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Repeat treatment with capsaicin 8% patch (179mg capsaicin cutaneous patch): Effects on pain, quality of life, and patient satisfaction in painful diabetic peripheral neuropathy: an open-label, randomized controlled clinical trial

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Reviewed By: ABSTRACT Dr. Negussie Boti Sidemo Objective: To determine long-term safety and effectiveness of repeat treatments with a high concentration capsaicin patch. Department: Methods: In this 52-week, open-label, randomized controlled study, patients with Reviewer/CMRO painful diabetic peripheral neuropathy (PDPN) received either capsaicin patch: (30or 60-min; 1–7 treatments to the feet) plus SOC or SOC alone. Effectiveness was assessed, by changes from baseline to end of study (EoS), in average and severity of pain, pain interference with daily function (Brief Pain Inventory-Diabetic Neuropathy version), responder rates, Patient Global Impression of Change (PGIC), and EuroQol 5-dimension (EQ-5D) questionnaire. Results: 468 patients were randomized (n=156 and n=157, 30 and 60-min respectively; SOC alone, n=155). Safety data have been reported previously. Changes in average pain from baseline to EoS (mean percentage (SD)) were: 30-min, -37.5%(32.9); 60-min, -40.8% (39.7); SOC alone, -13.9% (74.6). The difference between groups increased progressively from -17.7% and -18.6% at Month 1 for 30- and 60-min., respectively, to -21.9% and -24% at Month 12. More 30% responders occurred in the capsaicin groups (30-min, 67.3%; 60-min, 67.5%) and more felt: very much or much improved" (30-min, 24.2%; 60-min, 24.5%), compared with SOC alone (40.6% and 9.5% respectively). A greater mean improvement in EQ-5D utility index and EQ-5D visual analog scale score, from baseline to Month 12, was observed with the 30-min (0.12) and 60-min (0.15) versus SOC alone (0.07)and mean (SD), 30-min (10.4 [18.5]) and 60-min (11.2 [21.4]) versus SOC alone (5.5 [18.1]) respectively. Conclusion: Capsaicin 8% patch showed differential effectiveness over SOC alone, further increasing with repeat treatments. Key words: Diabetic peripheral neuropathy-capsaicin 8% patch-pain managementlong term efficacy-responder rates-Quality of Life

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1 INTRODUCTION:

Painful diabetic peripheral neuropathy (PDPN) has a significant humanistic and economic impact [1] and has been shown to affect many dimensions of patient quality of life (QoL), including mood, sleep, work, self-esteem, and social relationships; it has a particular impact on individuals for whom pain is not well managed [2, 3]. The burden of PDPN appears to be higher with increasing pain severity, whereby more severe pain leads to a higher degree of impairment in daily functioning, sleep, and health-related QoL (HRQoL) [1]. Approximately one in four people with type 2 diabetes will experience some level of PDPN [4], which often presents as numbness, tingling, burning, aching, electric shocks, or lancinating pains [5].

Many patients with PDPN remain undiagnosed or undertreated, and few experience complete resolution of pain. Pharmacological treatment is the mainstay in managing pain and has a direct positive effect on overall QoL. However, there is a clear unmet need for new therapeutic options to improve the current standard of care (SOC); available treatments such as antidepressants, anti-epileptic drugs, and opioids are often limited by contraindications and tolerability issues, and do not always result in adequate pain relief [6-8]. A retrospective analysis of a United States claims database found that most newly diagnosed patients with PDPN are prescribed anticonvulsants at lower than recommended doses, which potentially results in poor treatment outcomes and low levels of satisfaction. These findings, combined with poor tolerability at adequate dose levels, lead to frequent discontinuations of these treatments [9] or suboptimal response due to either dosing or compliance [10]. An alternative treatment is capsaicin 8% patch (179mg capsaicin cutaneous patch), which contains 179 mg or 8% weight-for-weight capsaicin and is formulated for rapid delivery of a high concentration of capsaic directly into the skin [11]. Topical capsaicin acts in the skin to attenuate cutaneous hypersensitivity and reduces pain by a process best described as 'defunctionalization' of nociceptor fibers. Defunctionalization is due to a number of effects that include temporary loss of membrane potential, inability to transport neurotrophic factors leading to altered phenotype, and reversible retraction of epidermal and dermal nerve fiber terminals. Defunctionalization of hyperactive nociceptors in the skin induced by the rapid delivery of capsaicin provides fast, targeted, and sustained pain relief after a single treatment [12]. Furthermore, local application of the capsaicin 8% patch provides minimal systemic absorption, without potential for drug-drug interactions or requirement for dose adjustment in elderly patients or patients with renal or hepatic impairment [13].

