

Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract: This 12-week study evaluated the efficacy and safety of capsaicin 8% patch versus placebo patch in painful diabetic peripheral neuropathy (PDPN). Patients aged 18 years or older with PDPN were randomized (1:1) to one 30-minute treatment (capsaicin 8% patch or placebo patch) to painful areas of the feet. Overall, 369 patients were randomized (capsaicin 8% patch, n = 186; placebo patch, n = 183). Percentage reduction in average daily pain score from baseline to between weeks 2 through 8 (the primary end point) was statistically significant for capsaicin 8% patch versus placebo (−27.4% vs −20.9%; $P = .025$); improvements in pain were observed from week 2 onward. Versus placebo, patients treated with capsaicin 8% patch had a shorter median time to treatment response (19 vs 72 days) and modest improvements in sleep interference scores from baseline to between weeks 2 through 8 ($P = .030$) and weeks 2 through 12 ($P = .020$). Apart from application site reactions, treatment-emergent adverse events were similar between groups. No indications of deterioration in sensory perception of sharp, cold, warm, or vibration stimuli were observed. In patients with PDPN, capsaicin 8% patch treatment provided modest pain relief and sleep quality improvements versus a placebo patch, similar in magnitude to other treatments with known efficacy, but without systemic side effects or sensory deterioration.

Perspective: To our knowledge, this is the first study of the capsaicin 8% patch versus placebo in patients with PDPN to show that one 30-minute capsaicin treatment provides modest improvements in pain and sleep quality. Results confirm the clinical utility of the capsaicin 8% patch in the diabetic population.

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Key words: Capsaicin 8% patch, painful diabetic peripheral neuropathy, NPRS average daily pain score, Brief Pain Inventory-Diabetic Neuropathy, phase 3 study.

Received October 20, 2015; Revised January 15, March 18, and April 25, 2016; Accepted September 29, 2016.

This study was funded by Astellas Pharma Europe B.V., Leiden, The Netherlands. Astellas developed the protocol in conjunction with the clinical investigators and provided the study drug. The authors received editorial support for manuscript preparation from Sarah Reynolds of NexGen Healthcare Communications, London, United Kingdom, and this assistance was supported by Astellas Pharma Europe Ltd. The authors, however, directed and are fully responsible for all content and editorial decisions for this report.

D.M.S. has consulted for and received research grants from Astellas Pharma, Acorda, and Viomed and received speaking honoraria from Acorda. N.K. was a paid consultant for Astellas Pharma to support the design of this study and received a research grant from Astellas Pharma. M.S., H.J., and R.J.S. are employed by Astellas Pharma Europe BV. D.S.S. is employed by Chiltern International (CRO) but was exclusively outsourced

to Astellas for the duration of the study. S.K.L. was employed by Astellas Pharma Europe BV at the time of the study. J.V., J.R.-P., and B.L. have no conflicts of interest to declare.

Supplementary data accompanying this article are available online at www.jpain.org and <http://www.sciencedirect.com/>.

ClinicalTrials.gov registration: NCT01533428.

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<http://dx.doi.org/10.1016/j.jpain.2016.09.008>

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Painful diabetic peripheral neuropathy (PDPN) is a debilitating condition and has been shown to affect approximately one-quarter of patients with type 2 diabetes mellitus.⁸ Limited consensus regarding the optimal management of PDPN has led to variable clinical management with antidepressants, anticonvulsants, or opioid medications.²² Each of these therapies act on the central nervous system and have limitations in clinical practice, including discontinuation because of adverse events (AEs), lengthy dose titration, drug–drug interactions, the need for frequent, repeat administration, and the risk of addiction, abuse, and withdrawal symptoms.^{11,21} Furthermore, the results of a systematic review and meta-analysis of pharmacotherapy for neuropathic pain in adults confirm the modest efficacy of treatment, and low-moderate tolerability for oral treatments.¹⁰

Recent treatment guidance for peripheral neuropathic pain (PNP) has proposed the capsaicin 8% patch as a second-line option.¹⁰ Capsaicin is a potent, highly selective vanilloid receptor subtype 1 agonist that causes depolarization of the neuron.¹ The capsaicin 8% patch contains 8% weight for weight capsaicin and is optimized for rapid delivery of a high concentration of capsaicin directly to the skin. This delivery of capsaicin induces defunctionalization of hyperactive nociceptors in the skin and provides rapid, targeted, and sustained pain relief after a single treatment.¹ Additionally, minimal systemic absorption limits the potential for drug–drug interactions, eliminates the need for dose adjustment in the elderly or patients with renal or hepatic impairment, and minimizes the risk of systemic AEs.²

Phase 3 studies of the capsaicin 8% patch in patients with postherpetic neuralgia (PHN) and HIV-associated distal sensory polyneuropathy (HIV-DSPN) showed that it provided at least 12 weeks of pain relief after a single application, whereas one trial in HIV-DSPN was negative.^{3,6,7,13,19} The ELEVATE study in nondiabetic patients with PNP reported that the capsaicin 8% patch provided pain relief noninferior to pregabalin, with a faster onset of action, fewer systemic side effects, and greater patient satisfaction with treatment.¹² The efficacy and safety of the capsaicin 8% patch in patients with PDPN has not yet been fully characterized. The present study, STEP, is to our knowledge, the first assessment of the efficacy and safety of the capsaicin 8% patch versus placebo in this population.

Methods

Study Design and Objectives

STEP was a phase III, randomized, double-blind, placebo-controlled, multicenter trial performed between February 2012 and February 2014 and conducted in the United States (ClinicalTrials.gov Identifier: NCT01533428). The study was approved by an independent ethics committee and was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations. Written informed consent was obtained from all patients.

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After a 12-day screening period, patients were randomized 1:1 to receive a single treatment with the capsaicin 8% patch (Qutenza; Acorda Therapeutics, Inc, Ardsley, NY; obtained from Astellas Pharma Europe BV, Leiden, The Netherlands) or identical placebo patch to painful areas of their feet for 30 minutes.

Randomization was coordinated through an interactive voice response system. Patients and study staff were blinded to treatment assignment but, because the application of capsaicin 8% patch often results in localized pain and erythema, additional measures were taken to maintain the study blind: 1) physicians and/or nurses who conducted clinical assessments and who had access to, and the responsibility to record, patients' efficacy and safety data were separate from those carrying out the patch application and from those measuring baseline dermal assessments; 2) results from the dermal assessments at baseline were recorded on paper, sealed in an envelope and not disclosed to any site staff apart from the physicians and/or nurses who performed the dermal assessments; 3) instructions to the patient stressed that they may or may not experience pain during or after the application of the patch; 4) all patients were pretreated with a eutectic mixture of local anesthetics (EMLA) containing lidocaine 2.5% and prilocaine 2.5%, to limit pain or discomfort during the application period; and 5) the patch application site was covered using stretchable socks immediately after patch application and for 24 hours subsequent to removal of the patch to prevent patient identification of erythema.

