Randomized Trial

Treatment Impact on Patient-Reported Outcomes in Peripheral Neuropathic Pain: Comparing Single Intervention With Topical High-Concentration Capsaicin to Daily Oral Pregabalin

Eric Viel, MD, PhD[1], Mariëlle Eerdekens, MD[2], and Prashanth Kandaswamy, MSc[2]

From: [1]Centre d'Étude et de Traitement de la Douleur, Pôle A.R.D.U., Centre Hospitalier Universitaire, France; [2]Grünenthal GmbH, Aachen, Germany

Address Correspondence: Eric Viel, MD, PhD Chef de Service, Centre d'Étude et de Traitement de la Douleur, Pôle A.R.D.U., Centre Hospitalier Universitaire, 30029 Nîmes cedex 9, France E-mail: eric.viel@chu-nimes.fr

Disclaimer: The study was sponsored by Astellas Pharma Europe Ltd. Medical writing was funded by Astellas Pharma Europe Ltd and then Grünenthal GmbH. Study investigators received clinical study payments from the study sponsor to carry out the study at their centers using fair market value principles to determine study costs.

Conflict of interest: None of the authors received funding or reimbursement for their work on this publication. Eric Viel has been a consultant for Grünenthal GmbH and was one of the investigators in the trial; Mariëlle Eerdekens and Prashanth Kandaswamy are employees of Grünenthal GmbH.

Manuscript received: 08-03-2020
Revised manuscript received: 12-07-2020
Accepted for publication: 12-17-2020

Free full manuscript: www.painphysicianjournal.com

Background: Peripheral neuropathic pain (PNP) is a complex, subjective experience affecting both physical and psychological aspects of functioning. Assessing patient-reported outcomes (PROs) beyond pain relief is important and aligns with the recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials). Moreover, PRO data are key to clinical decision-making when evaluating treatment options. However, direct comparisons between such options are scarce. High-concentration capsaicin 179 mg (8% w/w) cutaneous patch (HCCP) is applied to the skin at minimum intervals of 90 days under physician supervision; alternative recommended treatments for PNP are mostly orally administered on a daily basis. The ELEVATE study directly compared HCCP with pregabalin and found noninferior efficacy of HCCP to pregabalin in relieving pain after 8 weeks, with a significantly faster onset of action and fewer systemic side effects.

Objectives: The objective of this analysis was to compare PRO outcomes defined as secondary objectives of the ELEVATE study after a single intervention with HCCP to daily oral pregabalin for 8 weeks.

Study Design: ELEVATE was an open-label, randomized (1:1) multicenter study.

Setting: The study included 92 sites in 22 countries in Europe and Asia.

Methods: Five hundred fifty-nine non-diabetic patients with PNP received a single intervention with HCCP (n = 282; 1-4 patches at baseline) or oral daily pregabalin (n = 277; 150-600 mg, 8 weeks). At baseline (Day 0) and Week 8, patients completed the following PROs in addition to the regular pain assessments: Patient Global Impression of Change (PGIC), Medical Outcomes Study Cognitive Functioning scale (MOS-Cog), Medical Outcomes Study Sleep scale (MOS-Sleep), Treatment Satisfaction Questionnaire for Medication (TSQM), and EuroQol 5-Dimensions 5-levels (EQ-5D-5L) Utility Index (EQ-UI) and Visual Analog Scale (EQ-VAS).

Results: At Week 8, 76% and 75.9% of patients on HCCP and pregabalin, respectively, reported to be very much/much/minimally improved on the PGIC. HCCP application was associated with significant improvements from baseline vs. pregabalin in MOS-Cog (mean difference: 4.28 [95% CI: 2.90-5.66]; $P < 0.001$), EQ-VAS (3.11 [0.30-5.92]; $P = 0.030$), and TSQM global satisfaction (6.74 [2.29-11.20]; $P = 0.029$), particularly the side-effects dimension (21.23 [17.55-24.94]; $P < 0.0001$). No significant differences in improvements were noted for the MOS-Sleep, TSQM convenience, and EQ-UI.

Limitations: The ELEVATE study has an open-label design, with only one comparator (pregabalin); it was limited to 8 weeks. The sample size was determined for the primary endpoint.

Conclusions: A single intervention with HCCP showed benefits vs. daily pregabalin at Week 8 on several PROs. While HCCP has been approved in the United States for PNP treatment in diabetic and PHN patients, these observations provide information on how patients perceive the effects of distinct PNP treatments. They are complementing already existing knowledge on efficacy and safety of different treatment options with data on patient preferences and may help identify the appropriate treatment option in dialogue with the patients and shared decision-making.

IRB Approval: At the time of the study, the trial was approved either nationally or at site level. All approvals were granted prior to the initiation of the trial. A list of Ethics Committees that approved the trial is included as a supplemental file.

Clinical Trial Registration Number: NCT01713426.

Key words: Capsaicin; comparative study; ELEVATE study; neuropathic pain; pain; pain measurement; patient outcome assessment; pregabalin

Pain Physician 2021: 24:453-463

Neuropathic pain, defined as "pain caused by a lesion or disease of the somatosensory nervous system" (1), is a common debilitating disorder (2). Patients with neuropathic pain have lower health utility scores compared with the general population, indicating compromised health-related quality of life (HRQoL) (3); they report more sleep problems, anxiety, and depression relative to patients with chronic pain, and lower participation in the workforce (4,5).

First- and second-line options for the treatment of neuropathic pain recommended by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain include tricyclic antidepressants, selective reuptake inhibitors of serotonin and norepinephrine, calcium channel α2-δ ligands, opioids, and high-concentration capsaicin 179 mg (8% w/w) cutaneous patch (HCCP) (6). HCCP stands out on this list as the only recommended option for topical intervention directly at the painful area that is applied once every 3 months, whereas all other treatments are daily and orally administered medications that exert their effect following systemic exposure. Systemic drug treatments may be limited in efficacy and their associated side effects may be limiting factors when trying to reach the necessary dose, and may lead to poor compliance (7). They often require lengthy dose titration periods, may lead to drug-drug interactions, and require multiple daily dosing (8). For opioids and pregabalin, there is a risk of dependence, withdrawal symptoms, and abuse (8,9). Moreover, in case of insufficient treatment response, neuropathic pain guidelines recommend the combination of several of these systemically after oral treatments (10), which inevitably leads to polypharmacy that, in turn, may impact compliance (11).

