allodynia/hyperalgesia. If allodynia was present, then the most painful area plus any additional area(s) of allodynia beyond the most painful area were treated up to a maximum of 1120 cm^2, with highest priority for patch use given to treating the most painful area. Capsaicin 8% patch retreatment took place depending on investigator discretion and patient feedback. Patients who did not attend a further patch retreatment visit prior to Week 26 were recalled to determine if a further retreatment was required.

Assessments

Safety and tolerability

The primary objective of the study was to assess the long-term safety and tolerability, after repeated treatment, of the capsaicin 8% patch over a 52-week period. A treatment-emergent adverse event (TEAE) was defined as an adverse event observed after the start of capsaicin 8% patch application, or an adverse event which worsened in severity after patch application. A serious TEAE was any untoward medical occurrence that resulted in death, persistent or significant disability/incapacity, congenital anomaly, or birth defect, in-patient hospitalisation, led to prolongation of hospitalisation, was life threatening or considered a medically important event.

Sensory examination was performed to identify clinically relevant deficits in sensory function at baseline and before each capsaicin 8% patch treatment. Testing was performed at the screening visit, at all patch application visits (prior to patch application), at Week 26 (if applicable), and at the planned (Weeks 52–65) or early termination visit, by physicians who had been given study training. Sensory perception was assessed using standardised 'bedside tests' of response to light brush, pinprick, vibration, warm and cold (see protocol in Supplementary Text 1, Supplemental Digital Content 2, http://links.lww.com/CJP/A397). The examining physician was advised to test up to five locations within the affected area. For each sensory modality, except cold, a single scale was used that ranged from loss of sensation to increased sensitivity: not felt, barely felt, normally felt, increased and not paraesthetic/dysaesthetic, increased and paraesthetic/dysaesthetic, increased and painful. For perception of cold the categories used were: not cold, slightly cold, normally cold, cold but not paraesthetic/dysaesthetic, cold and paraesthetic/dysaesthetic, increased and painful. An unaffected mirror-image area, on the other side (PHN), or anterior thigh or upper forearm (HIV-AN), or other area, as appropriate, was used as a demonstration site. In addition, reflex testing involved assessment of the Achilles tendon reflex using the rating scale: no response, hypoactive, normal, hyperactive, clonus. The physician then chose one response that they considered to

be most clinically relevant. The sensory categories reported at baseline and study end were recorded for each patient and a category shift schema was developed to ascertain if a patient improved, had no change or experienced loss in sensory function during the study.

The areas of spontaneous pain and allodynia/hyperalgesia were also measured at each visit as part of the sensory examination. The composite term allodynia/hyperalgesia was used to describe presence of dynamic mechanical allodynia, cold allodynia (or hyperalgesia), heat allodynia (or hyperalgesia) and pinprick hyperalgesia. The area of allodynia/hyperalgesia and the most painful area were identified by patients, and mapped by the physician. Mapping of both was performed using a cotton swab to gently stroke the skin from outside the usual most painful or sensitive area(s) towards the centre, from six to eight directions (from above, below, left, right, etc.). The boundary was marked at the exact location where a light swab stroke became painful (if applicable), traced on a piece of tracing paper or plastic transparency film, and the area calculated.

Analgesic effectiveness

Assessment of analgesic effectiveness was a secondary endpoint in this study. Assessments included average daily pain (BPI question 5) and Patient Global Impression of Change (PGIC).

The BPI Modified Short Form is a widely used and validated, patient-completed, numeric rating scale that measures severity of pain and its interference with daily function.[24,25] Average daily pain was rated using a 0 to 10 numeric scale anchored at zero for "no pain" and 10 for "pain as bad as you can imagine" for severity. Average pain was recorded daily during screening and weekly from the first patch application visit until the planned or early termination visit. All responses were recorded on the same day of the week (± 2 days), as chosen by the patient during the first patch application visit.

The PGIC is a patient-rated instrument that measures changes in the overall status of patients on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).[26] Patients answered a PGIC questionnaire at patch application visits (except first patch application visit), 4 weeks after each patch

application visit, at Week 26 (if applicable), and at the planned or early termination visit. The EQ-5D visual analogue scale (VAS) score was also assessed at baseline and at the planned or early termination visit.

Statistical analyses

It was planned to enroll 300 eligible patients in the study. The sample size was based on clinical judgment to adequately assess the safety of repeated treatments of capsaicin 8% patch over 1 year. A sample size of 300 patients gave a 95% chance of observing at least one patient with an event with an incidence of 1%. The safety analysis set included all patients who received at least one capsaicin 8% patch and was used for all analyses of safety and effectiveness.

Descriptive statistics were used to describe the absolute values and changes from baseline for "pain now" scores, PGIC and areas of pain and allodynia. Summary statistics for change from baseline in average daily pain was also performed.

Post-hoc analyses of sensory and reflex testing were performed in patients who received three consecutive treatments and post-hoc analyses of pain scores, PGIC and EQ-5D were performed in patients who received four consecutive treatments. To assess variability in the change in pain scores among diagnostic groups, a post-hoc analysis was performed to calculate 95% CI for changes from baseline to Month 12.

A detailed post-hoc analysis was carried out for each sensory modality to identify any shift in the sensory category from baseline. Based on the mode of action of the capsaicin 8% patch and previous studies,[11] it was assumed that two types of shift in the sensation of the treated skin area could occur: deterioration/loss of sensory acuity or increased sensitivity. Deterioration/loss of sensation was considered to have occurred if the sensory category moved from increased sensitivity or normal sensation to "barely felt" ("slightly cold") or "not felt" ("not cold"), or from "barely felt" ("slightly cold") to "not felt" ("not cold") after treatment (Supplementary Table 2a, Supplemental Digital Content 3, http://links.lww.com/CJP/A398). If a patient shifted to the category "increased sensitivity and pain" by study end, they were considered to

have developed new hyperaesthesia/allodynia (Supplementary Table 2b, Supplemental Digital Content 3, http://links.lww.com/CJP/A398). However, if a patient with increased or inadequate sensation moved to "normal" or another improved category according to Supplementary Table 2c, Supplemental Digital Content 3, http://links.lww.com/CJP/A398 by study end, they were considered to have improvement of sensation. Patients who reported the same sensory category at baseline and study end were classified into the "no change" group. A total of four possible category shifts did not fit into the above categories and were designated "unclear change" (Supplementary Table 2d, Supplemental Digital Content 3, http://links.lww.com/CJP/A398).

Results

Patients

A total of 345 patients were screened and 306 patients received capsaicin 8% patch treatment, of whom 107 had a diagnosis of PHN, 99 had PNI, 80 had HIV-DSPN and 20 other peripheral NPs.

At baseline in the total population, the mean (standard deviation [SD]) age was 57.9 [15.0] years, average time since peripheral NP diagnosis 5.1 [5.5] years, and average daily pain score 6.6 [1.4] (Table 1). Baseline average pain scores in each diagnostic group were: PHN, 6.6 [1.5]; PNI, 6.8 [1.4]; HIV-DSPN, 6.4 [1.5]; other peripheral NP, 6.7 [1.2]. Other demographic and baseline characteristics such as age, time since diagnosis and ethnicity were similar between the pain diagnostic groups (Table 1).

Except for one patient in the PHN group, all patients used pre-application topical anaesthetics during the study (n=305; 99.7%): amides were the most frequent chemical subgroup (n=291; 95.1%). All patients used concomitant pain therapy during the study, and the most frequent medications used for neuropathic pain are summarised in Table 2 (Overall 77.8%, PHN, 79.4%; PNI, 83.8%; HIV-DSPN, 65.0%; other peripheral NP, 90.0%). Post-application medications (administered on days 1 to 5 after patch application) were used by 37.6% of patients (PHN, 43.9%; PNI, 38.4%; HIV-DSPN, 31.3%; other peripheral NP, 25.0%).