The treatment area was mapped at screening and application visits. Treatment borders were defined by the painful areas of the feet, up to a total combined surface area of 1,120 cm² for both feet.

Patients were required to call in daily and report their average pain over the past 24 hours. The baseline pain score was defined as the mean score during the 12-day baseline run-in period, during which patients were required to have at least 7 valid data entries. After the capsaicin 8% patch or placebo patch application, patients visited the clinic at weeks 2, 4, 8, and 12/end of study (EoS) for assessment.

Patients

Eligible patients were aged 18 years or older and had a diagnosis of PDPN due to type 1 or type 2 diabetes mellitus, for ≥ 1 year before screening. Further criteria for inclusion and key exclusion criteria are presented in [Table 1](#).

Efficacy and Safety Assessments

Primary Efficacy End Point

The primary efficacy end point of the study was the percentage change in the Numeric Pain Rating Scale (NPRS) average daily pain score as assessed over the previous 24 hours according to question 5 of the Brief Pain Inventory (BPI)-Diabetic Neuropathy (BPI-DN) from baseline to the mean score over weeks 2 through 8.²⁴

Table 1. Key Inclusion and Exclusion Criteria

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
<ul style="list-style-type: none"> • HbA1c \leq11% (96.7 mmol/mol) at 3 to 6 months before screening and at screening • <1% difference in HbA1c between screening and prescreening values • Patients with HbA1c >11% or >1% difference required rescreening, and could be enrolled if the investigator considered the HbA1c level was appropriately optimized for that patient • Stable doses of pain medications for more than 4 weeks before the screening visit. Use of any oral, transdermal, or parenteral opioids, or topical pain medications including nonsteroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics, or capsaicin products on or near the affected areas where study drug was to be applied, was not permitted. The use of other medications was permitted, including up to 2 analgesics from different drug classes (antidepressants and antiepileptics) at fixed doses • Minimum of 6 consecutive pain recordings during the screening period • Average NPRS score over the last 24 hours of \geq4 during the screening period 	<ul style="list-style-type: none"> • Primary pain associated with PDPN in the ankles or above • Pain that could not be clearly differentiated from, or conditions that might interfere with, the assessment of PDPN • Current or previous foot ulcer • Clinically significant cardiovascular disease within 6 months before screening; significant peripheral vascular disease • Oral, transdermal, or parenteral opioids, regardless of dose, within 7 days preceding patch application • Clinically significant foot deformities • Clinically significant abnormal electrocardiogram at screening • Any amputation of lower extremity • Use of any topical pain medication on the painful areas within 7 days preceding patch application or previous treatment with capsaicin 8% patch or hypersensitivity to capsaicin, capsaicin 8% patch excipients, EMLA ingredients, or adhesives • Body mass index \geq40 • Impaired glucose tolerance only without diabetes mellitus

The BPI is a widely used and validated numeric rating scale that measures severity of pain and its interference with daily function. Each BPI item is scored from 0 ('no pain' or 'does not interfere') to 10 ('pain as bad as you can imagine' or 'completely interferes') for severity and interference, respectively. The BPI-DN²⁴ is a version of the BPI that asks a patient to rate severity and interference items specifically for diabetes-related pain, encouraging the patient to focus on distal pain associated with their neuropathy.

Secondary Efficacy End Points

Secondary efficacy end points in this study were: 1) percentage change in NPRS average daily pain score (question 5 of the BPI-DN) from baseline to the mean score over weeks 2 through 12; 2) percentage change and mean change in average daily pain scores each week (calculated over weekly windows from week 1 [average of days 1–7] throughout the study to week 12 [average of Days 77–84]); 3) occurrence of \geq 30% and \geq 50% decrease in average daily pain score from baseline compared with the mean score over weeks 2 through 8 and 2 through 12 (responder analyses); 4) percentage change in sleep interference NPRS score (question 9F of the BPI-DN) from baseline compared with the mean score over weeks 2 through 8 and 2 through 12; 5) percentage change in sleep interference according to the NPRS score each week; 6) time to treatment response, defined as the first of 3 consecutive days on which the patient reported \geq 30% decrease in average daily pain score from baseline; 7) overall patient status using Patient Global Impression of Change at weeks 2, 8, and 12; 8) treatment satisfaction using the Self-Assessment of Treatment II questionnaire at baseline, weeks 8 and 12; and 9) change in EuroQol in 5 Dimensions from baseline to weeks 2, 8, and 12.

Subgroup Analyses of Primary Efficacy Variable

Prespecified subgroup analyses of the primary efficacy variable were performed on baseline average daily pain score ($<$ 7, \geq 7), glycated hemoglobin of A1c (HbA1c; $<$ 6.5%, \geq 6.5%), and duration of PDPN ($<$ 3 years, \geq 3 to $<$ 10 years, \geq 10 years). Subgroup analyses were also performed on maximum Neuropathic Pain Symptom Inventory (NPSI)⁵ dimensions performed at the baseline and EoS visit; patients were allocated to 1 of 5 dimensions of the NPSI (evoked pain, pressing subcutaneous pain, paroxysmal pain, paresthesia/dysesthesia, burning [superficial] spontaneous pain) according to their highest dimension score.

Safety and Tolerability Assessments

Assessments of the safety and tolerability of capsaicin 8% patch included: 1) treatment-emergent AEs (TEAEs) and serious AEs; 2) vital signs; 3) laboratory analyses; 4) dermal assessments (before application of topical anesthetic, within 15 and at 60 minutes after patch removal); 5) 'pain now' NPRS scores before and after patch application; 6) rescue pain medication use on days 1 through 5; and 7) 'bedside' sensory and reflex testing on feet at baseline and EoS to identify any clinically relevant deficits in sensory function. Sensory testing was performed as follows: warm, cold, and sharp assessments were rated as 'absent,' 'diminished,' 'normal,' or 'painful' at 3 points on the dorsal surface (dorsal surface of great toe, midpoint, and medial malleolus) and 2 points on the plantar surface (ball and midpoint) of both feet. Vibration assessment on the dorsal surface of the great toe was rated as 'absent,' 'markedly diminished,' 'mild loss,' or 'normal' sensation. Achilles tendon reflex assessment was rated as 'absent,' 'diminished,' 'normal,' 'hyperactive,' or 'clonus.' The sensory and reflex testing categories

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reported at baseline and EoS were recorded for each patient and a category shift schema was developed to ascertain if patients improved, stayed the same, or worsened in sensory or reflex function during the study (Fig 1).