The therapeutic potential of HCCP and its mechanism of action have been previously characterized as attenuation of cutaneous hypersensitivity and reduction of pain by a process best described as transient 'defunctionalization' of nociceptor fibers (12). Its mechanism of action clearly differs from that of pregabalin (13). HCCP is applied directly to the painful area by a health care professional, requires no dose titration and provides effective pain relief in patients with peripheral neuropathic pain (PNP) compared to a placebo. Characteristic side effects include transient mild to moderate application site reactions, such as pain and erythema. In the European Union, HCCP is indicated for the treatment of PNP in adults either alone or in combination with other medicinal products for the treatment of pain. In the United States, HCCP is indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia and neuropathic pain associated with diabetic peripheral neuropathy of the feet (14-16).

Direct comparisons between different treatment modalities in the same patient population are rare and research providing insights into the efficacy, safety, and the patient perception of these different treatments are not only of high scientific interest, but also of immediate relevance to prescribers and patients. Also, regulators have shown an increased interest in the inclusion of patient-reported outcomes (PROs) in drug development programs (17,18).

The efficacy and safety results of such an investigation comparing a single intervention with topical HCCP to daily oral, dose optimized pregabalin from an open-label, noninferiority trial in a broad population of non-diabetic PNP patients (ELEVATE study) have been published previously. The primary efficacy analysis showed that HCCP was noninferior to pregabalin in relieving pain after 8 weeks, with a significantly faster onset of action and fewer systemic side effects (19). The adverse event profile of HCCP in this trial was in line with that reported in the literature and the product information.

This manuscript focuses on comparison between HCCP and pregabalin on PROs. PROs provide insight into how patients perceive their health status and treatment effects, and how treatments impact outcomes, disease, and surgical interventions in many aspects of a patient's life. This is particularly pertinent to PNP patients because pain is a complex and subjective experience and PNP can adversely affect many aspects of physical and psychological functioning. It also aligns with the recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) which emphasize not only the assessment of pain severity, but also patient functioning and mood (20).

Methods

Study Design

ELEVATE (ClinicalTrials.gov NCT01713426) was an open-label, randomized, multicenter, 8-week, noninferiority trial. It was designed to compare the efficacy, safety, and PROs of a direct topical intervention with HCCP with oral daily pregabalin (19). It involved 92 sites in 22 countries in Europe and Asia (19).

Patients

Eligible patients were ≥ 18 years old and had documented probable or definite PNP due to postherpetic neuralgia, peripheral nerve injury (including post-surgical or post-traumatic neuropathic pain), or non-diabetic painful peripheral polyneuropathy. Patients were required to have an average pain score of at least 4 (in response to the following item of the Numeric Rating Scale (NRS): "average pain for the past 24 hours") for at least 4 consecutive days during the screening period. Patients were either pregabalin-naïve or, in the opinion of the investigator, had not received an adequate trial of treatment with pregabalin or gabapentin, including lack of effect or intolerability. Use of any topical pain medication within 7 days of the baseline visit or previous treatment with HCCP was not permitted. Other reasons for exclusion included complex regional pain syndrome, neuropathic pain related to previously administered radiotherapy, diabetes mellitus, or neuropathy associated with human immunodeficiency virus or located only on the face, above the hairline of the scalp, and/or in proximity to mucous membranes (19).

All procedures performed in the study involving patients were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual patients included in the study.

Interventions

Patients were randomly assigned to receive a single application of the HCCP on day 1 or oral pregabalin (75 mg capsules) for 8 weeks.

Patients assigned to HCCP were pretreated with a topical local anesthetic cream for up to 60 minutes prior to patch application. Patches (1-4) were applied to painful areas for 60 minutes, except when applied to the feet (30 minutes). A short acting pain medication for patch-related pain/discomfort was permitted for up to 5 days after patch application.

Pregabalin was given at a flexible dosage optimized to match clinical practice and not accordingly to the summary of product characteristics (21,22). The up- and/or down titration scheme was performed over 4 weeks. The dosage started at 75 mg/day and was increased to 150 mg/day after 3-4 days. Further up-titration was permitted in 75 mg increments every 3-4 days at the discretion of the investigator (maximum dosage: 600 mg/day in 2-3 divided doses). A single down-titration was permitted (minimum dosage: 150 mg/day) in cases of unacceptable adverse effects. The optimal dose arrived at, in this fashion, was chosen for the maintenance dose for the remainder of the study (Week 4-Week 8).

Existing neuropathic pain medications were permitted in all patients provided doses were stable for more than 4 weeks prior to study entry; local/topical pain therapy or non-pharmacologic treatments were not permitted.

Outcomes

The PROs selected were based on a conceptual model developed for PNP patients (23). Five different self-reported instruments or questionnaires were used (Table 1): Patient Global Impression of Change (PGIC) (24), Medical Outcomes Study Cognitive Functioning scale (MOS-Cog) (25), Medical Outcomes Study Sleep scale (MOS-Sleep) (26), Treatment Satisfaction Questionnaire for Medication (TSQM) (27), and EuroQol 5-Dimensions 5-levels (EQ-5D-5L) (28). A description of the rationale for use in the trial based on literature (29-34) is provided in Table 1.

Patients completed questionnaires at the clinic via a handheld electronic device at the same time points described in Table 1.

Randomization

Randomization was coordinated centrally using an Interactive Web Response System which assigned eligible patients to one of two treatment arms (1:1). Randomization was stratified by gender and country. No replacement subjects were allowed.

Statistical Methods

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined at the 0.05 level.