Overall, 176 patients (57.5%) completed the study after receiving treatment (Figure 1). In total, 130 patients (42.5%) discontinued after treatment was initiated, most commonly due to lack of effectiveness (n=54; 17.6%), withdrawal by patient (n=33; 10.8%) and loss to follow up (n=17; 5.6%). The average interval between each capsaicin 8% patch retreatment was 107.0 days. The majority of patients received only one capsaicin 8% patch treatment (n=76; 24.8%) in this study, and the proportion of patients subsequently receiving further capsaicin treatments steadily decreased throughout the duration of the study (Figure 2a). In total, 52% (159/306) of patients received three capsaicin 8% patch treatments and 32.7% (100/306) received four treatments during the study (Figure 2b). When analysed by study visit, the proportion of patients who discontinued decreased throughout the study and the proportion of completers increased (Supplementary Figure 1, Supplemental Digital Content 4, http://links.lww.com/CJP/A399 ; ad-hoc analysis).

Safety and tolerability

TEAEs

A total of 252 patients (82.4%) reported a TEAE and the proportions were similar between the diagnostic groups (Table 3). The maximum reported severity was mild for 78 patients (25.5%), moderate for 104 patients (34.0%) and severe for 70 patients (22.9%), which corresponded to 142 reported severe TEAEs (Table 3). The most commonly reported TEAE was application site pain (36.6%). An increase in blood pressure that was considered by the study investigator to be unusual for the patient, or that required further intervention, was observed in 7 patients (2.3%). Eleven patients (3.6%) discontinued treatment due to TEAEs (reported only once); five from the PHN group (application site erythema, application site pain, and PHN in one patient, and cerebral haemorrhage, facial neuralgia, pain, squamous cell carcinoma in the other four patients); four from PNI group (burning sensation, complex regional pain syndrome, neuralgia, renal colic); one from HIV-DSPN group (pneumonia); and one from other peripheral NP group (allodynia). Three deaths occurred during the study period and none were considered to be related to

study treatment, as assessed by the study investigator. Two deaths occurred in the PHN group (cerebral haemorrhage and squamous cell carcinoma) and one in the HIV-DSPN group (pneumonia).

Drug-related TEAEs

Drug-related TEAEs were reported by 207 patients (67.6%) (Table 3). The maximum reported severity was mild for 84 patients (27.5%), moderate for 82 patients (26.8%) and severe for 41 patients (13.4%). Application site pain (22/306 patients; 7.2%) was the most common severe drug-related TEAE, reported by ≥5% patients in all diagnostic groups. Three patients (1.0%) discontinued due to drug-related TEAEs: one patient in PHN group (application site erythema, application site pain and PHN); one patient in PNI group (neuralgia); and one patient in other peripheral NP group (allodynia). The proportion of patients who experienced drug-related TEAEs did not change over the course of the study (130/230 [56.5%] patients between first and second treatment; 87/159 [54.7%] between second and third; 57/100 [57.0%] between third and fourth; 26/52 [50.0%] between fourth and fifth treatment; 7/16 [43.8%] between fifth and sixth).

Sensory perception and reflex testing

In the total population, sensory category shift analyses in patients who attended at least two sensory testing visits (n=278 for all tests except warm, n=277), found that 50.4% (n=140) reported sensory deterioration/loss in at least one modality by study end versus baseline. The number of patients with deterioration/loss in one, two, three or four tests by study end was 26.6% (n=74), 14.0% (n=39), 5.8% (n=16) and 2.5% (n=7), respectively. A total of four patients had sensory deterioration/loss in all five sensory tests by study end versus basline. The diagnostic groups and most painful areas were as follows: PHN, n=1 (torso); HIV-DSPN, n=1 (legs); PNI, n=2, (feet, arms). In these four patients, sensory deterioration/loss occurred at treatments one, two, six and end of study, respectively.

At study end, 40.7–49.3% (depending on test) of patients showed no sensory change compared with baseline, and 25.2%–32.0% (depending on test) reported an improved sensory category by study end

(Table 4). Between 1.1% and 3.6% of patients (depending on the test) reported new hyperaesthesia/allodynia at study end. With regards to reflex testing, an improved response was observed in 11.3% of patients by study end compared with baseline.

Analysis of pain in patients with sensory deterioration/loss and improvement (according to scheme in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A396) in the total population by study end, found mean changes in average pain from baseline to EoS ranged from -1.2 to -1.6 (depending on test) in patients who reported deterioration/loss of sensory perception, and from -1.3 to -2.2 in patients who reported an improvement in sensory perception. In addition, analysis of quality of life changes from baseline to end of study found mean changes in EQ-5D VAS score ranged from -2.0 to 5.4 in patients who reported a deterioration/loss of sensory perception, and -2.8 to 8.8 in patients who reported improved sensory perception.

Following three consecutive capsaicin 8% treatments (n=100 for all tests except warm, n=99), the majority of patients either showed no sensory change (41.0–48.0% depending on test) or actual improvement (28.0%–37.0%) before fourth treatment (Table 5). Sensory category shift analyses from baseline found that 50.0% of patients (n=50) reported sensory deterioration/loss in at least one modality by study end versus baseline, while the number of patients with sensory deterioration/loss in one, two, three, four or five tests was 23.0% (n=23), 20.0% (n=20), 3.0% (n=3), 2.0% (n=2), and 2.0% (n=2), respectively.

Area of allodynia/hyperalgesia

In the total population, the mean [SD] area of allodynia/hyperalgesia decreased from 241.9 cm^2 [259.1] (interquartile range [IQR]: 62.5–323.5) before first application (n=224) to 219.9 cm^2 [286.7] (IQR: 36.0–282.0) at end of study (n=245). In patients with PHN, the area decreased from 251.1 cm^2 [219.5] (IQR: 106.0–323.5) before first application (n=96) to 192.3 cm^2 [212.8] (IQR: 37.0–255.0) at end of study (n=105).

In the subset of patients who received four consecutive capsaicin 8% patch treatments, the area of allodynia/hyperalgesia decreased from 227.4 cm^2 [268.5] (IQR: 51.5–282.5) before first treatment (n=80) to 213.4 cm^2 [254.4] (IQR: 43.0–299.0) before fourth treatment (n=84).

Area of spontaneous pain

The majority of patients reported painful areas at the torso (41.2%) or the feet (34.6%) before first treatment, and the distribution of painful areas remained similar throughout the study. In the total population, the mean [SD] area of maximal spontaneous pain decreased from 365.0 cm^2 [313.9] (IQR: 117.0–519.0) before first application to 322.7 cm^2 [324.2] (IQR: 82.0–472.0) at end of study. In patients with PHN (n=107), the area of pain decreased from 327.2 cm^2 [235.2] (IQR: 155.0–467.0) to 254.0 cm^2 [225.6] (IQR: 82.0–331.0).

In the subset of patients who received four consecutive capsaicin 8% patch treatments (n=100), the area of pain decreased from 310.1 cm^2 [275.4] (IQR: 97.5–437.5) to 268.5 cm^2 [254.4] (IQR: 74.5–409.5).

Analgesic effectiveness

Average daily pain

For the total population and each individual diagnostic group, a sustained reduction in average daily pain intensity was observed during the study (Figure 3a). The average daily pain [SD] was 6.6 [1.43] at baseline and 4.7 [2.27] at Month 12. The overall change in mean daily pain intensity was -1.9 [SD 1. 89; 95% CI: -2.19, -1.59] from baseline to Month 12. In patients with assessments at baseline and Month 12 (n=174), no differences in average daily pain reduction were observed between the total population and any of the individual diagnostic groups (data not shown).

In the subset of patients who received four consecutive capsaicin 8% patch treatments (n=100), a reduction in average daily pain was observed following each successive capsaicin treatment, and pain

relief was sustained between treatments (Figure 3b). The change in average daily pain intensity was -2.1 [SD 1.7; 95% CI: -2.46, -1.78] from baseline to Month 12 in this subset of patients.