Statistical Methods

To provide 90% power to detect a 12% difference in 'average daily pain' NPRS score (average at baseline vs average between weeks 2–8), a sample size of 320 patients (160 per treatment group) was planned. Average daily pain score and sleep interference were analyzed using an analysis of covariance model, which included treatment, gender, and pain score at baseline, HbA1c at screening, and study site as factors/covariates. In addition, a repeated measures analysis of covariance model was used for inferential analyses, which included treatment, study week, Treatment \times Week interaction, gender, pain score at baseline, HbA1c at screening, and study site as factors/covariates. Regarding imputation, a baseline or last observation carried forward approach was used as the primary method, and also in instances in which a patient left the trial early but had an observation after day 8. For missing data on days 1 through 7 or day 8 and ≥ 1 more consecutive day(s), the baseline observation carried forward (BOCF) approach was used. For day 9 and any day thereafter, the last observation carried forward was imputed. If all post-treatment scores were missing (including day 1), BOCF was used. To assess

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the effect of the baseline or last observation carried forward missing data imputation method, sensitivity analyses were performed using the BOCF approach to impute any missing post-treatment daily score for which a patient left the trial early with missing postbaseline values. All statistical comparisons were made using 2-sided tests at the 5% significance level and all confidence intervals (CIs) were calculated with a 2-sided 95% confidence level, unless specifically stated otherwise. Median time to treatment effect for each treatment group was estimated using the Kaplan–Meier method. Overall, no adjustments for multiple comparisons were performed for reported *P* values.

The intention to treat (ITT) population included all randomized patients who received capsaicin 8% patch or placebo patch application, and was the primary data set for efficacy analysis. The per-protocol set (PPS) was comprised of a subset of patients from the ITT population. Exclusion criteria from the PPS included: patch application <24 minutes (<80% of planned duration) or >37 minutes (>125% of planned duration); no valid measurements of the primary efficacy variable between weeks 2 through 8; use/change in dose of prohibited/restricted concomitant medication; nonadherence to inclusion or exclusion criteria; and patch application to 1 foot only. The safety analysis set included all patients who received the study patch application. All results presented are for the ITT population; unless otherwise specified, results from the PPS analysis supported those for

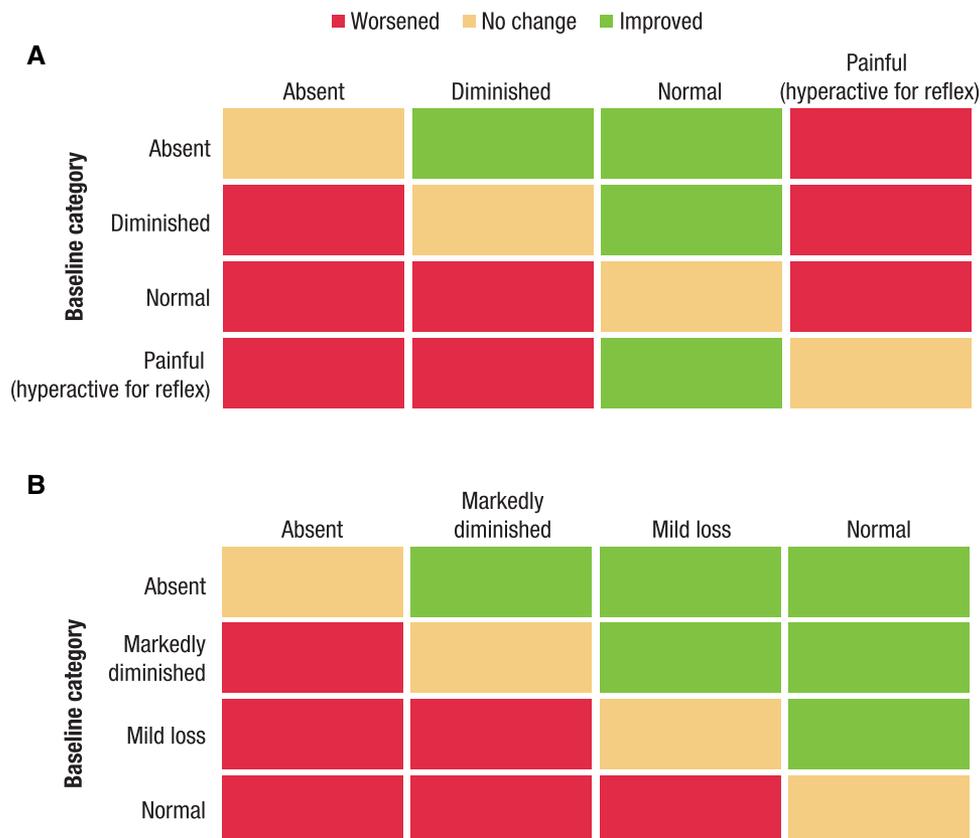


Figure 1. Category shift schema used to judge whether patients improved, stayed the same, or worsened in sensory or reflex function from baseline to EoS. (A) Sharp, warm, cold, and reflex testing; (B) vibration testing.

the ITT population. All safety analyses were performed on the safety analysis set.

Results

Patient Disposition

Of the 761 patients screened, 369 patients were randomized at 29 centers in the United States (186 to capsaicin 8% patch; 183 to placebo patch; Fig 2). The single most common reason for screening failure was the stringent criterion set for stability of glycemic control (HbA1c $\leq 11\%$ [96.7 mmol/mol] at 3–6 months before screening and at screening, with $<1\%$ difference between screening and prescreening values). All patients who were randomized (the ITT population) received treatment. A total of 17 patients discontinued from the study after treatment was initiated. In the capsaicin 8% patch group, 9 patients discontinued; 7 chose to withdraw from the study and 2 were lost to follow-up. In the placebo patch group, 8 patients discontinued; 6 chose to withdraw from the study, 1 was lost to follow-up and 1 discontinued because of a TEAE. In the capsaicin and placebo groups, the mean (SD) number of patches used was 2.7 (1.1) and 2.7 (1.1), respectively, with a mean application duration of 30.3 minutes (1.4) and 30.4 minutes (1.7), respectively. Most patients were Caucasian (71.3%) and baseline characteristics such as age, body mass index, HbA1c, average daily pain, and duration of PDPN were similar in both treatment groups (Table 2). The percentage of patients taking pain medication during the study was 76.3% in the capsaicin 8% patch group and 71.6% in the placebo patch group (Table 3).

Efficacy

Average Daily Pain

There was a modest and statistically significant reduction in average daily pain from baseline to between weeks 2 through 8 in the capsaicin 8% patch group versus placebo patch (mean [SD] = -27.4% [26.79%] vs -20.9% [28.92%], respectively; $P = .025$; Fig 3A). Analysis of change in average daily pain score from baseline to between weeks 2 through 12 showed that this reduction

Table 2. Baseline Characteristics (Safety Analysis Set)

PARAMETER	CAPSAICIN 8% PATCH (N = 186)	PLACEBO PATCH (N = 183)
Sex, n (%)		
Male	114 (61.3)	101 (55.2)
Female	72 (38.7)	82 (44.8)
Ethnicity, n (%)		
Caucasian	132 (71.0)	131 (71.6)
African American	36 (19.4)	38 (20.8)
Asian	4 (2.2)	4 (2.2)
Other	14 (7.5)	10 (5.4)
Mean age [SD], y	63.9 [10.6]	62.0 [10.8]
Mean body mass index [SD]	32.2 [4.5]	31.6 [5.0]
Mean duration of PDPN [SD], y	5.8 [4.0]	5.7 [4.0]
HbA1c at screening		
Mean % [SD]*	7.4 [1.3]	7.2 [1.2]
$<6.5\%$ (<47.5 mmol/mol), n (%)	49 [26.3]	57 [31.1]
$\geq 6.5\%$ (≥ 47.5 mmol/mol), n (%)	137 [73.7]	126 [68.9]
Baseline average daily pain*	6.6 (1.4)	6.4 (1.5)
Pain medications before baseline, n (%)	125 (67.2)	132 (72.1)
Analgesic agents†	90 (48.4)	101 (55.2)
Anti-epileptic drugs	71 (38.2)	82 (44.8)
Anti-inflammatory/ antirheumatic products	46 (24.7)	41 (22.4)
Topical joint/muscular pain products	46 (24.7)	45 (24.6)

*Data for ITT population.