The PROs were secondary endpoints intended to yield supportive evidence of benefit of an exploratory nature. No multiplicity adjustments were thus

Table 1. *Overview of patient-reported outcomes measures.*

Instrument (ref.)	Completion	Description	Assessment
PGIC (24)	Week 4, Week 8	Single-item instrument designed to measure change in overall health status. Commonly used in clinical research to rate the response of a condition to a therapy (29). A pooled analysis of data in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia demonstrated a relationship between pain relief and PGIC scores (30).	7-point scale ranging from 1 (very much improved) to 7 (very much worse). Patients were clinically improved if they reported to be "minimally", "much", or "very much improved".
MOS-Cog, revised version (25)	Day 1, Week 8	Instrument designed to assess any potential impact of treatment on cognitive functioning using 6 measures: reasoning, concentration/ thinking, confusion, memory, attention, psychomotor (25). Oral treatments for PNP have been reported to impair cognitive function, which may further exacerbate existing cognitive impairment in patient with PNP (31).	Patients answer questions based on their experiences over the past 4 weeks. Each question is rated on a 6-point Likert scale ranging from "all of the time" to "none of the time". The responses to each are summed and then transformed to a scale of 0 to 100, with a higher score indicating better cognitive functioning.
MOS-Sleep, revised version (26)	Day 1, Week 4, Week 8.	12-item instrument designed to provide a concise assessment of sleep organized into 6 dimensions: initiation, quantity, maintenance, respiratory problems, perceived adequacy, somnolence (26). MOS-Sleep has been shown to be a sensitive, reliable and valid measure of perceived sleep quantity/quality in patients with a broad range of neuropathic pain etiologies (32,33).	10 items are rated on a 6-point Likert scale ranging from "all of the time" to "none of the time". Item "sleep initiation" rated on a 5-point scale (0 to 15 min., 16 to 30 min., 31 to 45 min., 46 to 60 min., > 60 min.). Sleep quantity is the average number of hours' sleep per night. Two summary indices are calculated: - Sleep problems index I (short form: 6 items, sleep disturbance, n=2; sleep adequacy, n=2; shortness of breath, n=1; daytime somnolence, n=1; - Sleep problems index II (long form: 9 items, sleep disturbance, n=4; sleep adequacy, n=2; shortness of breath, n=1; daytime somnolence, n=2). All domain scales and indices are scored on a transformed 0-100 scale, with a higher score indicating fewer sleep-related problems.
TSQM, version 1.4 (27)	Week 4, Week 8	14-item instrument used to evaluate patients' satisfaction with their medication (27). At the time of the study, not reported to have been used previously in patients with PNP, but validated in diverse patient populations	Four summary scores: side-effects (5 items), effectiveness (3 items), convenience (3 items), global satisfaction (3 items). TSQM summary scores range from 0–100, with a higher score indicating greater treatment satisfaction.
EQ-5D-5L (28)	Day 1, Week 8	Generic measure of HRQoL developed to provide a self-completed profile of health status on the day of assessment (28,34). Instruments organized into 5 dimensions (index: mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a VAS assessing overall health status. A study of patients receiving treatment for neuropathic pain showed that clinical pain scores were significantly associated with EQ-5D scores (35)	Each dimension is graded on a 5-level scale (ranging from "no problems" to "extreme problems"). Responses to the EQ-5D-5L descriptive profile were converted to a single index value (utility index, UI) using an interim crosswalk which maps the EQ-5D-3L (3 levels) value sets to EQ-5D-5L (32), as value sets for EQ-5D-5L were not available at the time of study analysis. Using this system, EQ-UIs range from -0.594 (worst possible health) to 1 (full health). For EQ-VAS, overall health status is rated between 0 and 100, where 100=best health imaginable.

EQ-5D: EuroQol 5-Dimensions; EQ-5D-5L: EuroQol 5-Dimensions 5-levels; EQ-UI: EuroQol-Utility Index; EQ-VAS: EuroQol-Visual Analog Scale; HRQoL: Health-Related Quality of Life; MOS-Cog: Medical Outcomes Study Cognitive Functioning scale; MOS-Sleep: Medical Outcomes Study Sleep scale; n: Number of subjects; PGIC: Patient Global Impression of Change; PNP: Peripheral Neuropathic Pain; TSQM: Treatment Satisfaction Questionnaire for Medication.

performed for the current analyses. Analyses were conducted in the full analysis set (FAS) (all randomized patients who initiated study treatment), excluding patients with missing baseline scores. Categorical variables were summarized as frequencies and percentages and continuous variables with descriptive statistics. Treatment effect was explored using an ANCOVA (analysis of covariance) model for continuous variables with baseline score, sex, and country group included as possible effect modifiers. Data were presented as

mean effects with 95% confidence intervals (CIs) for continuous variables or as odds ratios (ORs) with 95% confidence limits (CLs) for categorical variables. For summary scores, missing values were imputed using baseline observation carried forward (BOCF) or last observation carried forward (LOCF). BOCF was used for EQ 5D 5L utility index (EQ-UI) and Visual Analog Scale (EQ-VAS), MOS Sleep index I and index II, and MOS-Cog, and LOCF for PGIC and TSQM.

The required sample size was calculated for the primary objective of the ELEVATE study (19).

Results

Patients

As described previously, 568 patients were randomized to study treatment. Of these, 559 (HCCP, n = 282; pregabalin, n = 277) received study treatment and completed the study; they constituted the FAS. The overall completion rate for the FAS was 96.5% for HCCP and 83.7% for pregabalin (19).

PGIC, MOS-Cog, MOS-Sleep, TSQM, and EQ-5D-5L questionnaires were completed by 86%-99% of patients as predefined at baseline or Week 4 (Table 1) and by 89%-93% of patients at Week 8.

Patients Baseline Characteristics

The main baseline characteristics of the FAS are presented in Table 2; they were comparable between-treatment arms. Scores on the PROs measured at baseline were similar (Table 3). Subscores (when applicable) were similar except for the "mobility" subscore on the EQ-5D-5L: more patients treated with HCCP (45.7%) reported no problems compared to pregabalin (31.6%).