The capsaicin 8% patch is well tolerated and provides effective relief of pain for a variety of types of peripheral neuropathic pain (PNP), including post-herpetic neuralgia, human immunodeficiency virus-associated neuropathy, diabetic peripheral neuropathy, post-operative neuropathic

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pain and chemotherapy-induced neuropathic pain [12, 14–20]. In patients with PDPN, treatment with a single capsaicin 8% patch has demonstrated significant improvements in pain relief versus a placebo patch over a period of 12 weeks and was well tolerated with no deterioration in sensory function [21].

This trial was designed primarily as a long-term safety study, evaluating the long-term safety and effectiveness of the capsaicin 8% patch repeat treatment plus SOC, compared with SOC alone, over 52 weeks in patients with PDPN. The safety data were previously published by Vinik et al, 2016 [21] and showed that repeat treatment with the capsaicin 8% patch was well tolerated without negatively impacting the sensory function [19]. The current paper presents the results for the effectiveness, QoL, and patient satisfaction endpoints of this study. Throughout the paper the terms 179mg capsaicin cutaneous patch and capsaicin 8% patch are used interchangeably.

2 METHODS:

Study design:

This was a Phase 3, multinational, open-label, randomized controlled, 52-week safety study, conducted in Europe between November 2011 and February 2014 (ClinicalTrials.gov Identifier: NCT01478607). The primary objective was to evaluate the safety of repeat treatment with the capsaicin 8% patch in patients with PDPN. Secondary objectives included the evaluation of effectiveness.

Following a screening visit, patients were assigned a sixdigit subject number allocated sequentially according to site and randomized to capsaic n 8% patch (with 30-minute application) plus SOC, capsaicin 8% patch (with 60-minute application) plus SOC, or SOC alone in a 1:1:1 ratio by chronological order of enrollment to receive treatment with the capsaic n 8% patch to painful areas of the feet for either 30 minutes (30-min) plus SOC, 60 minutes (60-min) plus SOC, or SOC alone. 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. Duration of application was selected to reflect similar durations as investigated in previous trials with capsaicin 8% patch and to ensure sufficient exposure to investigate its safety and tolerability. SOC was optimized for each patient at the discretion of each investigator and assessed at clinic visits, with no constraints imposed on the mode of treatment. The treatment area was mapped at screening and baseline visits, and re-mapped before treatment. Mapping of the treatment area(s) was identified based primarily on the patient self-report in response to specific questioning and confirmation by sensory testing. Treatment borders were defined by the most painful areas of the feet, up to a total combined surface area of 1,120 cm^2 (four patches) for both feet. Assessments were scheduled every 2 months; clinic visits were scheduled for Months 2, 4, 6, 8, 10, and 12, and telephone contact was scheduled for Months 1, 3, 5, 7, 9, and 11. Capsaicin 8% patch retreatment could occur at both scheduled and unscheduled

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clinic visits at the investigator's discretion, but only after at least 8 weeks had elapsed since the last treatment Figure 1. Patients could not receive more than seven capsaicin 8% patch treatments during the study.

Patients:

Patients were aged ≥ 18 years with a diagnosis of PDPN due to type 1 or type 2 diabetes mellitus for ≥ 1 year prior to the screening visit. Key criteria for inclusion and exclusion are presented in Table 1

Effectiveness endpoints:

Brief Pain Inventory-Diabetic Neuropathy:

The Brief Pain Inventory (BPI) is a widely used and validated numeric rating scale that measures severity of pain and its interference with daily function. Each BPI item uses a 0 to 10 numeric rating scale anchored at zero for 'no pain' and 10 for 'pain as bad as you can imagine' for severity, and 'does not interfere' to 'completely interferes' for interference. The four severity items and the seven interference items can also each be averaged to form two composite scores: the Pain Severity Index and the Pain Interference Index.

The Brief Pain Inventory-Diabetic Neuropathy (BPI-DN) is a version of the BPI that asks a patient to rate severity and interference items specifically for diabetic neuropathyrelated pain, encouraging the patient to focus on pain associated with their neuropathy [22]. This has been achieved by adding the words 'due to your diabetes' to all items (e.g. 'Please rate your pain due to your diabetes at its worst over the past 24 hours'). The following BPI endpoints were evaluated: (1) change from baseline in average daily pain score (item 5 of BPI); (2) Pain Severity Index and component questions; and (3) Pain Interference Index and other component questions. In addition, 30% and 50% responder rates were determined, based on average pain over the past 24 hours.