Patient Global Impression of Change

The majority of patients in the total population, as well as the individual diagnostic groups, reported an improvement in their overall status during the study. Of the total population, 31.6% of patients reported themselves to be 'very much improved' or 'much improved' by the end of the study (Figure 4). In patients who received four capsaicin 8% patch treatments (n=100), 48.1% reported themselves to be 'very much improved' or 'much improved' 4 weeks after their fourth treatment.

Discussion

The present study investigated for the first time the safety and tolerability of up to six capsaicin 8% patch treatments over 52 weeks in a large cohort of non-diabetic patients with various peripheral NP aetiologies. Of note, two thirds of patients received chronic pain medication, suggesting a relatively refractory pain condition. Results showed that capsaicin 8% patch repeat treatment over 52 weeks was well tolerated regardless of aetiology, with variable alteration in sensory function and a minimal risk of complete sensory loss. In addition, capsaicin 8% patch repeat treatment induced substantial and sustained reductions in pain over 52 weeks, with progressive reductions in line with the periods of each consecutive retreatment.

Methodological considerations of this study that are important to highlight include the study design and safety assessment. The study was designed so that patch application was dependent on the effectiveness and safety experienced by patients, reflecting use in routine clinical practice. Safety was assessed using a standardised neurological examination, which enabled qualitative categorisation of deficit and pain.

As capsaicin causes defunctionalisation of hyperactive nociceptors, which leads to pain relief,[11] impaired sensory perception may have been a potential effect of the patch following repeat treatment. In addition,

regenerating small diameter fibres may be sensitive[27] and can therefore lead to unwanted cutaneous tenderness or frank pain. Indeed, both types of sensory changes were seen across all sensory modalities. The development of new hyperalgesia/allodynia in a minority of patients may be considered an unfortunate adverse effect, but it appears not to have had an effect on the total pain of these patients. There was no substantial difference in pain scores or EQ-5D VAS scores in patients with worsened versus improved sensory perception. In some patients there was a surprising change in large diameter fiber-mediated sensory function (touch, vibration), the cause of which is not entirely clear. However, improvement of such functions could lead to increased detection of applied stimuli. It is therefore important to put these findings in clinical context and it is noteworthy that complete loss of sensation after treatment was seen in only four patients. In one of these patients the patch was applied over the feet and in the others it is was applied over the leg, torso and arm, where such sensory deterioration/loss would have likely had less clinical effect. A total of 74 and 39 patients had sensory deterioration/loss in one and two tests, respectively, while only 7 patients had sensory deterioration/loss in four tests. Sensory deterioration in one or two tests is of limited clinical significance in this patient setting, and clinically may be regarded as acceptable. In addition, following three consecutive treatments, no increase in sensory deterioration was observed in patients, speaking against any cumulative sensory alteration at the application site. In a recent exploratory study of 20 patients with peripheral NP, no significant deterioration was shown in any sensory function other than warm detection following a single application of the capsaicin 8% patch[28]. This result may seem to contradict findings of the present study; however, sensory changes in the exploratory study were based on whole group analyses, whereas in the present study the change in each sensory function in each individual was recorded. Given the main aim of safety and the greater number of patch applications in the present study, we believe our method is better suited to identify patients who might be particularly susceptible to adverse sensory effects of high concentration capsaicin.

Although sensory deterioration/loss was reported by a proportion of patients, it is also noted that improvement in sensation was seen in 25.2–32.0% of treated patients by study end. Our putative hypothesis is that following capsaicin treatment, the phenotype of regenerated fibers may be closer to those unaffected by the disease, resulting in restoration of sensory perception; however, this hypothesis requires further study.

The secondary outcome of the present study concerned the analgesic effectiveness of repeated treatment with the capsaicin 8% patch. Repeated treatment with the capsaicin 8% patch induced a sustained reduction in average daily pain intensity for the total population, which similarly affected each individual diagnostic group and also the subgroup who received four consecutive capsaicin 8% patch treatments. The reduction in pain was consistent after each treatment, with no or minimal increase before retreatment. These results were supported by the global impression of improvement reported by about one-third of patients at the end of the study.

While the open-label design of this study may be considered more reflective of clinical practice, it is a major limitation, and as patients knew which treatment they were receiving, the findings related to analgesic effectiveness should be interpreted with caution. There was a high rate of patient discontinuation, which is consistent with the study design, but may also be considered a limitation. This was also a single-arm study, preventing comparison of results in patients who did not receive capsaicin. Regarding sensory testing, a single scale that only allowed the examiner to identify the most intense sensation may have masked other important sensory changes. Recovery of a patient with allodynia at baseline could have unmasked the presence of sensory deficit. The inherent inaccuracy in this methodology could have been avoided by using separate scales for sensory detection and suprathreshold stimuli, and further strengthened by application of quantitative sensory testing.[29] Possible variation between investigators in the ‘bedside tests’ of sensory function and concomitant opioid use also need to be considered. The large number of centers involved was a major reason for the present choice of methodology, even if this may have compromised the accuracy of sensory assessment. Topical

anaesthetics were used by all but one patient prior to capsaicin 8% patch treatment, with amides being the most common group. It is noted that lidocaine has been shown to have differential effects on sensory function.[30] Detection thresholds were significantly elevated for touch, pinprick pain and mechanically induced wind-up after lidocaine 5% patch application in a randomised, double-blind study conducted in 20 healthy volunteers.[30] However, this effect was completely reversed in 2–3 days, probably due to clearance of lidocaine from the skin. In the present study, sensory testing was performed several weeks after the previous application of the capsaicin 8% patch, making any impact from the use of topical anaesthetics on the results unlikely.

Conclusion

Capsaicin 8% patch repeat treatment over 52 weeks in various perjpheral NP aetiologies was well tolerated, with mostly local adverse effects, resulted in variable sensory alteration, and no increase in area of allodynia or of maximum pain. Both improvement and worsening of sensation were observed with a minimal chance of complete sensory loss. No accumulation of any adverse effects was seen after three or four capsaicin 8% patch treatments. Sustained reductions in average pain intensity were also observed. The findings from this study demonstrate that capsaicin 8% patch repeat treatment is a well tolerated and effective long-term treatment option in patients with peripheral NP.

References

1. Torrance N, Smith BH, Bennett MI, et al. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* 2006;7, 281–289.

2. Bouhassira D, Lantéri-Minet M, Attal N, et al. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008;136,380–387.

3. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology* 2007;68:1178–1182.

4. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150, 573–581.

5. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–173.

6. Tesfaye S, Vileikyte L, Rayman G, et al. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab Res Rev* 2011;27:629–638.

7. Gahr M, Freudenmann RW, Hiemke C, et al. Pregabalin abuse and dependence in Germany: results from a database query. *Eur J Clin Pharmacol* 2013;69:1335–1342.

8. Smith BH, Higgins C, Baldacchino A, et al. Substance misuse of gabapentin. *Br J Gen Prac* 2012;62:406–407.

9. Schwan S, Sundström A, Stjernberg E, et al. A signal for an abuse liability for pregabalin – results from the Swedish spontaneous adverse drug reaction reporting system. *Eur J Clin Pharmacol* 2010;66:947–953.

10. Güloğlu C, Orak M, Üstündağ M, et al. Analysis of amitriptyline overdose in emergency medicine. *Emerg Med J* 2011;28:296–299.

11. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011;107:490–502.

12. 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;31:502–510.

13. Kennedy WR, Vanhove GF, Lu SP, et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. *J Pain* 2010;11:579–587.

14. European Medicines Agency. Summary of product characteristics: QUTENZA™ 179 mg cutaneous patch. October 8, 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000909/WC500040453.pdf. Accessed February 16, 2016.

15. Backonja M, Wallace MS, Blonsky RE, 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.

16. Brown S, Simpson DM, Moyle G, et al. NGX-4010, a capsaicin 8% patch, for the treatment of painful HIV-associated distal sensory polyneuropathy: integrated analysis of two phase III, randomized, controlled trials. *AIDS Res Ther* 2013;10:5.