†Analgesic agents were categorized according to analgesics, anilides, natural opium alkaloids, other analgesics and antipyretics, other opioids, and salicylic acid and derivatives.

in average daily pain was maintained (-28.0% [27.3%] vs -21.0% [29.4%], respectively; $P = .018$; Fig 3B). Absolute average (SD) daily pain scores at baseline, baseline to between weeks 2 through 8, and baseline to between weeks 2 through 12 were 6.6 (1.4), 4.9 (2.2), and 4.8 (2.2) in the capsaicin 8% patch group, respectively, and 6.4 (1.5), 5.0 (2.2), and 5.0 (2.2) in the placebo patch group, respectively. Results for the sensitivity analyses were consistent with the primary analysis.

With regard to pain response throughout the study, a greater numerical percentage reduction from baseline in average daily pain score each week became apparent from week 2 in the capsaicin 8% patch group compared with the placebo group (Fig 4).

Responder Analyses

Whereas a similar proportion of patients in both groups achieved at least a 30% reduction in average daily pain score from baseline to between weeks 2 through 8 (capsaicin 8% patch, 39.8%; placebo, 32.8%; $P = .108$), analysis of between weeks 2 through 12 indicated that more patients were responders in the capsaicin 8% patch group during this period (40.9% vs 31.7%, respectively; $P = .050$; Fig 5). Similar proportions of patients in both groups achieved at least a 50% reduction in average daily pain score from baseline to weeks 2 through 8 (21.0% vs

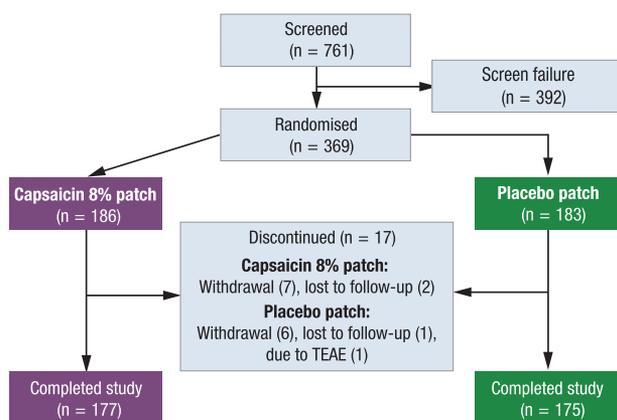


Figure 2. Patient flow.

Table 3. Pain Medication During the Study (Safety Analysis Set)

PAIN MEDICATION	CAPSAICIN 8% PATCH (N = 186)	PLACEBO PATCH (N = 183)
Overall, n (%)	142 (76.3)	131 (71.6)
Category, n (%)		
Analgesic agents*	107 (57.5)	105 (57.4)
Antiepileptic drugs	72 (38.7)	82 (44.8)
Anti-inflammatory/ antirheumatic products	57 (30.6)	40 (21.9)
Topical joint/muscular pain products	56 (30.1)	43 (23.5)
Drug, n (%)		
Acetylsalicylic acid	79 (42.5)	75 (41.0)
Gabapentin	58 (31.2)	71 (38.8)
Ibuprofen	30 (16.1)	23 (12.6)
Naproxen	21 (11.3)	15 (8.2)
Pregabalin	14 (7.5)	14 (7.7)
Cyanocobalamin	10 (5.4)	10 (5.5)
Duloxetine	6 (3.2)	9 (4.9)

*Analgesic agents were categorized according to analgesics, anilides, natural opium alkaloids, other analgesics and antipyretics, other opioids, and salicylic acid and derivatives.

18.0%, respectively; $P = .403$) and weeks 2 through 12 (22.0% vs 19.1%, respectively; $P = .446$).

Time to Treatment Response

The median time to treatment response was shorter with the capsaicin 8% patch versus placebo patch, with 50% of patients achieving at least a 30% reduction in average daily pain after 19 days (95% CI for median, 12.0–37.0) in the capsaicin 8% patch group versus 72 days (95% CI for median, 19.0–not calculable) in the placebo group (Fig 6).

Sleep Interference

A greater mean percentage reduction in BPI-DN sleep interference NPRS score was seen in the capsaicin 8% patch group versus the placebo patch group from baseline to between weeks 2 through 8 and weeks 2 through 12 ($P = .030$ for weeks 2–8; $P = .020$ for weeks 2–12; Fig 7A); this was maintained throughout the study with a greater numerical percentage reduction in sleep interference observed in the capsaicin 8% patch group compared with the placebo group from week 2 (Fig 7B).

Additional Efficacy Analyses and End Points

Subgroup analyses of the primary end point using baseline pain score, HbA1c, and duration of PDPN (<3 years and ≥ 3 to <10 years only) supported the results for the primary end point within the overall population; however, analysis using maximum NPSI dimension resulted in mixed observations (Supplementary Fig 1). Of note, patients whose primary pain type on the NPSI was ‘paroxysmal pain’ showed the largest numerical treatment response to capsaicin 8% patch compared with placebo (estimated mean difference = -13.8% ; 95% CI, -29.8% to 2.1%). Numerically more patients in the capsaicin 8% patch group reported being “very much improved” or “much improved” in Patient Global Impression of Change status compared with placebo at week 8 (39.4% vs 30.2%; $P = .075$) and week 12 (40.5% vs 29.7%; $P = .169$). There were no notable differences observed at any time point for the change from baseline in EuroQol in 5 Dimensions total score. At week 12, there was an association between treatment and outcome favoring capsaicin 8% patch for 2 questions on the Self-Assessment of Treatment II: “Over the past 7 days, how much has the study treatment improved your pain level?” ($P = .026$, no adjustment for multiple