The BPI-DN was administered at the screening visit (Day -7 ± 3 days), the baseline visit that included the first patch application [Day 1], at the bimonthly patch (re)-application visits, and at the planned or early termination visit.

Patient Global Impression of Change:

The Patient Global Impression of Change (PGIC) is a patient-rated instrument that measures patients' impression of how much (and in what direction) they have changed since starting treatment, on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Patients answered a PGIC questionnaire at the bimonthly patch (re)application visits and at the planned or early termination visit, prior to any procedures relating to the painful areas.

The PGIC variable of interest was counts by combined categories, as follows: (1) very much + much improved; (2) very much + much + minimally improved; (3) no change; and (4) minimally worse + much worse + very much worse.

Quality of life: EQ-5D:

The EuroQol 5-dimension (EQ-5D) questionnaire was used as a measure of HRQoL. The questionnaire has two components: health state description and evaluation. In the description part, health status is measured in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The mobility dimension asks about the person's walking ability; the selfcare dimension asks about the ability to wash or dress by oneself; and the usual activities dimension measures performance in work, study, housework, family, or leisure activities. In the pain/discomfort dimension, the patient is asked how much pain or discomfort they have; and in the anxiety/depression dimension, the patient is asked how anxious or depressed they are. Patients self-rated their level of severity for each dimension using a three-level scale. In the evaluation part, the respondents evaluated their overall health status using the visual analog scale (VAS).

Patients completed the EQ-5D assessment at the bimonthly patch (re)-application visits and at the planned or early termination visit, prior to any procedures relating to the painful areas.

Variables of interest were: (1) dimension counts for each of the three response categories at end of study (EoS): no problems with activity/pain or discomfort/anxiety or depression; some problems with activity/moderate pain or discomfort/moderate anxiety or depression; unable to perform activity/extreme pain or discomfort/extreme anxiety or depression; (2) change from baseline in the VAS at EoS; and (3) change from baseline in the utility index at EoS.

Patient satisfaction with treatment:

The Satisfaction with Treatment (SAT) assesses treatment satisfaction by using a 5-point Likert-type scale ranging from -2 (a strong negative response) to 2 (a strong positive response); zero indicates a neutral response. The questionnaire contains the following questions: (1) How do you assess your pain level after treatment in this study?; (2) How do you assess your activity level after treatment in this study?; (3) How has your QoL changed after treatment in this study?; (4) Would you undergo this treatment again?; (5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?

The SAT variable of interest for questions 1 to 3 was counts by combined categories, as follows: worse: (-2)+(-1); better: (1)+(2). The variable of interest for question 4 was counts of the yes and no responses. The variable of interest for question 5 was counts of the number of patients expressing preference for 179mg capsaicin cutaneous patch compared with those expressing preference for their previous treatment.

$Statistical \ methods:$

Since the primary objective of this study was the assessment of the long-term safety of repeat administration of 179mg capsaicin cutaneous patch, sample size was determined with reference to the primary safety outcome measure, namely the Norfolk Quality of Life - Diabetic Neuropathy (QOL-DN) scale (21). Only one analysis set was defined for the trial, i.e. the safety analysis set (SAS) that included all patients who received study treatment. Differences between active treatment and SOC alone are derived using a one-way analysis of variance, with treatment group as fixed effect, and described by least squares means and the 95% confidence intervals (CIs) for the average daily pain scores, or 90% CIs for all other efficacy variables. No formal



Figure 1. Study design. *Capsaicin 8% patch treatment (Groups 1 and 2) took place at visit 2 and if warranted at scheduled visits (P) or unscheduled visits at intervals of atleast 8 weeks. EoS visit for Groups 1 and 2 took place between 8 and 12 weeksafter last patch application if patch was applied at Visit 8 (Month 12) andbetween Week 52 and 56 for patients without a patch application at Visit 8(Month 12). EoS visit for Group 3 took place between Week 52 and 56. EoS, end of study; SOC, standard of care.