17. Irving GA, Backonja MM, 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 Med* 2011;12:99–109.

18. Simpson DM, Brown S, Tobias J: NGX-4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology* 2008;70:2305–2313.

19. Maihöfner C, Heskamp ML. Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8% cutaneous patch in 1044 patients with peripheral neuropathic pain: first results of the QUEPP study. *Curr Med Res Opin* 2013;29:673–683.

20. Maihöfner C and Heskamp ML. Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study. *Eur J Pain* 2014;18:671–679.

21. Haanpa¨ a¨ M, Cruccu G, Nurmikko T, et al. Capsaicin 8% cutaneous patch versus oral pregabalin in patients with peripheral neuropathic pain. *Eur J Pain* 2016;(2):316–328.

22. Stoker M, Katz N, Van J. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomised, double-blind, placebo-controlled study [abstract no. 64 plus oral]. In: 51st EASD Annual Meeting. 2015.

23. Vinik AI, Perrot S, Vinik EJ. Capsaicin 8% patch repeat treatment versus standard of care in painful diabetic peripheral neuropathy: a randomised, open-label, 52-week study [abstract no. 1068 plus poster]. In: 51st EASD Annual Meeting. 2015.

24. Cleeland CS. Pain assessment in cancer. In: Osoba D, ed. *Effect of Cancer on Quality of Life*., Boca Raton, Fl: CRC Press, 1991: 293–304.

25. Cleeland CS. Brief Pain Inventory User Guide. Pain Research Group, Houston, TX, USA, 2009.

26. Guy W. ECDEU assessment manual for psychopharmacology, DHEW Publication No. ADM 76–338, US Government Printing Office, Washington, DC, USA, 1976.

27. Gilron I, Watson PN, Cahill CM, et al. Neuropathic pain : a practical guide for the clinician. *CMAJ* 2006;175:265–275.

28. Mainka T, Malewicz NM, Baron R, Enax-Krumova EK, Treede RD, Maier C. Presence of hyperalgesia predicts analgesic efficacy of topically applied capsaicin 8% in patients with peripheral neuropathic pain. *Eur J Pain* 2016;20:116–129.

29. Backonja MM, Walk D, Edwards RR, et al. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *Clin J Pain* 2009;25:641–647.

30. Wehrfritz A, Namer B, Ihmsen H, Mueller C, Filitz J, Koppert W, Leffler A. Differential effects on sensory functions and measures of epidermal nerve fiber density after application of a lidocaine patch (5%) on healthy human skin. Eur J Pain 2011;15:907–912.

Figure legends

Figure 1. Patient flow during study

Figure 2a. Maximum number of treatments with capsaicin 8% patch (safety analysis set)

Figure 2b. Exposure to capsaicin 8% patch treatment (safety analysis set)

Figure 3a. Change from baseline in average daily pain throughout the study (safety analysis set)

Figure 3b. Change from baseline in average daily pain in patients who received four capsaicin 8% patch applications (post-hoc analysis)

Figure 4. Patient Global Impression of Change by end of the study (safety analysis set)

Table 1. Baseline demographics and characteristics (safety analysis set)

Characteristics	**PHN (n=107)**	**PNI (n=99)**	**HIV-DSPN (n=80)**	**Other peripheral NP (n=20)**	**Total (N=306)**
Sex, n (%)					
Male	57 (53.3)	44 (44.4)	65 (81.3)	8 (40.0)	174 (56.9)
Ethnicity, n (%)					
Caucasian	104 (97.2)	95 (96.0)	66 (82.5)	19 (95.0)	284 (92.8)
Black or African American	1 (0.9)	4 (4.0)	14 (17.5)	1 (5.0)	20 (6.5)
Asian	2 (1.9)	0 (0)	0 (0)	0 (0)	2 (0.7)
Age, years [SD]	70.5 [10.9]	49.7 [13.5]	51.5 [11.0]	56.5 [10.8]	57.9 [15.0]
Time since pain diagnosis, years† [SD]	3.9 [5.0]	4.0 [4.3]	7.4 [5.8]	7.7 [8.0]	5.1 [5.5]
Pain severity index (BPI questions 3, 4, 5, 6)†† [SD]	6.2 [1.6]	6.4 [1.6]	5.9 [1.7]	6.3 [1.4]	6.2 [1.6]
Pain interference index (BPI questions 9a to 9g)†† [SD]	4.4 [2.3]	5.5 [2.0]	5.4 [2.4]	5.1 [2.2]	5.1 [2.3]
Worst pain in last 24 h (BPI question 3)†† [SD]	7.2 [1.7]	7.3 [1.7]	6.6 [2.1]	7.0 [1.3]	7.1 [1.8]
Least pain in last 24 h	5.2 [2.3]	5.3 [2.2]	4.9 [2.2]	5.2 [1.8]	5.2 [2.2]

(BPI question 4)[††] [SD]					
Average pain in last 24 h (BPI question 5) [SD]	6.6 [1.5]	6.8 [1.4]	6.4 [1.5]	6.7 [1.2]	6.6 [1.4]
<5, n (%)	17 (15.9)	6 (6.1)	13 (16.3)	1 (5.0)	37 (12.1)
≥5, n (%)	90 (84.1)	93 (93.9)	67 (83.8)	19 (95.0)	269 (87.9)
Prior pain medication, n (%)*	13 (12.1)	10 (10.1)	4 (5.0)	3 (15.0)	30 (9.8)
Analgesics	4 (3.7)	1 (1.0)	2 (2.5)	1 (5.0)	8 (2.6)
Antiepileptics	5 (4.7)	1 (1.0)	1 (1.3)	1 (5.0)	8 (2.6)
Anti-inflammatory and anti-rheumatics	2 (1.9)	1 (1.0)	0	1 (5.0)	4 (1.3)
Topic joint/muscular pain products	2 (1.9)	5 (5.1)	0	0	7 (2.3)

Data are mean [SD], unless otherwise indicated

[†]Time since diagnosis = ("date of baseline visit" – "date of diagnosis" + 1 day) / 365.25

[††] Assessed at baseline in 278 patients (97 with PHN, 94 with PNI, 69 with HIV-DSPN, 18 with other peripheral NP)

*Used before baseline date, which was either ongoing at the time of baseline date or stopped prior to baseline date

NP, neuropathic pain

Table 2. Pain medication used by ≥5% of patients during the study (safety analysis set)

Medication class, n (%)	PHN (n=107)	PNI (n=99)	HIV-DSPN (n=80)	Other peripheral NP (n=20)	Total (N=306)
Overall	85 (79.4)	83 (83.8)	52 (65.0)	18 (90.0)	238 (77.8)
Analgesics	77 (72.0)	74 (74.7)	41 (51.3)	16 (80.0)	208 (68.0)
Other analgesics and antipyretics	60 (56.1)	51 (51.5)	29 (36.3)	12 (60.0)	152 (49.7)
Anilides	32 (29.9)	20 (20.2)	11 (13.8)	4 (20.0)	67 (21.9)
Other opioids	19 (17.8)	28 (28.3)	9 (11.3)	4 (20.0)	60 (19.6)
Natural opium alkaloids	23 (21.5)	21 (21.2)	10 (12.5)	3 (15.0)	57 (18.6)
Analgesics	9 (8.4)	7 (7.1)	3 (3.8)	5 (25.0)	24 (7.8)
Antiepileptics	68 (63.6)	55 (55.6)	36 (45.0)	14 (70.0)	173 (56.5)
Other antiepileptics	60 (56.1)	51 (51.5)	30 (37.5)	13 (65.0)	154 (50.3)
Benzodiazepine derivatives	9 (8.4)	7 (7.1)	7 (8.8)	3 (15.0)	26 (8.5)
Psychanaleptics	28 (26.2)	29 (29.3)	16 (20.0)	12 (60.0))	85 (27.8)
Non-selective monoamine reuptake inhibitors	16 (15.0)	22 (22.2)	11 (13.8)	7 (35.0)	56 (18.3)
Other antidepressants	12 (11.2)	10 (10.1)	3 (3.8)	5 (25.0)	30 (9.8)
Urologicals	14 (13.1)	11 (11.1)	4 (5.0)	5 (25.0)	34 (11.1)
Antiinflammatory and antirheumatic products	7 (6.5)	17 (17.2)	5 (6.3)	1 (5.0)	30 (9.8)
Topical products for joint and muscular pain[†]	7 (6.5)	15 (15.2)	6 (7.5)	1 (5.0)	29 (9.5)
Cardiac therapy	12 (11.2)	10 (10.1)	4 (5.0)	1 (5.0)	27 (8.8)
Other gynaecologicals*	5 (4.7)	10 (10.1)	3 (3.8)	0 (0)	18 (5.9)

Treatments used for neuropathic pain, ongoing or starting on or after the baseline visit until end of study visit. A medication which could be classified into several therapeutic and/or chemical subgroups is presented in all therapeutic and chemical subgroups.