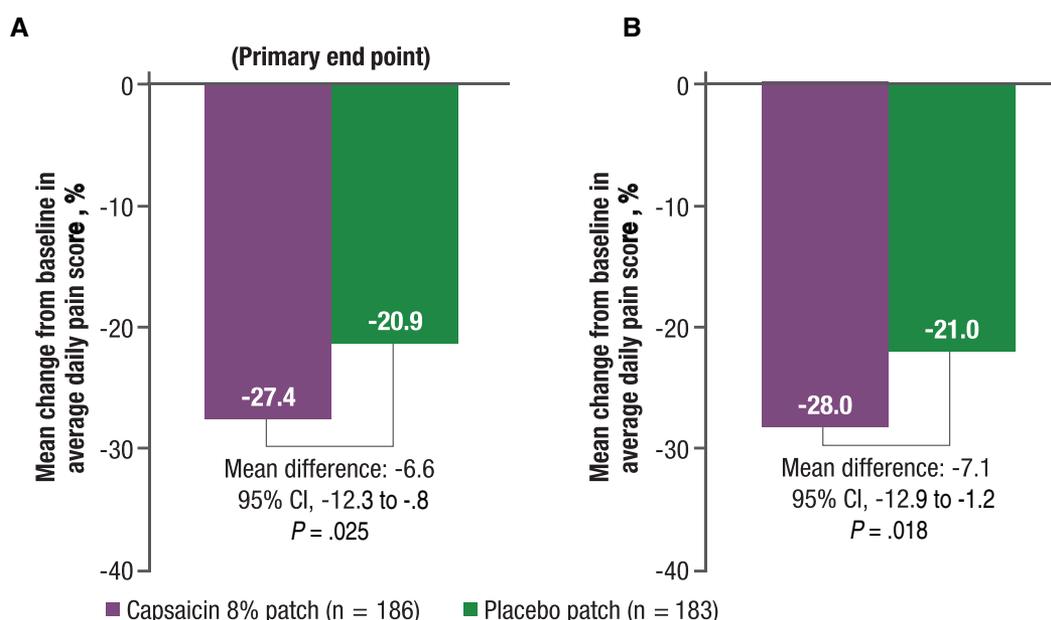
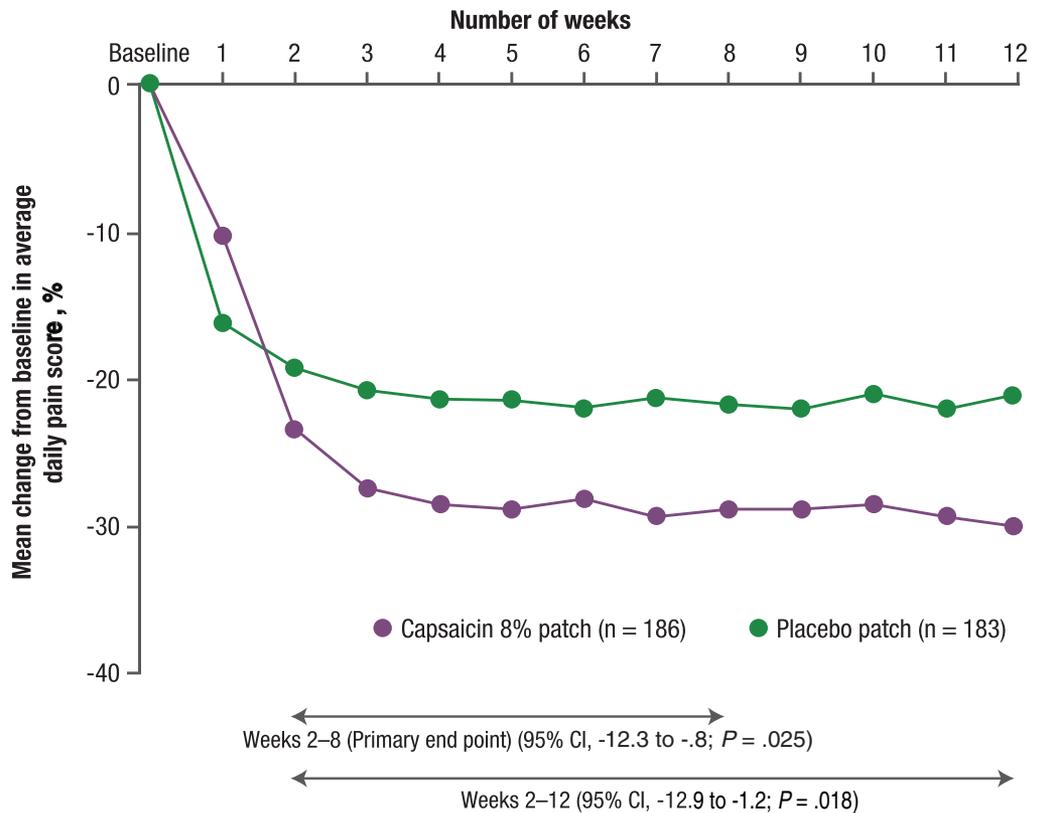


Figure 3. Mean percentage change in average daily pain from baseline to between (A) weeks 2 through 8 and (B) weeks 2 through 12 (baseline or last observation carried forward; ITT). Between group differences were estimated using the least squares method.



Weekly 95% CI	N/A	-10.4, 2.3	-13.1, -0.4	-13.5, -0.8	-13.6, -1.0	-12.6, 0	-14.4, -1.8	-13.5, -0.8	13.2, -0.6	-13.9, -1.2	-13.7, -1.1	-15.3, -2.7
Weekly P value	N/A	.208	.036	.027	.024	.051	.012	.026	.032	.020	.022	.005
Number of patients												
Capsaicin	186	186	186	186	186	186	186	186	186	186	186	186
Placebo	183	183	183	183	183	183	183	183	183	183	183	183

Figure 4. Mean percentage change from baseline in average daily pain score throughout the study (ITT).

comparisons) and “Over the past 7 days, how much has the study treatment improved the following aspects of your life: mood, temperament, or outlook on life?” ($P = .015$, no adjustment for multiple comparisons).

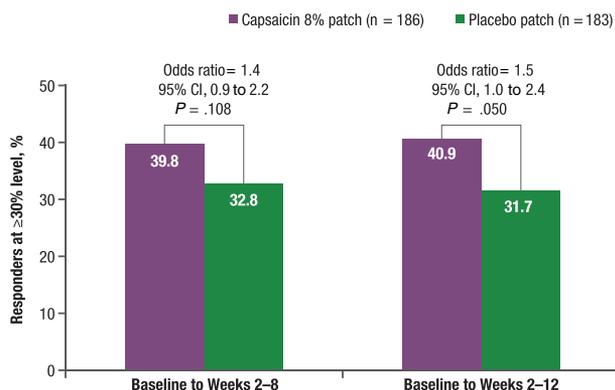


Figure 5. Proportion of patients who achieved a $\geq 30\%$ reduction in average pain score from baseline to between weeks 2 through 8 and weeks 2 through 12 (baseline or last observation carried forward; ITT).