Table 1. Key inclusion and exclusion criteria

Inclusion criteria A red > 18 means with a diamagia of	Exclusion Criteria	Dain that could not be alcould
Aged \geq 18 years with a diagnosis of	Primary pain associated with PDPN in	Pain that could not be clearly
PDPN confirmed by a score ≥ 3 on the	the ankles or above	differentiated from, or conditions that
MNSI	Significant pain (moderate or above) due	might have interfered with, the
$HbA1c \le 9\%$ (74.9 mmol/mol) at 3–6	to an aetiology other than PDPN	assessment of PDPN, e.g., claudication,
months prior to screening and at	Any amputation of lower extremity	fasciitis tendinitis and arthritis
screening	Clinically significant cardiovascular	Current or previous foot ulcer
Stable glycaemic control for ≥ 6 months	disease within 6 months prior to	Severe renal disease as defined by a
prior to screening visit	screening visit	creatinine clearance $< 30 \text{ mL/min}$
Average daily pain score over the last 24	Any active signs of skin inflammation	Significant peripheral vascular diseasea
$h \ge 4$ (question 5 of BPI-DN) at the	around onychomycosis sites such as	Impaired glucose tolerance only –
screening and the baseline visit	tenderness, redness, swelling or drainage	without diabetes mellitus
	Body mass index $\geq 40 \text{ kg/m2}$	Previous treatment with capsaic in 8%
	Hypersensitivity to capsaic any	patch
	capsaicin 8% patch excipients, EMLA	Use of any topical pain medication on
	ingredients, or adhesives	the painful areas within 7 days preceding
	Use of oral or transdermal opioids within	patch application at baseline
	7 days preceding patch application at	
	baseline	

BPI-DN Brief pain inventory-diabetic neuropathy version, EMLA eutectic mixture of local anaesthetics, HbA1c glycosylated haemoglobin of A1c, MNSI Michigan neuropathy screening instrument, PDPN painful diabetic peripheral neuropathy aIntermittent claudication or lack of pulsation of either the dorsal pedis of posterior tibias artery, or ankle-brachial systolic BP index of 0.80

statistical testing was performed to calculate p-values for the difference between the capsaicin treatment groups and SOC alone. At EoS, for each subject, the last available observation was used with the last observation carried forward (LOCF) imputation method.

3 **RESULTS:**

Patient disposition:

Of the 555 screened patients, a total of 468 patients were randomized at 71 centers across 11 European countries (30min plus SOC, n=156; 60-min plus SOC, n=157; SOC alone, n=155). A total of 388 patients completed the study (30min plus SOC, n=132; 60-min plus SOC, n=128; SOC alone, n=128); and 80 patients (17.1%) discontinued the study post baseline, most commonly due to withdrawal of consent (n=44) and adverse events (n=18;Figure 2).

SOC: standard of care.

A total of 468 patients were randomized to capsaicin 30-min plus SOC (n=156), capsaicin 60-min plus SOC (n=157), or SOC alone (n=155).

Baseline characteristics were similar and groups were comparable across age (mean 60.4 years (SD 10.52)), BMI (mean 30.44, (SD 4.836), glycated hemoglobin (mean 7.38 (SD 1.003)), average daily pain (5.6 (SD 1.32)), duration of PDPN (4.3 years (SD 3.72)), and use of prior treatments for PDPN (including pain medications and SOC) [21]. The most commonly prescribed categories of pain medications at baseline and during the study were analgesics and antiepileptics Table 2; the most commonly prescribed individual drugs for pain during the study were gabapentin and pregabalin Table 3.

The average interval between each capsaicin re-treatment was 68.4 days in the capsaicin 30-min group and 68.3 days in the 60-min group. The mean number of patches used per application was similar between capsaicin groups (30min, 1.53; 60-min, 1.42) and the mean duration of patch application was 30.2 minutes in the 30-min group and 60.2 minutes in the 60-min group.

Over half of the patients in the capsaicin 8% patch groups received the maximum seven capsaicin treatments (167/313 [53.4%]; Table 4).

Efficacy :

Average pain:

Greater mean percentage reductions in average pain were seen, versus SOC alone, with both capsaicin plus SOC groups throughout the study period from Month 1, and this difference was maintained and increased by Month 12.

From baseline to EoS, mean percentage (standard deviation [SD]) changes in average pain were: -37.5% (32.9) for the 30-min group, -40.8% (39.7) for the 60-min group, and -13.9% (74.6) for SOC alone. The estimated mean between-group differences versus SOC alone (95% CI) were -23.7% (-35.5, -11.9) for the 30-min group and -26.9% (-38.7, -15.2) for the 60-min group.