*Antiinflammatory products for vaginal administration

†Anti-inflammatory preparations and non-steroidals for topical use

HIV-DSPN, human immunodeficiency virus-associated distal sensory polyneuropathy; PHN, post-herpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury nerve injury; NP, peripheral neuropathic pain

Table 3. Summary of treatment-related adverse events and drug-related treatment-related adverse events (safety analysis set)

Event, n (%)	**PHN (n=107)**	**PNI (n=99)**	**HIV-DSPN (n=80)**	**Other peripheral NP (n=20)**	**Total (N=306)**
TEAEs	87 (81.3)	86 (86.9)	62 (77.5)	17 (85.0)	252 (82.4)
TEAEs identified as application site reactions	74 (69.2)	68 (68.7)	30 (37.5)	13 (65.0)	185 (60.5)
Most commonly reported TEAEs (≥5.0% of patients)					
Application site pain	46 (43.0)	40 (40.4)	21 (26.3)	5 (25.0)	112 (36.6)
Erythema	29 (27.1)	29 (29.3)	1 (1.3)	3 (15.0)	62 (20.3)
Application site erythema	24 (22.4)	19 (19.2)	2 (2.5)	6 (30.0)	51 (16.7)
Burning sensation	11 (10.3)	20 (20.2)	8 (10.0)	6 (30.0)	45 (14.7)
Pain	13 (12.1)	16 (16.2)	6 (7.5)	8 (40.0)	43 (14.1)
Pain in extremity	2 (1.9)	5 (5.1)	11 (13.8)	1 (5.0)	19 (6.2)
Nausea	4 (3.7)	8 (8.1)	1 (1.3)	3 (15.0)	16 (5.2)

TEAEs leading to treatment discontinuation	5 (4.7)	4 (4.0)	1 (1.3)	1 (5.0)	11 (3.6)
Drug-related TEAEs*	78 (72.9)	73 (73.7)	42 (52.5)	14 (70.0)	207 (67.6)
Most commonly reported drug-related TEAEs* (≥5.0% of patients)					
Application site pain	46 (43.0)	40 (40.4)	21 (26.3)	5 (25.0)	112 (36.6)
Erythema	29 (27.1)	29 (29.3)	1 (1.3)	3 (15.0)	62 (20.3)
Application site erythema	24 (22.4)	19 (19.2)	2 (2.5)	6 (30.0)	51 (16.7)
Burning sensation	11 (10.3)	19 (19.2)	8 (10.0)	6 (30.0)	44 (14.4)
Pain	7 (6.5)	11 (11.1)	4 (5.0)	7 (35.0)	29 (9.5)
Drug-related TEAEs* leading to treatment discontinuation	1 (0.9)	1 (1.0)	0 (0)	1 (5.0)	3 (1.0)
Mild TEAEs[†]	23 (21.5)	32 (32.3)	19 (23.8)	4 (20.0)	78 (25.5)
Moderate TEAEs[†]	38 (35.5)	31 (31.3)	27 (33.8)	8 (40.0)	104 (34.0)
Severe TEAEs[†]	26 (24.3)	23 (23.2)	16 (20.0)	5 (25.0)	70 (22.9)
Serious TEAEs	14 (13.1)	13 (13.1)	8 (10.0)	2 (10.0)	37 (12.1)
Drug-related serious TEAEs*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths[††]	2 (1.9)	0 (0.0)	1 (1.3)	0 (0.0)	3 (1.0)

*Possible or probable, as assessed by the investigator, or records where relationship is missing.

[†]Severity refers to maximum severity of TEAEs reported by patient.

[††]All deaths were unrelated to capsaicin 8% patch treatment.

HIV-DSPN, human immunodeficiency virus-associated distal sensory polyneuropathy; NP, neuropathic pain; PHN, post-herpetic neuralgia; PNI, peripheral nerve injury; TEAEs, treatment-emergent adverse events

Table 4. Summary of sensory category shift changes from baseline to end of study (safety analysis set)

Sensory shift, n (%)*	Pinprick (n=278)	Light brush (n=278)	Vibration (n=278)	Warm (n=277)	Cold (n=278)
Sensory deterioration/loss	45 (16.2)	41 (14.7)	50 (18.0)	54 (19.5)	58 (20.9)
New hyperaesthesia or allodynia	6 (2.2)	9 (3.2)	12 (4.3)	3 (1.1)	10 (3.6)
No change	130 (46.8)	137 (49.3)	113 (40.7)	121 (43.7)	130 (46.8)
Sensory improvement	70 (25.2)	73 (26.3)	89 (32.0)	86 (31.1)	71 (25.5)
Unclear change	27 (9.7)	18 (6.5)	14 (5.0)	13 (4.7)	9 (3.2)

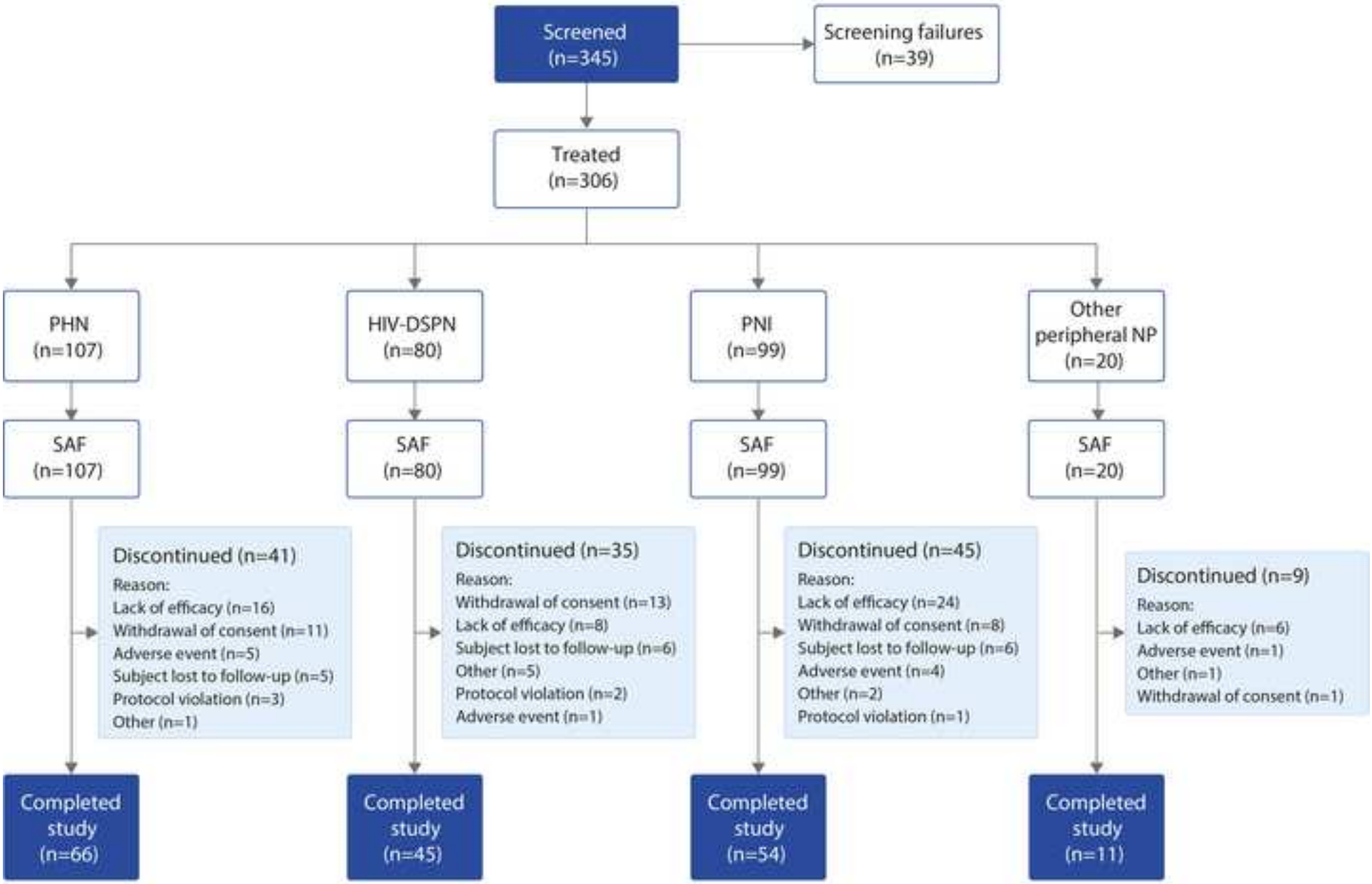
*Definition of shift analyses shown in Supplementary Table 1.
The end of study (EoS) is the planned or early termination visit (9 weeks after last patch application) if available, otherwise the latest post-baseline assessment is used. Only those values of EoS that occurred after first patch application have been included into this analysis.