In the HCCP group, 1-4 patches were applied per patient, with a mean standard deviation (SD) of 1.38 (1.08). In the pregabalin group, the mean optimal maintenance dose was 364.4 (137.0) mg/day.

Table 2. *Summary of demographic and baseline characteristics in the FAS.*

Variable	HCCP (n = 282)	Pregabalin (n = 277)
Gender, n (%)		
Male	123 (43.6)	122 (44.0)
Female	159 (56.4)	155 (56.0)
Age, years		
Median (range)	57 (20–81)	57 (19–80)
Type of neuropathic pain, n (%)		
Peripheral nerve injury	146 (51.8)	137 (49.5)
Post-surgical neuropathic pain	78 (27.7)	67 (24.2)
Post-traumatic neuropathic pain	65 (23.0)	68 (24.5)
Other	3 (1.1)	2 (0.7)
Postherpetic neuralgia	63 (22.3)	73 (26.4)
Non-diabetic painful peripheral		
Polyneuropathy	73 (25.9)	67 (24.2)
Chemotherapy-induced neuropathy	15 (5.3)	12 (4.3)
Small-fiber neuropathy	14 (5.0)	13 (4.7)
Other	44 (15.6)	42 (15.2)
NPRS average score		
Mean (SD)	6.5 (1.2)	6.7 (1.2)
< 7, n (%)	162 (57.4)	150 (54.2)
≥ 7, n (%)	120 (42.6)	127 (45.8)
Neuropathic pain grading, n (%)		
Probable	154 (54.6)	149 (53.8)
Definite	128 (45.4)	128 (46.2)
Duration of neuropathic pain, years		
Median (range)	1.1 (0–36.2)	1.0 (0–19.3)
Previous use of pregabalin/gabapentin, n (%)		
No	224 (79.4)	210 (75.8)
Yes	58 (20.6)	67 (24.2)

FAS: Full Analysis Set; HCCP: High-Concentration Capsaicin 179 mg Patch; n: Number of patients; NRS: Numeric Rating Scale; SD: Standard Deviation.

Patient-Reported Outcomes

Descriptive statistics of responses to PGIC and other PRO instruments are presented in Supplementary Table 1 (Table S1). Table 4 presents the adjusted estimates of treatment effect for HCCP vs. pregabalin for each of the questionnaire summary scores.

For the PGIC, at Week 8 (LOCF), the overall status was "very much improved/much improved/minimally improved" in 211/278 (75.9%) patients in the HCCP group compared with 200/263 (76.0%) patients in the pregabalin group; overall status was "minimally worse/much worse/very much worse" in 14 (5.0%) patients in the HCCP group compared with 23 (8.7%) patients in the pregabalin group (Fig. 1). There was no statistically significant difference between the HCCP and pregabalin groups with respect to PGIC responses at Week 8: OR=1.03 [95% CL: 0.68-1.57] (Table 4).

The mean observed MOS-Cog overall score at Week 8 (BOCF) increased compared to baseline (Fig. 2). The adjusted mean MOS-Cog overall score was significantly ($P < 0.0001$) improved in favor of the HCCP compared with pregabalin by 4.3 units (Table 4). Significantly

Table 3. *Summary of HRQoL scores(a) in the FAS.*

Variable	HCCP (n = 282)	Pregabalin (n = 277)
MOS-Cog, n	276	274
Mean score (SD)	46.6 (10.6)	44.9 (12.0)
MOS-Sleep problems index I, n	276	273
Mean score (SD)	46.1 (10.9)	45.7 (10.0)
MOS-Sleep problems index II, n	276	273
Mean score (SD)	46.3 (10.6)	45.7 (9.8)
EQ-UI, n	276	272
Mean score (SD)	0.59 (0.19)	0.54 (0.21)
EQ-VAS, n	276	272
Mean score (SD)	61.4 (17.5)	58.5 (17.4)

EQ-5D-5L: EuroQol 5-Dimensions 5-levels; EQ-UI: EuroQol-Utility Index; EQ-VAS: EuroQol-Visual Analog Scale; FAS: Full Analysis Set; HCCP: High-Concentration Capsaicin 179 mg Cutaneous Patch; HRQoL: Health-Related Quality of Life; MOS-Cog: Medical Outcomes Study Cognitive Functioning scale; MOS Sleep: Medical Outcomes Study Sleep scale; n: Number of patients; SD: Standard Deviation.
(a) Baseline assessment not performed for TSQM (Treatment Satisfaction Questionnaire for Medication) or PGIC (Patient Global Impression of Change). For further information, please see Haanpää et al.(15).

greater improvements with HCCP vs pregabalin were evident in the following MOS-Cog items: "difficulty reasoning and solving problems" (OR=1.62 [95% CL: 1.11-2.28]), "difficulty doing activities" (OR=1.91 [95% CL: 1.31-2.79]), "confusion over activities" (OR=1.51 [95% CL: 1.02-2.25]), and "slow reaction time" (OR=1.60 [95% CL: 1.07-2.41]). The other MOS Cog items showed no statistically significant differences between treatment groups.

Mean observed scores for MOS-Sleep problem index I and index II showed small improvements from baseline with similar outcomes in the HCCP and pregabalin groups at Week 8 (Fig. 2); respectively, mean values for problems index I and index II were 50.9 and 51.3 vs. 46.1 and 46.3 at baseline, and 50.1 and 50.2 vs. 45.7 and 45.7 at baseline (Table S1). Mean adjusted estimates of treatment effect for the MOS Sleep problems index I and index II (0.7 and 0.9 respectively) were suggestive of similar outcomes with both HCCP and pregabalin; neither estimate was statistically significant (Table 4). Analysis of the MOS

Table 4. *Estimates of differences in health-related quality-of-life outcomes for HCCP vs. pregabalin.*