Pain intensity:

A greater reduction in the total BPI-DN Pain Severity Index was observed for both capsaicin plus SOC groups versus SOC alone from baseline to EoS Figure 4. The mean (SD) change from baseline to EoS was -1.9 (1.8), -2.2 (1.9), and -0.9 (1.7) with capsaicin 30-min plus SOC, capsaicin 60-min plus SOC, and SOC alone, respectively. The estimated mean difference (90% CI) between capsaicin 30-min and 60-min versus SOC was -0.9 (-1.3, -0.6) and -1.2 (-1.6, -0.9), respectively.

Greater reductions from baseline to EoS were observed in worst daily pain, least daily pain, average daily pain, and pain right now in both capsaicin plus SOC groups versus SOC Figure 4.

Pain interference:

A greater reduction in total BPI-DN Pain Interference Index was also observed with both capsaicin plus SOC groups versus SOC alone from baseline to EoS Figure 4. The mean (SD) change from baseline to EoS was -1.9 (2.1), -2.0(2.3), and -0.8 (1.9) with capsaicin 30-min plus SOC, capsaicin 60-min plus SOC, and SOC alone, respectively. The mean difference (90% CI) for capsaicin 30-min and 60-min versus SOC was -1.0 (-1.4, -0.6) and -1.2 (-1.6, -0.8), respectively. Greater reductions from baseline to EoS were observed in pain interference with general activity, mood, walking ability, normal working relations, sleep and enjoyment of life in both capsaicin plus SOC groups than in the SOC alone group (Figure 4).

Responder analyses:

A greater proportion of patients in the capsaicin plus SOC groups had \geq 30% reduction in average pain (30-min, 67.3%; 60-min, 67.5%), compared with SOC alone (40.6%) Figure 5. By Month 1, 28.6% of patients in the 30-min group and 22.6% in the 60-min group achieved a 30% response, compared with 14.3% of patients receiving SOC alone. These trends were similar for the proportion of patients with \geq 50% reduction in average pain (30-min, 44.8%; 60-min, 48.4%; SOC, 23.8%) (Figure 5). By Month 1, 20.0% of patients in the 30-min group and 21.1% of those in the 60-min group achieved a 50% response, compared with no patients receiving SOC alone.

In a post-hoc analysis of all subjects who received seven applications of 179mg capsaicin cutaneous patch (n=167), the ³30% responder rate increased steadily with each application from 32.3% to 47.0%, 50.0%, and finally to 74.1%, 2 months after the first, second, third, and seventh (i.e. last application), respectively Figure 6.

Patient Global Impression of Change

By EoS, greater improvements in the patients' impression of how much they had changed since starting treatment were observed in both capsaicin plus SOC groups versus SOC alone Figure 4. More patients in both capsaicin plus SOC groups (30-min, 24.2%; 60-min, 24.5%), compared with SOC alone (9.5%) felt 'very much improved' or 'much improved' and fewer felt worse by EoS Figure 7.

Quality of life: EQ-5D utility index:

A greater mean (SD) improvement in EQ-5D utility index from baseline to Month 12 was observed with capsaicin 8%patch 30-min plus SOC (0.12) and 60-min plus SOC (0.15) versus SOC alone (0.07).



Figure 2. Patient flow

Table 2. S	ummary of der	nographics and	baseline c	haracteristics(safety a	analysis set).
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Parameter	Capsaicin 8% patch $(30 \text{ min}) + \text{SOC}$ (n=156)	Capsaicin 8% patch (60 min) + SOC $(n=157)$	SOC (n=155)
Pain medications before baseline, n			
(%)			
Overall	70 (44.9)	71 (45.2)	79 (51.0)
Analgesicsa	56 (35.9)	54(34.4)	59(38.1)
Antiepileptics	44 (28.2)	49 (31.2)	52(33.5)
Psycholeptics	22 (14.1)	19 (12.1)	24(15.5)
Anti-inflammatory/antirheumatic products	14 (9.0)	12 (7.6)	17 (11.0)
Topical joint/antirheumatic products	14 (9.0)	11 (7.0)	15 (9.7)
<u> </u>			

BPI-DN Brief pain inventory diabetic neuropathy, HbA1c glycosylated haemoglobin of A1c, PDPN painful diabetic peripheral neuropathy, QOL-DN Quality-of-life questionnaire for diabetic neuropathy, SD standard deviation, SOC standard of care aAnalgesics included anilides, natural opium alkaloids, other analgesics and antipyretics, other opioids, pyrazolones and salicylic acid and derivatives

Anti-inflammatory preparations, non-steroidals for topical use, preparations with salicylic acid derivatives

Regarding the EQ-5D items, a greater proportion of patients at EoS in both capsaicin plus SOC arms, versus SOC alone, had no problems with mobility, self-care, usual activities, pain or discomfort, and anxiety or depression Figure 8.