Safety and Tolerability

Adverse Events

In the capsaicin 8% patch group, 46.8% of patients reported TEAEs compared with 33.9% of patients in the placebo patch group (Table 4). This difference was largely because of application site TEAEs; 33.9% of patients in the capsaicin group and 8.2% in the placebo group reported any application site reactions, the most frequent being application site pain. The percentage of patients reporting TEAEs peaked on day 2, plateaued by day 6, and only 1 patient reported a serious TEAE that was unrelated to treatment after day 13. One patient in the placebo group discontinued from the study because of a TEAE (hypertension), which was not considered drug-related. The proportion of patients with drug-related TEAEs was higher in the capsaicin 8% patch group (34.9%) compared with the placebo group (12.6%). Most were mild to moderate in severity; only 3 patients (all in the capsaicin 8% patch group) had severe drug-related TEAEs (severe burning sensation [$n = 2$] and severe application site pain [$n = 1$]). No discontinuations because of drug-related

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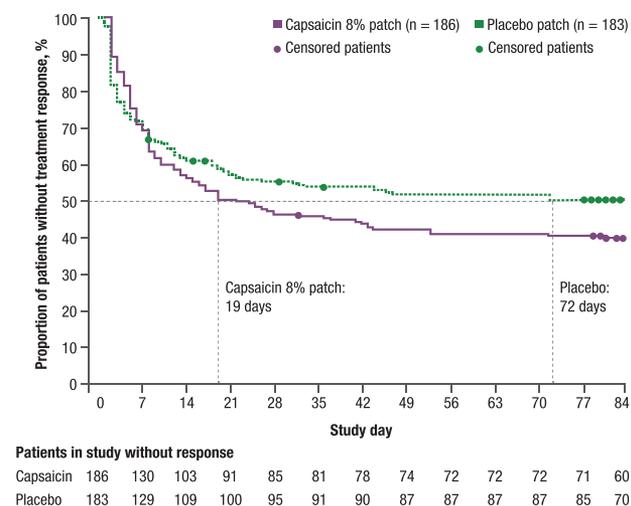


Figure 6. Kaplan–Meier curves for median time to treatment response ($\geq 30\%$ reduction in average daily pain; safety analysis set).

TEAEs occurred in either group. The proportion of patients reporting serious TEAEs was low in both groups, and no drug-related serious TEAEs were reported. No deaths were reported in this study.

Sensory Perception and Reflex Testing

Assessment of changes in sensory perception and reflex testing at EoS versus baseline found that most patients either had no change (52.5% to 83.8% across tests) or improved (12% to 30% across tests) in the capsaicin and placebo groups (Fig 8A; Supplementary Fig 2). Overall, worsened sensation was reported by a lower proportion of patients (4.5% to 21.2% across tests) and a numerically similar proportion in both groups at EoS compared with baseline (Fig 8A; Supplementary Fig 2). The reporting of ‘absent’ sensation decreased for all tests except cold at the ball of the foot in the capsaicin 8% patch group, and for all tests in the placebo patch group. In the capsaicin 8% patch group, patients reporting ‘mild loss’ vibration sensation increased by 7.9%, and reports of ‘diminished’ and ‘absent’ vibration reduced by 2.8% and 4.5%, respectively (Fig 8B). In addition, by EoS, the proportion of patients reporting ‘normal’ sensation had increased and the proportion reporting ‘painful’ sensation had reduced for most tests in both groups (Fig 8C).

Other Safety Findings

Assessment of systolic/diastolic blood pressure and pulse from before to after patch application found that a higher proportion of patients in the capsaicin 8% patch group had a clinically relevant (an increase or decrease of ≥ 20 mm Hg) increase in systolic blood pressure compared with placebo (8.6% vs 2.7%, respectively); no clinically significant abnormal electrocardiograms were recorded.

For dermal assessments, the proportion of patients with no evidence of irritation was similar in both groups at baseline (capsaicin 8% patch, 91.4%; placebo patch,

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94.5%) and at EoS (capsaicin, 95.0%; placebo, 97.2%). The mean change in ‘pain now’ NPRS scores was similar in both groups from before EMLA application to within 15 minutes after patch application (-1.6 and -2.0 for capsaicin and placebo, respectively) and from before EMLA application to within 60 minutes after patch application (-1.8 and -2.2 for capsaicin and placebo, respectively). More patients in the capsaicin 8% patch group used rescue pain medication for pain caused by patch application compared with those in the placebo patch group (18.8% vs 5.5%, respectively), with the anilides chemical subgroup (eg, acetaminophen) the most commonly used (10.8% vs 4.9%, respectively).

Discussion

In patients with PDPN, a single capsaicin 8% patch treatment provided modest improvements in pain relief compared with a placebo patch over a period of 12 weeks. These findings are of similar magnitude to the effects of other treatments with known efficacy in neuropathic pain. With regard to secondary end points, a higher proportion of patients achieved at least a 30% reduction in average daily pain score from baseline to between weeks 2 through 12 with capsaicin 8% patch vs placebo, and the median time to treatment response was substantially shorter with the capsaicin 8% patch. The modest improvements in sleep quality observed with the capsaicin 8% patch were an important finding of this study, because PDPN is often associated with sleep disturbance.²³ Furthermore, sensory testing found no evidence of deterioration in sensation with capsaicin 8% patch treatment and most patients reported the same or improved sensation by EoS. These changes were predominantly in patients who transitioned from the rating categories of ‘absent’ to ‘diminished’ or to ‘normal’ sensation during the study, and these interesting findings have been further evaluated in a long-term study.²²

No new safety issues were observed in this study, which, to our knowledge, is the first double-blind study of the capsaicin 8% patch in patients with diabetes. Capsaicin 8% patch treatment in patients with PDPN was most commonly associated with transient application site reactions, consistent with observations in previous studies involving patients with PHN and HIV-DSPN.^{3,6,13,19} There were no discontinuations because of drug-related TEAEs, and no serious TEAEs that were considered to be drug-related. Taken overall, the results of this pivotal study, in a group of patients who are often difficult to treat, extends the range of PNP etiologies for which the capsaicin 8% patch has shown efficacy and safety, and led to regulatory approval in patients with diabetes in Europe.²

The primary end point in this study—percentage change in average daily pain from baseline to between weeks 2 through 8—has not been used in previous studies in PDPN, which commonly measured the difference in average pain score at specific time points.^{16,17} Measuring the primary end point over a prolonged period of time enables assessment of patients’ longitudinal experience rather than providing a