Table 5. Summary of sensory category shift changes following three consecutive capsaicin treatments

Sensory shift, n (%)*	**Pinprick (n=100)**	**Light brush (n=100)**	**Vibration (n=100)**	**Warm (n=99)**	**Cold (n=100)**
Sensory deterioration/loss	14 (14.0)	20 (20.0)	17 (17.0)	19 (19.2)	20 (20.0)
New hyperaesthesia or allodynia	1 (1.0)	4 (4.0)	2 (2.0)	1 (1.0)	4 (4.0)
No change	48 (48.0)	44 (44.0)	39 (39.0)	41 (41.4)	41 (41.0)
Sensory improvement	26 (26.0)	28 (28.0)	37 (37.0)	32 (32.3)	31 (31.0)
Unclear change	11 (11.0)	4 (4.0)	5 (5.0)	6 (6.1)	4 (4.0)

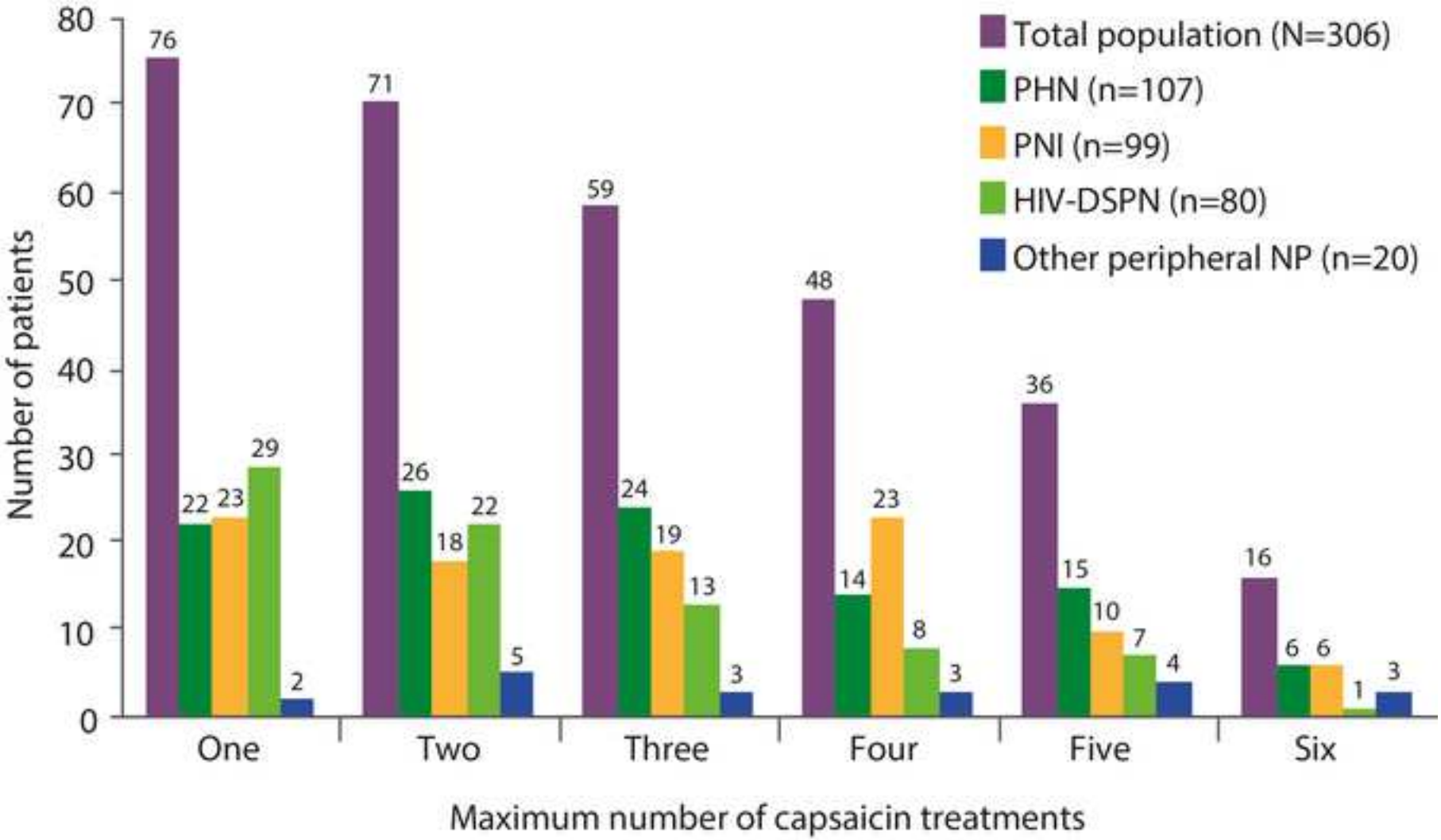
*Definition of shift analyses shown in Supplementary Table 1.