EQ-5D VAS:

A greater improvement in mean (SD) EQ-5D VAS score was observed from baseline to the EoS with the capsaicin 30-min plus SOC (10.4 [18.5]) and capsaicin 60-min plus SOC (11.2 [21.4]) versus SOC alone (5.5 [18.1]) Figure 9. The mean (95% CI) difference with capsaicin 30-min and

60-min versus SOC alone was 4.9 (1.1-8.6) and 5.7 (2.0-9.4), respectively.

Self-Assessment of Treatment (SAT)

At EoS, a greater proportion of patients in both capsaicin plus SOC groups versus SOC alone reported improvements in pain level, activity level, and QoL. A greater proportion of 179mg capsaicin cutaneous patch-treated patients also indicated their willingness to undergo treatment again, and also preferred 179mg capsaicin cutaneous patch treatment over their previous treatment Figure 10. The improvements

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Table 3. Pain medicationused during the study: most commonly used drugs (>5% patients in any group).

Pain	Capsaicin 8% patch	Capsaicin 8% patch	SOC (n =
medicationa	(30 min) + SOC (n = 156)	(60 min) + SOC (n = 157)	155)
Overall, n (%)	98(62.8)	105 (66.9)	107 (69.0)
Most commonly us	ed drugs ($>5\%$ patients in any group), n (%)		
Gabapentin	26 (16.7)	26 (16.6)	35(22.6)
Pregabalin	24 (15.4)	22 (14.0)	39(25.2)
Paracetamol	23 (14.7)	36 (22.9)	6(3.9)
Tramadol	16(10.3)	14 (8.9)	6(3.9)
Diclofenac	12 (7.7)	13(8.3)	12(7.7)
Ibuprofen	11 (7.1)	15 (9.6)	14 (9.0)
Metamizole	10(6.4)	10(6.4)	5(3.2)
Duloxetine	9(5.8)	3(1.9)	10(6.5)
Carbamazepine	7(4.5)	14 (8.9)	10(6.5)
Alpha lipoic	3(1.9)	1(0.6)	8(5.2)
acid			

SOC standard of care

aMedication identified as 'pain medication" YES on electronic case report from (eCRF)

Table 4. Percentage of patients per number of 179mg capsaicincutaneous patch applications during the study.

Number of patch	QUTENZA	QUTENZA	QUTENZA	
applications	(30 min) + SOC	(60 min) + SOC	+ SOC	
	(N=156)	(N=157)	(N=313)	
	n (%)	n (%)	n (%)	
1 Application	7(4.5)	6(3.8)	13(4.2)	
2 Applications 5 (3.2)	12 (7.6) 17 (5.4)			
3 Applications	15 (9.6)	8(5.1)	23(7.3)	
4 Applications	7(4.5)	11(7.0)	18(5.8)	
5 Applications	14 (9.0)	10(6.4)	24(7.7)	
6 Applications	24(15.4)	27(17.2)	51 (16.3)	
7 Applications	84(53.8)	83 (52.9)	167(53.4)	
N: Number of patient	s in the intention to treat set: n	Number of patients in the sample: SO	C: Standard of care.	



Figure 5. Proportion of \geq 30% and \geq 50% average pain responders during the study (SAS).

were comparable between the capsaicin groups.

Concomitant Pain Medication

In general, the use of concomitant pain medication remained stable in all treatment arms from baseline to EoS. The most frequently used treatments were anti-epileptic drugs by approximately one-third of the patients at baseline



Figure 6. Proportion of patients with $\geq 30\%$ reduction from baseline in average daily pain (Numeric Pain RatingScale score) who received seven applications of 179mg capsaicin cutaneouspatch.

across treatment arms. In the 179mg capsaicin cutaneous patch arms, the proportion of patients using anti-epileptics at EoS was comparable with the proportion reported at baseline. In contrast, at EoS, the proportion of patients using anti-epileptic drugs had increased by >10% in the SOC alone arm.