Patient Reported Outcome	n	HCCP vs PREGABALIN			
		Mean Difference[a] (95% CI)	*P*-value	Standardized Difference[b] (95% CI)	*P*-value
PGIC (range 1-7 points)					
Mean score	541	1.03 (0.68-1.57)[c]	0.875	–	–
MOS-Cog (0-100)					
Mean score	550	4.28 (2.90-5.66)	< 0.0001	35.9 (16.7-65.2)	< 0.0001
MOS-Sleep					
Problems index I (6 items)	549	0.70 (–0.59-2.00)	0.288	0.13 (0-9.14)	0.288
Problems index II (9 items)	549	0.91 (–0.32-2.14)	0.147	1.11 (0-11.67)	0.147
TSQM					
Global satisfaction	541	6.74 (2.29-11.20)	0.003	7.80 (1.0-24.4)	0.003
Effectiveness	541	4.28 (0.45-8.11)	0.029	3.79 (0-17.3)	0.029
Side effects	541	21.23 (17.52-24.94)	< 0.0001	125.0 (84.0-177.3)	< 0.0001
Convenience	541	–0.95 (–4.09-2.19)	0.551	–0.65 (0-6.46)	0.551
EQ-5D-5L					
EQ-UI	548	0.03 (–0.01, 0.06)	0.062	–	–
EQ-VAS	548	3.11 (0.30, 5.92)	0.030	–	–

CI: Confidence Interval; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels; EQ-UI: EuroQol-Utility Index; EQ-VAS: EuroQol-Visual Analogue Scale; HCCP: High-Concentration Capsaicin 179 mg Patch; MD: Mean Difference; MOS-Cog: Medical Outcomes Study Cognitive Functioning scale; MOS-Sleep: Medical Outcomes
Study Sleep scale; OR: Odds Ratio; PGIC: Patient Global Impression of Change; TSQM: Treatment Satisfaction Questionnaire for Medication.
[a] Based on a least squares linear model which included treatment group, baseline score, gender, and country group (Group 1: Armenia, Greece, Turkey; Group 2: Russia; Group 3: Belarus, Bulgaria, Romania; Group 4: Czech Republic, Hungary, Poland, Slovakia, Slovenia; Group 5: Austria, Belgium, France, Germany; Group 6: Finland, Great Britain, Sweden; Group 7: Italy, Portugal, Spain) as covariates.
[b] Comparison of differences on a common scale.
[c] Odds ratio (with 95% confidence limits) is reported as the mean effect.

Sleep subscales showed that somnolence (i.e., "feeling drowsy," "trouble staying awake," and "daytime naps") was significantly improved with HCCP compared with pregabalin (mean difference: 3.68 [95% CI: 2.34-5.02]). All other MOS Sleep subscales and individual questionnaire items showed no statistically significant differences between treatment groups, except for "hours of sleep each night" and "trouble falling asleep" which were favorable for pregabalin over HCCP.

More patients reported "no problems" on all dimensions of the EQ-5D-5L scale (i.e., mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) at Week 8 (BOCF) compared to baseline in both treatment groups. Moreover, the proportion of patients reporting "no problems" was consistently slightly higher with HCCP compared to pregabalin (i.e., 0.7-12% higher). There were small differences between treatment groups at Week 8 in the mean observed scores for the EQ-UI and EQ-VAS. For the EQ-UI, there was a mean adjusted difference of 0.03 units in favor of the HCCP compared with pregabalin, although the effect size was not statistically significant (P = 0.062). For the EQ-VAS, the score was significantly (P = 0.030) improved with the HCCP compared with pregabalin (mean difference: 3.11).

Patients in the HCCP group reported greater treatment satisfaction with regards to TSQM side effects at Week 8 (LOCF) vs patients in the pregabalin group: mean value 97.0 vs 76.3 (Table S1). A greater improvement in favor of HCCP was also evident for TSQM global satisfaction (P = 0.003), and TSQM effectiveness (P = 0.029), but not for the TSQM convenience score (Fig. 3). The adjusted mean difference in the TSQM side-effects score (Table 4) was 21.23 units in favor of HCCP compared with pregabalin (P < 0.0001); the mean adjusted OR for the side-effects item (yes/no) was also significant (OR = 0.10 [95% CL: 0.06-0.16]). A significant difference in favor of the HCCP was also evident for the mean adjusted TSQM global satisfaction score (6.74 units; P = 0.003) and TSQM effectiveness score (4.28 units; P = 0.029) compared with pregabalin, but not for the convenience score (Table 4).

When the estimates of relative treatment effect were standardized to a common scale (Table 4), the benefit with HCCP vs. pregabalin was greatest for the TSQM side effect score (125.0), followed by the MOS-Cog overall score (35.9). Standardized estimates of treatment effect for all other summary scores were much lower (< 8).

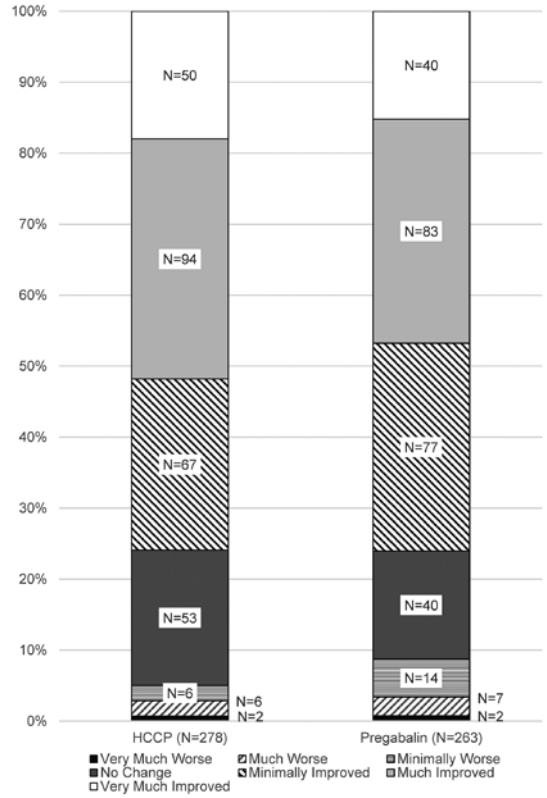

Fig. 1. *Patient Global Impression of Change (PGIC) ratings by treatment group at Week 8.*
Patients rated changes in their overall status from the start of study treatment on a 7-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse). HCCP (High-Concentration Capsaicin 179 mg Cutaneous Patch), n = 278; Pregabalin (oral daily intake), n = 263.