Figure 1. Patient flow during study



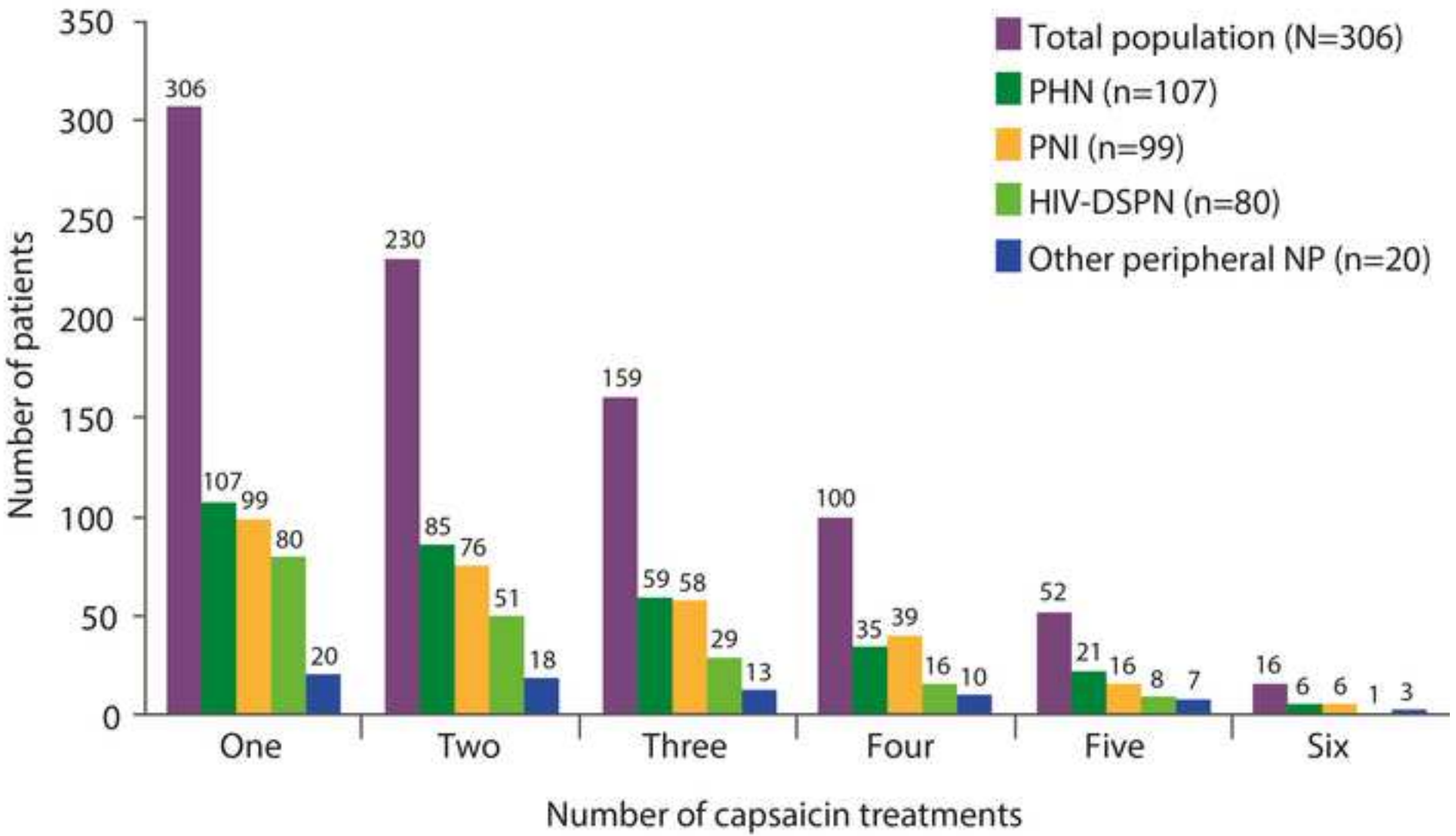
HIV-DSPN, human immunodeficiency virus-associated distal sensory polyneuropathy; NP, neuropathic pain; PHN, postherpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury; SAS, safety analysis set

Figure 2a. Maximum number of treatments with capsaicin 8% patch (safety analysis set)



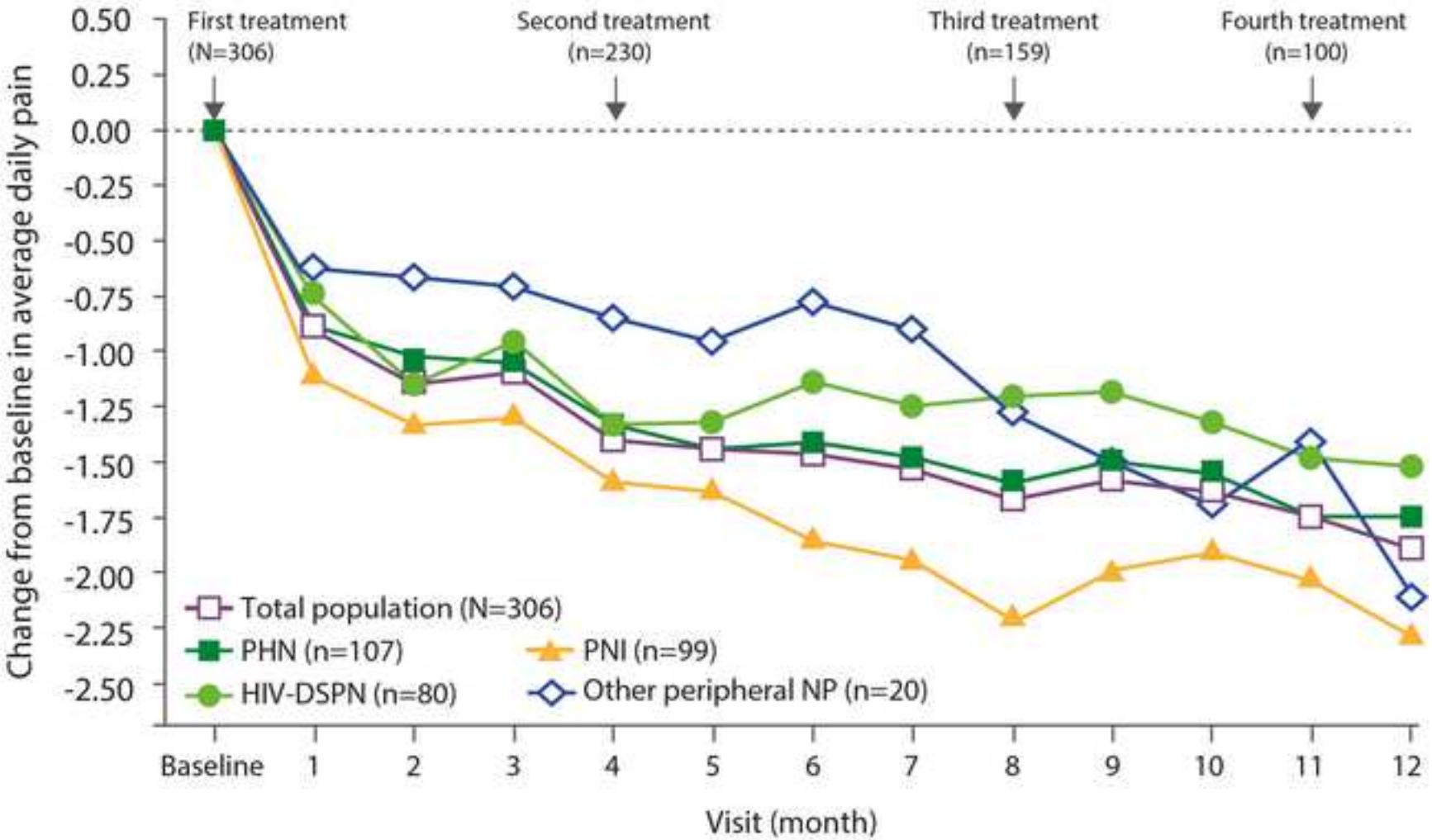
HIV-DSPN, HIV-associated distal sensory polyneuropathy; PHN, post-herpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury; NP, neuropathic pain

Figure 2b. Exposure to capsaicin 8% patch treatment (safety analysis set)



HIV-DSPN, HIV-associated distal sensory polyneuropathy; PHN, post-herpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury; NP, neuropathic pain

Figure 3a. Change from baseline in average daily pain throughout the study (safety analysis set)



Arrows show the average day of successive capsaicin treatments and number of patients receiving treatment: second treatment, 98.9 days after first (Day 99); third treatment, 109.5 days after second (Day 208); fourth treatment, 99.3 days after third (Day 308). Time estimated for second, third and fourth treatments.