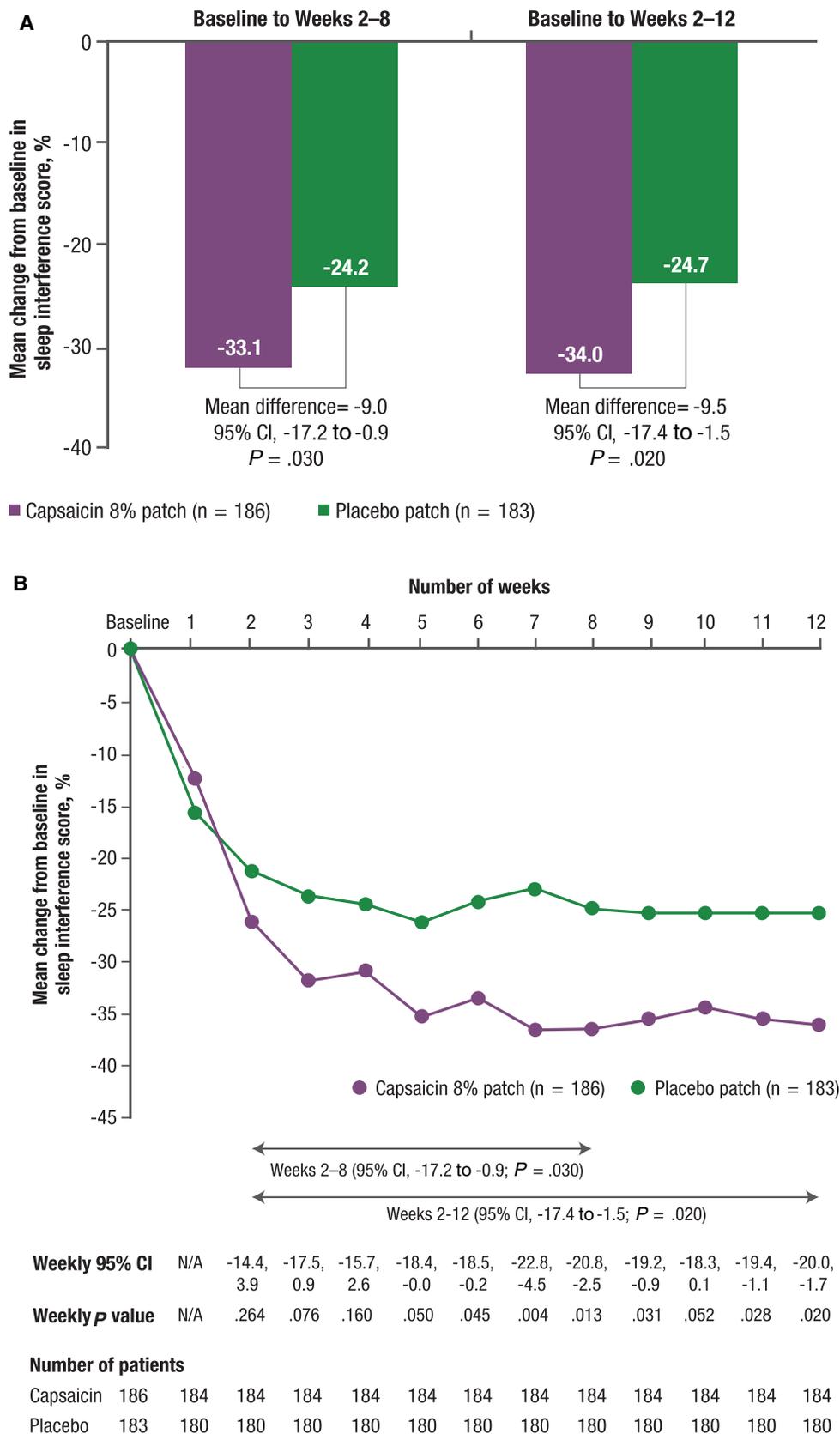


Figure 7. (A) Mean percentage change in sleep interference score from baseline to between weeks 2 through 8 and weeks 2 through 12 (ITT). Between group differences were estimated using the least squares method. **(B)** Mean percentage change from baseline in sleep interference score throughout the study (ITT).

Table 4. Summary of TEAEs and Drug-Related TEAEs (Safety Analysis Set)

<i>EVENT, N (%)</i>	<i>CAPSAICIN 8% PATCH (N = 186)</i>	<i>PLACEBO PATCH (N = 183)</i>
TEAEs	87 (46.8)	62 (33.9)
Most commonly reported TEAEs (>3.0% patients in overall study population)		
Burning sensation	26 (14.0)	5 (2.7)
Pain in extremity	20 (10.8)	10 (5.5)
Application site pain	18 (9.7)	4 (2.2)
TEAEs identified as application site reactions	63 (33.9)	15 (8.2)
Most commonly reported TEAEs (≥2 patients in either treatment group)		
Burning sensation*	26 (14.0)	4 (2.2)
Application site pain*	18 (9.7)	4 (2.2)
Pain in extremity*	17 (9.1)	8 (4.4)
Erythema	2 (1.1)	0 (0)
TEAEs identified as application site pain†	60 (32.3)	14 (7.7)
TEAEs leading to permanent discontinuation	0 (0)	1 (0.5)
Hypertension‡	0 (0)	1 (0.5)
Drug-related TEAEs (>2.0% patients in either treatment group)§	65 (34.9)	23 (12.6)
Drug-related TEAEs leading to permanent discontinuation§	0 (0)	0 (0)
Severe TEAEs	4 (2.2)	8 (4.4)
Drug-related severe TEAEs§	3 (1.6)	0 (0)
Severe burning sensation	2 (1.1)	1 (0.5)
Severe application site pain	1 (0.5)	0 (0)
Serious TEAEs	2 (1.1)	7 (3.8)
Drug-related serious TEAEs§	0 (0)	0 (0)
Deaths	0 (0)	0 (0)

*Also TEAEs identified as application site pain.

†Comprised of application site pain, pain in extremity, and burning sensation.

‡Not considered drug-related.

§Possible or probable, as assessed by the investigator, or records for which relationship was missing.

snapshot at a fixed time point. The lack of consistent methodology in studies of PDPN makes comparison of this study with previous studies of other pain-relieving agents difficult. The optimal approach to comparing the efficacy of 2 drug treatments is a head-to-head comparison within the same study, because only this approach is not beset by differences in study design and conduct that affect the validity of meta-analyses.²⁰ Results from ELEVATE, a head-to-head comparison of capsaicin 8% patch with pregabalin in nondiabetic patients with PNP, showed that the capsaicin 8% patch was noninferior to pregabalin in pain relief. This head-to-head study also reported the capsaicin 8% patch to be associated with a faster onset of action, greater patient satisfaction with treatment, and fewer systemic side effects,¹² replicating the safety profile seen in this and previous studies with the capsaicin 8% patch.

The median time to treatment response with the capsaicin 8% patch in this study was 19 days, compared

Capsaicin 8% Patch in PDPN: The STEP Study with 72 days with placebo patch. Although pain relief was substantially faster with capsaicin 8% than placebo, it occurred approximately 1 week later than in studies in PHN and HIV-DSPN.^{3,6,13,19} Although further research is required to ascertain the reason for this difference, there are several factors that may help explain this observation. Physiological characteristics of the skin of patients with PDPN, such as thickened stratum corneum, waxy skin,¹⁵ and reduced hydration state,¹⁸ may differ from that of patients with PHN and HIV-DSPN, potentially slowing the absorption of capsaicin and delaying pain relief. In addition, patients with PDPN may have reduced numbers of vanilloid receptor subtype 1 receptors, potentially creating a rate-limiting effect on the speed of capsaicin 8% patch response.