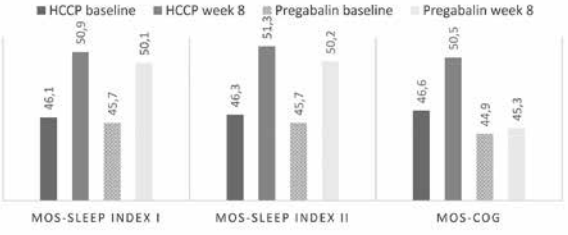

Fig. 2. *Mean MOS-Cog and MOS-Sleep scores by treatment group at Week 8.*
MOS-Cog: Medical Outcomes Study Cognitive Functioning scale. MOS-Sleep: Medical Outcomes Study Sleep scale.
The range was 1 to 100 (higher score indicates better cognitive functioning/sleep).

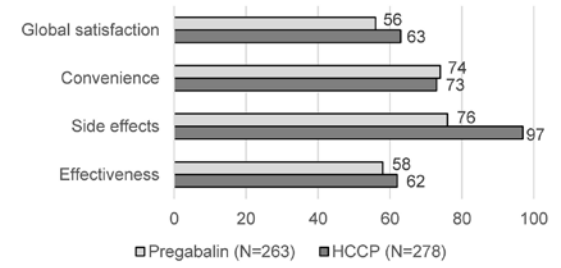

Fig. 3. *Mean TSQM scores by treatment group at Week 8.* TSQM: Treatment Satisfaction Questionnaire for Medication. The range was 1 to 100 (greater the treatment satisfaction, higher the score).

Discussion

Few large randomized, controlled clinical trials provide direct comparisons between recommended first- and second-line treatments of PNP. As a result, currently comparisons between such treatments rely mostly on meta-analysis. To our knowledge, the current ELEVATE study is, to date, the only study that directly compares a single intervention at the site of pain with a topically applied HCCP with a systemic oral daily treatment (pregabalin) within a randomized controlled clinical trial setting. The primary efficacy analysis of the ELEVATE study demonstrated that direct topical intervention with HCCP was noninferior to dose-optimized daily pregabalin in relieving pain in non-diabetic PNP patients, and that the median time to onset of pain relief was significantly faster and systemic side effects were fewer with the HCCP (19). According to our analyses, there are also clear and measurable differences between HCCP and pregabalin in several facets of PROs. The most prominent was a marked improvement in the TSQM side effects score with HCCP vs. pregabalin. Patients' perception of cognitive functioning (MOS-Cog) was also improved in the HCCP group compared with pregabalin. Statistically significant differences in favor of HCCP vs. pregabalin were also evident in overall HRQoL as measured by EQ-VAS, and medication effectiveness and overall satisfaction with medication as measured by TSQM. These observations supplement the efficacy and safety data from the ELEVATE study (19), and provide some insight as to how patients perceive the effects of these 2 treatments.

In our analyses, mean differences between treatments were estimated for the top-level or summary scores for each PRO questionnaire. However, a statistically significant between-group difference does not necessarily indicate a clinically meaningful change. At the time of the study, no minimally clinically important difference had been defined for EQ 5D-5L, MOS-Cog, or TSQM in any patient population, so it is difficult to evaluate the clinical relevance of the differences observed in our analyses. For MOS-Sleep, it has been suggested that an effect size of -0.68 in the MOS-Sleep problem index II is indicative of a minimal improvement in patients with painful diabetic neuropathy (36). Our estimate of the difference between groups on this scale (0.91) slightly exceeds this cut-off value, suggesting a clinically meaningful difference between groups.

The distinctive tolerability profiles of the 2 treatments in the ELEVATE study may have been an important contributing factor to some of the PRO differences. Pregabalin is associated with several well characterized central nervous system (CNS) side effects and HCCP with application-site reactions. In the ELEVATE study, the most common adverse events associated with pregabalin were dizziness (18.4%), somnolence (15.5%), and nausea (10.8%), other adverse events reported in > 5% of patients being headache (9.4%), weight increased (6.1%), and vertigo (5.1%); the most common adverse events associated with HCCP were pain (23.8%), erythema (20.9%), and burning sensation (15.6%) at application site (19). The large between-group difference in the TSQM side-effects score appears to reflect the different tolerability profiles between HCCP and pregabalin. It also seems likely that the CNS events associated with pregabalin contributed to the consistently poorer outcomes on the MOS-Cog scale observed in this group. Psychomotor and cognitive functions after 2 weeks with pregabalin (300-600 mg/day) have been assessed objectively in patients with diabetic neuropathic pain (37): daytime functioning was significantly impaired with pregabalin compared with duloxetine and amitriptyline, and change in psychomotor speed, CNS arousal, information processing, and/or memory was minimal. Our findings are suggestive of more important cognitive impairment, which may be the result of the longer treatment period in our study compared with the previous study (37).

Both MOS-Sleep problem indexes I and II indicated that HCCP and pregabalin had similar beneficial effects overall on sleep-related issues (i.e., ≈13%-16% improvement from baseline in both groups). However, data from individual MOS-Sleep items indicated some differences between the treatment arms: HCCP improved day-time drowsiness and somnolence, and

reduced both sleep latency and quantity compared with pregabalin. A meta-analysis of pregabalin randomized clinical trials in neuropathic pain showed similar findings with respect to the effect of pregabalin on sleep as measured by MOS-Sleep problem indexes (38).

The overall positive effects of HCCP on the sleep may be positively correlated with improved cognitive functioning (e.g., reasoning/solving problems and doing activities) observed with HCCP.