Use of antidepressants and opioids was relatively low (<20%) with small increases observed from baseline to EoS – more so in the SOC alone group Table 5.



In patients who received a capsaicin treatment at Month 12 and had an end of study visit at Month 14, mean [SD] change in average pain score by Month 14 was: 30 min, -44.6% [27.4] (n=88); 60 min, -41.4% [35.7] (n=84).

Cap 30, capsaicin 8% patch (30 min); Cap 60, capsaicin 8% patch (60 min); LS, least squares; SAS, safety analysis set; SOC, standard of care

Figure 3. Mean percentage change from baseline in average painduring the study (SAS).

4 **DISCUSSION:**

While the efficacy of a single capsaicin 8% treatment has been previously described in patients with PDPN in a double-blind controlled trial [19], the present study, designed primarily to assess the safety and tolerability of multiple applications of 179mg capsaicin cutaneous patch, was also the first to assess the long-term effectiveness of repeated treatment over 52 weeks in this patient population. Measuring effectiveness over a prolonged period of time has the advantage of enabling assessment of patients' longitudinal experience of the capsaicin 8% patch, compared with the more limited experience afforded by a typical 12-week study.

Patients in the groups receiving 30-minute or 60-minute applications of the capsaicin 8% patch plus SOC had a greater reduction in average pain compared with those receiving SOC alone from Month 1 onward. Importantly, this differential treatment effect was not only sustained, but increased progressively throughout the 52 weeks of the study, as illustrated by the 30% and 50% responder rates. At EoS, the 30% responder rate was substantially higher in both Capsaicin 8% patch 30 minutes + SOC (n=156)

- Capsaicin 8% patch 60 minutes + SOC (n=157)
- SOC (n=155)



BPI-DN, Brief Pain Inventory-Diabetic Neuropathy; LOCF, last observation carried forward; SOC, standard of care

Figure 4. Mean change from baselineto end of study in BPI-DN pain severity and interference indices and componentquestions (LOCF; SAS).



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.

SAS, safety analysis set; SOC, standard of care



	QUTENZA	QUTENZA	SOC alone
	(30 min) + SOC	(60 min) + SOC	(N = 155)
	(N = 156)	(N = 157)	
Baseline			
	156	157	155
Antidepressants	17 (10.9)	8 (5.1)	12 (7.7)
Antiepiletic drugs	44 (28.2)	49 (31.2)	50 (32.3)
Opioids	17 (10.9)	9 (5.7)	13 (8.4)
End of study			
	146	147	146
Antidepressants	16 (11.0)	10 (6.8)	22(15.1)
Antiepileptic	43 (29.5)	53(36.1)	63(43.2)
drugs			
Opioids	16 (11.0)	12 (8.2)	17(11.6)
The medication was su	mmarized on the day before baseline visi	t and on the day before the end of study	visit,
N. Number of patients	n. Number of patients in the sample SC	C Standard of care	

Table 5. Neuropathic pain medication at baseline and E	oS.
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No problems with activity/pain or discomfort/anxiety or depression

Some problems with activity/moderate pain or discomfort/anxiety/depression

Unable to perform activity/extreme pain or discomfort/anxiety/depression



C30 + SOC, capsaicin 8% patch (30 minutes) + SOC (n=156); C60 + SOC, capsaicin 8% patch (60 minutes) + SOC (n=157); EQ-5D, European Quality of life in 5 Dimensions; LOCF, last observation carried forward; SAS, safety analysis set; SOC, standard of care (n=155)



capsaicin 8% patch groups (both >67%) versus SOC alone (41%). The corresponding figures for the 50% responder rate were 45% for the capsaicin 8% groups, compared with 24% for SOC alone. By Month 1, the 30% responder rates for the capsaicin 8% groups were approximately double those for SOC alone, while the 50% responder rates for the capsaicin 8% groups (20.0% and 21.1% for 30-min and 60-min groups, respectively) contrasted with no patients in the SOC alone achieving 50% response. These findings reflect substantial differences between treatment with capsaicin 8% plus SOC and SOC alone.