An interesting finding in this study was the duration of response after treatment with the placebo patch. In 2 previous double-blinded studies with the capsaicin 8% patch versus active control (.04% capsaicin) in patients with PHN, the response in the control group was maintained for 12 weeks and this was thought to be due to the use of active control that caused mild burning and erythema, but had no effect on epidermal nerve fiber density.^{3,13} Although a placebo patch without capsaicin was used in this study, the placebo response was also maintained for 12 weeks. This was an interesting finding from this study and is in line with a recent analysis of placebo response in PNP studies by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), who reported that the likelihood of study failure and magnitude of placebo response are greater in studies in PDPN compared with PHN.⁹

Overall, more patients in the capsaicin 8% patch group (33.9%) reported application site TEAEs compared with the placebo group (8.2%). It is possible that application site reactions may have led to functional unblinding of patients in the capsaicin group and that this may have influenced the results obtained from the study. Because a "masking assessment" was not performed at the final visit, the likelihood of such functional unblinding cannot specifically be determined. The results of the study should therefore be considered with this limitation in mind. Another important limitation to consider with this study is the treatment delta observed in the primary analysis, which was narrow because of the substantial placebo response observed. The placebo response was not unexpected, because in this study patients in the capsaicin and placebo groups were given a physical patch application. However, the difference between capsaicin 8% patch and placebo was within the boundary of statistical significance in the primary analysis ($P = .025$ for capsaicin vs placebo). Because of the small effect size observed, relative to placebo, and in common with other treatments for PDPN, clinicians will need to consider the clinical meaningfulness on the basis of an individual patient's needs and preferences. This important issue of clinical meaningfulness should be evaluated in all future studies of neuropathic pain. 'Bedside' sensory testing was performed in this multicenter study because it was not feasible to provide adequate training on the

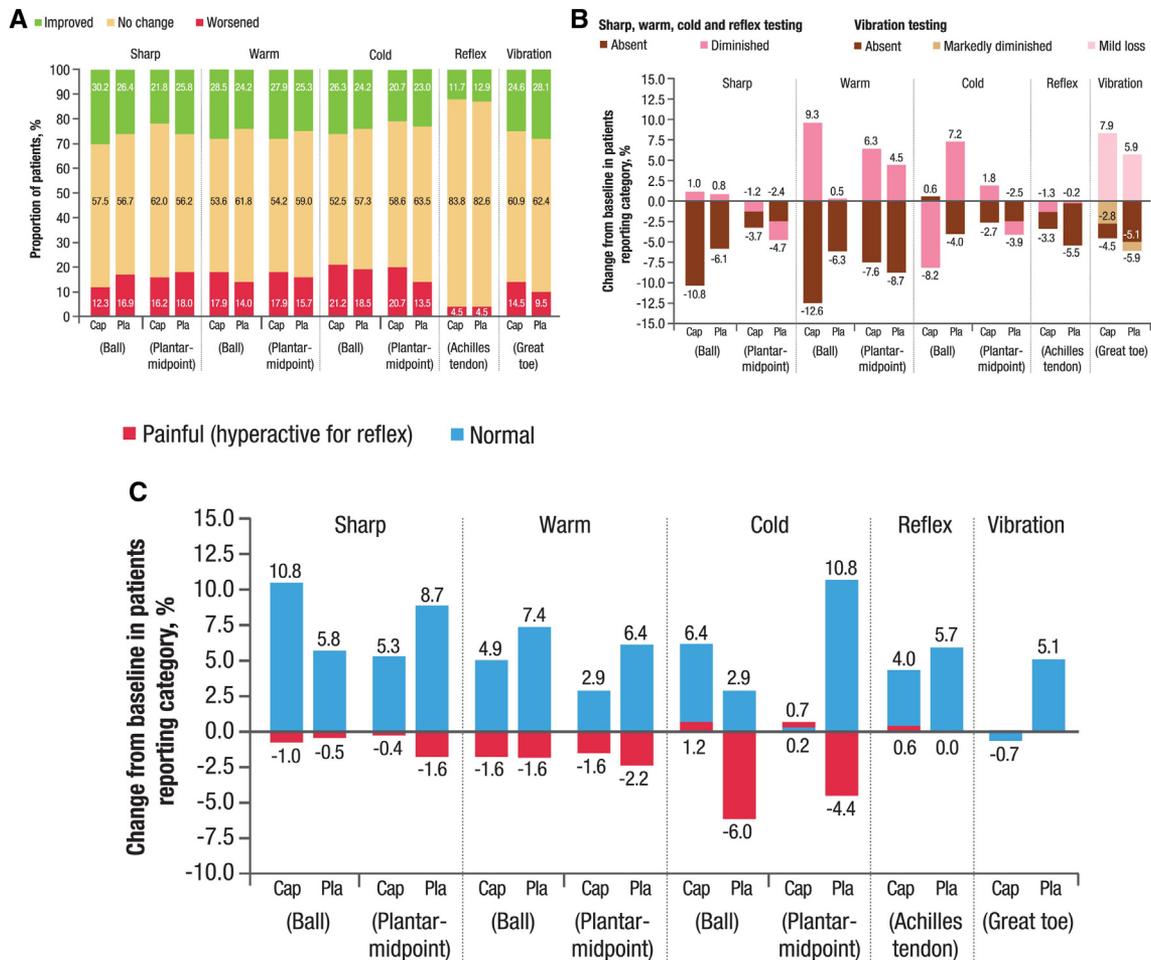


Figure 8. (A) Proportion of patients who reported improved, remained the same, or worsened sensory or reflex function by EoS (safety analysis set; SAS). (B) Change in proportion of patients reporting sensory and reflex testing categories from baseline to EoS (SAS). (C) Change in proportion of patients reporting sensory and reflex testing categories from baseline to EoS (SAS). Abbreviations: Cap, capsaicin 8% patch; Pla, placebo.

Quantitative Sensory Testing (QST) technique across all centers, or standardize all assessments in all study centers, and undertaking the full array of QST techniques imposes a significant time burden on clinicians. However, potential advantages of QST are a quantification of sensory deficits and allodynia/hyperalgesia, and standardized values for several painful sites.^{4,14} Although not feasible in this multicenter study, one cannot exclude that QST would have been more sensitive to detect small variations of thermal or mechanical deficits. The overall study findings may be perceived as limited by the duration of 12 weeks and assessment of a single treatment with the capsaicin 8% patch. A separate open-label study has therefore assessed the long-term safety and tolerability (primary end point) and efficacy of capsaicin 8% patch repeat treatment with standard of care versus standard of care alone over 52 weeks in patients with PDPN (NCT01478607).²²

Conclusions

This study showed that, in patients with PDPN, the capsaicin 8% patch provided modest and statistically

significant improvements in pain relief and improved sleep quality compared with a placebo patch, was well tolerated, and was not associated with any sensory deterioration or new safety concerns. The efficacy of the capsaicin 8% patch is similar to that of other drug treatments for neuropathic pain, but with a lack of systemic AEs, and therefore should be considered for a place in treatment.

Acknowledgments

David Simpson, MD, is the Coordinating Investigator of this study. The authors thank all study investigators (for full list see [Supplementary Table 1](#)) and Faysal Riaz of Astellas Pharma Europe Ltd, Chertsey, United Kingdom, for critical review and his valuable comments.

Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.pain.2016.09.008>.

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