The PROs selected for the ELEVATE study were identified from a conceptual model developed for patients with PNP (23). Concept elicitation, through qualitative research (literature reviews, focus groups, and/or interviews), is a key step to understanding a disease from a patient's perspective and ensuring content validity (39). The key concepts identified from the conceptual model were pain, sleep disturbances, detrimental drug related effects, general effects on HRQoL, and anxiety and depression (23). Thirty-seven instruments were screened for review before selecting the final instruments for the ELEVATE study. These included the NRS to assess pain (primary study endpoint), MOS-Sleep, EQ-5D-5L, and PGIC, all of which are recommended in the NeuPSIG guidelines for pain assessment (40). In the absence of an existing patient-reported measure suitable for assessing the impact of HCCP and pregabalin side effects, a general treatment satisfaction measure (TSQM) and MOS-Cog were selected. Anxiety and depression were not measured using condition-specific instruments in the ELEVATE study because the 8-week treatment period was considered too short to evaluate changes in these conditions accurately, although the EQ-5D-5L questionnaire includes an anxiety/depression dimension.

One head-to-head comparison of a daily administered topical treatment (lidocaine 5% medicated plasters) and oral pregabalin in patients with postherpetic neuralgia or diabetic polyneuropathy (n = 300) has been reported (41). The study had a randomized, open-label, non-inferiority, 2-stage design which included a 4-week comparative phase. Similar to the ELEVATE study, the EQ-UI improved more with daily topical treatment vs. pregabalin and PGIC ratings were comparable with both treatments (41). In this trial, patient satisfaction with treatment, which was assessed using a simple 5-point rating scale, was similar between treatment groups (41), whereas in ELEVATE patients treated with the HCCP reported greater satisfaction with treatment on TSQM compared to those treated with pregabalin.

Patients with neuropathic pain have impaired HRQoL compared with the general population (3) and experience higher prevalence of depression, anxiety, and sleep disturbances (5). Therefore, it is important that treatments for PNP not only reduce levels of pain, but also improve PRO and overall functioning. Evidence suggests that the observed impact of treatment may vary based on PRO domain examined, different measures of PRO may have different sensitivity levels, and any beneficial impact of treatment on one domain is likely to be accompanied by improvements in others (42). Furthermore, although there are several instruments that can measure individual aspects of PRO related to PNP (e.g., cognition or sleep), perhaps further research is needed to develop instruments specific for PNP that may reduce the burden associated with completing multiple questionnaires.

The strengths of this study include a large population (n > 550) of non-diabetic PNP patients from 22 countries, and, therefore, the findings could be considered broadly generalizable to other PNP patients. The effects of interventional treatment with HCCP were compared with daily oral pregabalin, which is one of several first- or second-line treatment options recommended for neuropathic pain (6). The questionnaire completion rates in the ELEVATE study were high, particularly in the HCCP group, therefore, the sample size for all analyses was large and the need for imputation of missing values was minimal.

Limitations

In the ELEVATE study, the observation period was limited to 8 weeks and a single intervention with HCCP. A longer observation period and repeated treatments with HCCP over, for example, 6 months are needed to ascertain the long-term PRO effects of pregabalin and HCCP. Of note is that in a long-term trial of 52 weeks in which HCCP on top of Standard of Care (SoC) was compared to SoC treatment alone in a population of diabetic PNP patients, a greater proportion of patients treated with HCCP reported improvements in pain level, activity level, HRQoL, and willingness to undergo the same treatment again than with SoC alone (43). Other limitations of the ELEVATE study are its open-label design and that pregabalin was the only study comparator. Therefore, it is unknown how the PRO effects of the HCCP compare with other treatments for neuropathic pain or placebo. Furthermore, the statistical power of the ELEVATE study was determined for the primary endpoint, rather than the secondary endpoints

which included the PRO assessments. The statistical findings from our analyses should, therefore, be interpreted with this in mind.

Conclusion

In conclusion, a single intervention with HCCP showed benefits vs. daily pregabalin in terms of cognitive functioning, somnolence, treatment satisfaction, and patients' perception of side effects. These observations supplement the already reported efficacy and safety data of HCCP. They provide information on how patients perceive the effects of the 2 distinct treatments (i.e., a single intervention locally acting and an oral daily treatment relying on systemic exposure). Finally, in clinical practice, in a context of growing interest in shared-decision making, these results may help physicians to open the dialogue with their patients offering them the choice between different treatment options, balancing treatment efficacy, tolerability, and perception.

Acknowledgments

Professor Nancy Devlin and Mike Herdman, from The Office of Health Economics Ltd, contributed to the analysis and interpretation of study results. Medical writing support was provided by Harriet Lamb and Tyrone Daniel from Bioscript Medical and then by Matthieu Chanard and Fabienne Péretz from Abelia Science.

Author Contributions

Eric Viel reviewed the protocol and contributed to the data acquisition. All authors discussed the results, provided key intellectual input, commented on the manuscript, and approved the final version for submission.

Supplemental material available at www.painphysicianjournal.com

References

1. International Association for the Study of Pain (IASP). IASP terminology: Neuropathic pain. Accessed 04/23/2020. www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698
2. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies [published correction appears in Pain 2014; 155:1907]. *Pain* 2014; 155:654-662.
3. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: A systematic review and meta-analysis of health utilities. *Pain* 2010; 149:338-344.
4. Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: Results of a French nationwide survey. *Pain* 2011; 152:2836-2843.
5. Langley PC, Van Litsenburg C, Cappelleri JC, Carroll D. The burden associated with neuropathic pain in Western Europe. *J Med Econ* 2013; 16:85-95.
6. 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.
7. Üçeyler N, Sommer C. High-Dose capsaicin for the treatment of neuropathic pain: What we know and what we need to know. *Pain Ther* 2014; 3:73-84.
8. Haanpää ML, Gourlay GK, Kent JL, et al. Treatment considerations for patients with neuropathic pain and other medical comorbidities. *Mayo Clin Proc* 2010; 85(suppl 3):S15-S25.
9. Gahr M, Freudenmann RW, Hiemke C, Kölle MA, Schönfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: Results from a database query. *Eur J Clin Pharmacol* 2013; 69:1335-1342.
10. Bates D, Schultheis BC, Hanes MC, et al. A comprehensive algorithm for management of neuropathic pain. *Pain Med* 2019; 20(suppl 1):S2-S12.
11. Murray MD, Kroenke K. Polypharmacy and medication adherence: Small steps on a long road. *J Gen Intern Med* 2001; 16:137-139.
12. 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.
13. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet* 2010; 49:661-669.
14. Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: A randomised, double-blind study [published correction appears in Lancet Neurol 2009; 8:31]. *Lancet Neurol* 2008; 7:1106-1112.
15. 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.
16. 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.
17. Federal Drug Administration (2009). Federal Drug Administration: Guidance for industry — patient-reported outcomes measures: Use in medical product development to support labeling claims. Accessed 04/23/2020. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
18. European Medicines Agency (2006). European Medicines Agency (EMEA) and the Committee for Medicinal Products for Human Use (CHMP). Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of