Compared with SOC alone, repeat treatment with the capsaicin 8% patch plus SOC over 52 weeks was also associated with greater improvements in the BPI Pain Severity Index (a composite score including pain at its worst and at its least in the last 24 hours, average pain, and pain right now) and the extent to which pain interfered with a range of activities. These findings were further supported by results from the PGIC, which demonstrated that substantially more patients in the capsaicin plus SOC groups reported very much or much improvement by EoS. Furthermore, a

greater proportion of patients in the capsaicin plus SOC groups reported improvement in QoL, compared with SOC alone. Coretti et al (2014) [23] reported that the minimal clinically importance difference for the EQ-5D utility index across 18 studies, including a range of diseases, ranged from 0.03 to 0.54, with a raw average across all studies of 0.18. In the present study, the change from baseline in this index was 0.12 and 0.15 for 179mg capsaicin cutaneous patch, 30-min plus SOC and 60-min plus SOC, respectively, and 0.07 for SOC alone. In addition to the aforementioned measures of effectiveness, patient satisfaction with treatment was also assessed in this study. Pain relief and patient satisfaction are distinct concepts identified by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) as central to evaluating treatment of chronic pain. Pain relief measures are used to determine whether the patient has actually benefited from an intervention and provide valuable information on how effectively pain is being managed. In contrast, patient satisfaction measures capture the personal evaluation of the intervention provided. Patient satisfaction has been shown



Treatment comparisons are least squares mean difference (90% Cl)

EoS, end of study; EQ-5D, European Quality of life in 5 Dimensions; LOCF, last observation carried forward; SAS, safety analysis set; SOC, standard of care



to affect patients' health-related decisions and treatmentrelated behaviors, which in turn, can substantially impact the success of treatment outcomes. Patients' satisfaction with their treatment also predicts continuance of pharmaceutical treatment, correct medication use, and compliance with medication regimens [24]. In this study, there was a noteworthy difference between treatments, with a greater proportion of patients in both capsaicin plus SOC groups versus SOC alone reporting improvements in pain level, activity level, QoL, and willingness to undergo the same treatment again. Patients indicated their preference for 179mg capsaicin cutaneous patch treatment, compared with their previous treatment, despite the inconvenience and discomfort associated with capsaicin patch application.

The use of concomitant pain medications during this study was comparable at baseline across treatment arms and remained generally stable from baseline to EoS in the 179mg capsaicin cutaneous patch arms for antidepressants, anti-epileptics, and opioids. However, a 10.9% increase in number of patients using anti-epileptic drugs was observed in the SOC alone arm from baseline to EoS with smaller increases of 7.4% and 3.2% for antidepressants and opioids, respectively. This was, perhaps, indicative of lower efficacy in the SOC alone arm, such that more patients required pain medication over time in this group.

There were a number of limitations associated with this study. Perhaps the most significant arises from the open-

label study design. Although the open-label design of this study may be more representative of capsaicin 8% patch repeat treatment in clinical practice than in a double-blind design, the observed efficacy evaluations may have been biased by this approach. Differences between treatment groups in an open-label study may, at least in part, arise from the fact that patients are aware of which treatment they are receiving.

The LOCF imputation method employed in this study is a conservative method to estimate the treatment effect. The underlying assumption is that subjects who withdraw have worse efficacy than those who stay in the trial. The LOCF imputation method used the data of withdrawn patients and therefore, theoretically, gave worse results in this study than from a non-imputed analysis. As the limitations of the LOCF for missing data methodology are recognized, the data were also analyzed using the baseline observation carried forward method, and no differences in the results were observed.

5 CONCLUSION:

In patients with PDPN, capsaicin 8% patch repeat treatment plus SOC over 52 weeks demonstrated greater effectiveness than SOC alone. 179mg capsaicin cutaneous patch provided sustained pain relief, improved HRQoL, and im-



C30 + S0C, capsaicin 8% patch (30 minutes) + S0C (n=156); C60 + S0C, capsaicin 8% patch (60 minutes) + S0C (n=157); L0CF, last observation carried forward; SAS, safety analysis set; S0C, standard of care (n=155)

Figure 10. Patient self-assessment of treatment at EoS (LOCF; SAS).

proved overall health status reflected by the stable number of patients using concomitant pain medication. Furthermore, our results show that the magnitude of the differential treatment effect of 179mg capsaicin cutaneous patch increases over time from the first to the last patch application.

Transparency:

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Author Contributions:

Aaron I. Vinik, Serge Perrot, Etta J. Vinik, Ladislav Pazdera, Malcolm Stoker, Robert J. Snijder, Enrique Ortega, and Nathaniel Katz, were involved in the conception, design and drafting the paper. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement:

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials:

Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: a randomised, 52-week, open-label, safety study. BMC Neurology 2016;16:251.

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