HIV-DSPN, HIV-associated distal sensory polyneuropathy; PHN, post-herpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury; NP, neuropathic pain

Figure 3b. Change from baseline in average daily pain in patients who received four capsaicin 8% patch applications (post-hoc analysis)

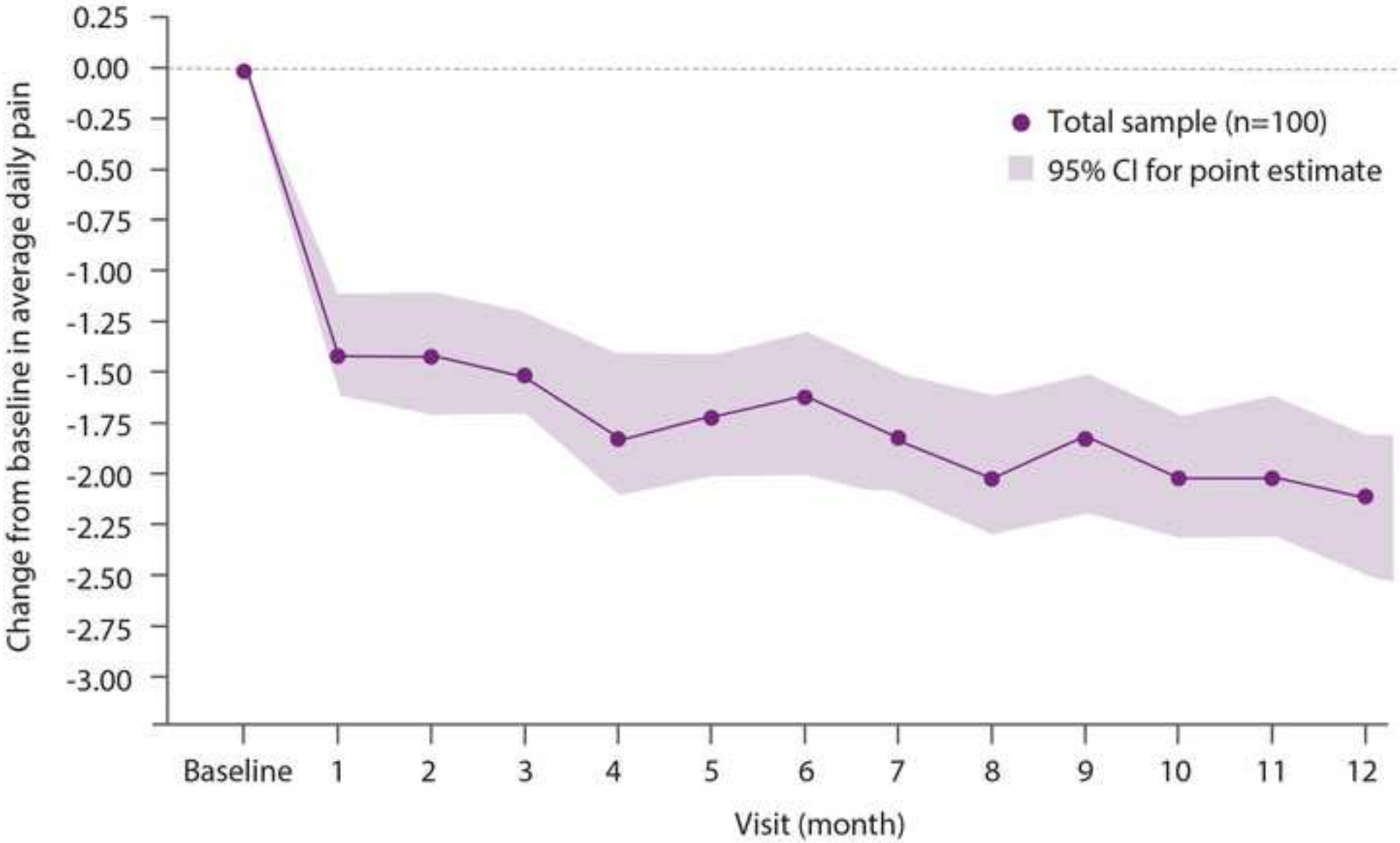
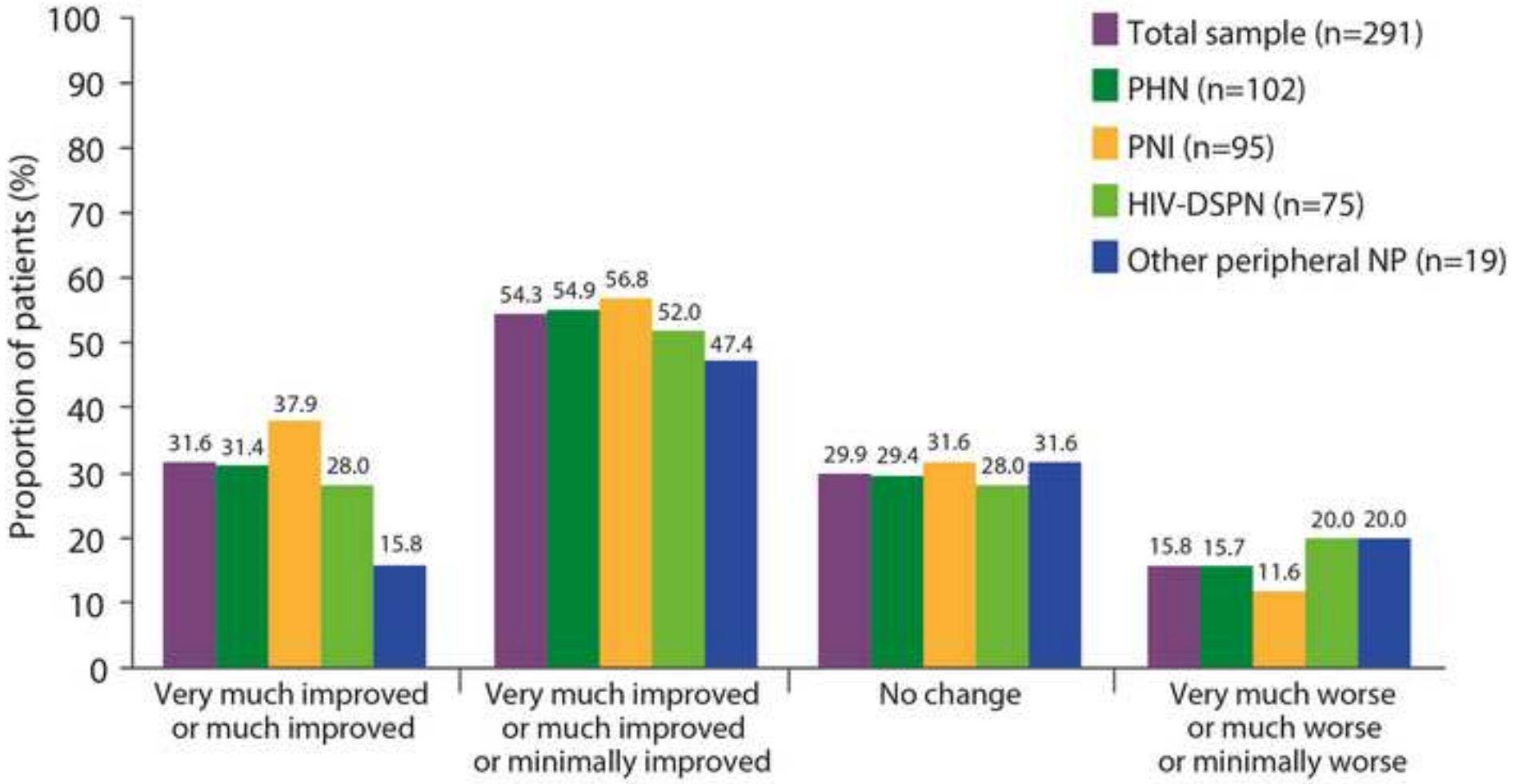


Figure 4. Patient Global Impression of Change by end of the study (safety analysis set)



This figure shows the 'very much improved' and 'much improved' categories twice to illustrate the difference between those patients who were at least much improved versus those with any degree of improvement; n is number of patients with non-missing data.

HIV-DSPN, HIV-associated distal sensory polyneuropathy; PHN, post-herpetic neuralgia; PNI, post-traumatic or post-surgical nerve injury; NP, neuropathic pain