medicinal products. Accessed 04/23/20. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf

19. Haanpää M, Cruccu G, Nurmikko TJ, et al. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. *Eur J Pain* 2016; 20:316-328.
20. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; 113:9-19.
21. Pfizer Limited UK (2009). Lyrica summary of product characteristics. Accessed 04/23/2020. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf
22. Freynhagen VR, Junker U. [Chameleon neuropathic pain: Do you know all facets of excruciation pain?] *MMW Fortschr Med* 2005; 147:40-42.
23. Chambers C, Ernault E, van Nooten F. Conceptual model development and pros for non-diabetic peripheral neuropathic pain. *Value Health* 2014; 17:A205.
24. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther* 2004; 27:26-35.
25. Stewart A, Ware J Jr, Sherbourne C, Wells K. Psychological distress/well-being and cognitive measures. In: *Stewart A, Ware J Jr (eds) Measuring Functioning and Well-being: The Medical Outcomes Study Approach*. Duke University Press, Durham, NC, 1992, pp 102-142.
26. Hays R, Stewart A. Sleep Measures. In: *Stewart A, Ware J Jr (eds) Measuring Functioning and Well-being: The Medical Outcomes Study Approach*. Duke University Press, Durham, NC, 1992, pp 235-239.
27. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004; 2:12.
28. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; 20:1727-1736.
29. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: A review of strengths and weaknesses and considerations for design. *J Man Manip Ther* 2009; 17:163-170.
30. Vinik A, Emir B, Cheung R, Whalen E. Relationship between pain relief and improvements in patient function/quality of life in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia treated with pregabalin. *Clin Ther* 2013; 35:612-623.
31. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. *Prog Neurobiol* 2011; 93:385-404.
32. Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the medical outcomes study sleep measure. Sleep Med 2005; 6:41-44.
33. Rejas J, Ribera MV, Ruiz M, Masrramón X. Psychometric properties of the MOS (Medical Outcomes Study) sleep scale in patients with neuropathic pain. *Eur J Pain* 2007; 11:329-340.
34. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012; 15:708-715.
35. Gu NY, Bell C, Botteman MF, Ji X, Carter JA, van Hout B. Estimating preference-based EQ-5D health state utilities or item responses from neuropathic pain scores. *Patient* 2012; 5:185-197.
36. Viala-Danten M, Martin S, Guillemin I, Hays RD. Evaluation of the reliability and validity of the medical outcomes study sleep scale in patients with painful diabetic peripheral neuropathy during an international clinical trial. *Health Qual Life Outcomes* 2008; 6:113.
37. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care* 2012; 35:2451-2458.
38. Onakpoya IJ, Thomas ET, Lee JJ, Goldacre B, Heneghan CJ. Benefits and harms of pregabalin in the management of neuropathic pain: A rapid review and meta-analysis of randomised clinical trials. *BMJ Open* 2019; 9:e023600.
39. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: Part 1--eliciting concepts for a new PRO instrument. *Value Health* 2011; 14:967-977.
40. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; 152:14-27.
41. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: An open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin* 2009; 25:1663-1676.
42. 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.
43. Vinik IA, Perrot S, Vinik E, et al. Repeat treatment with capsaicin 8% patch (179 mg capsaicin cutaneous patch): Effects on pain, quality of life, and patient satisfaction in painful diabetic peripheral neuropathy: An open-label, randomized controlled clinical trial. *Curr Med Res Opin* 2019; 2:388-401.

Supplemental Table 1. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		**PREGABALIN (n = 277)**	
PGIC	n (%)				
Week 4	n	268		239	
	Very Much Improved	21	(7.8%)	12	(5.0%)
	Much Improved	110	(41.0%)	104	(43.5%)
	Minimally Improved	74	(27.6%)	73	(30.5%)
	No Change	52	(19.4%)	36	(15.1%)
	Minimally Worse	10	(3.7%)	8	(3.3%)
	Much Worse	1	(0.4%)	6	(2.5%)
	Very Much Worse	0		0	
Week 8	n	262		246	
	Very Much Improved	48	(18.3%)	39	(15.9%)
	Much Improved	93	(35.5%)	78	(31.7%)
	Minimally Improved	59	(22.5%)	73	(29.7%)
	No Change	48	(18.3%)	36	(14.6%)
	Minimally Worse	6	(2.3%)	13	(5.3%)
	Much Worse	6	(2.3%)	5	(2.0%)
	Very Much Worse	2	(0.8%)	2	(0.8%)
Week 8 (LOCF)	n	278		263	
	Very Much Improved	50	(18.0%)	40	(15.2%)
	Much Improved	94	(33.8%)	83	(31.6%)
	Minimally Improved	67	(24.1%)	77	(29.3%)
	No Change	53	(19.1%)	40	(15.2%)
	Minimally Worse	6	(2.2%)	14	(5.3%)
	Much Worse	6	(2.2%)	7	(2.7%)
	Very Much Worse	2	(0.7%)	2	(0.8%)
MOS-Cog					
Baseline	n	276		274	
	Mean (SD)	46.6	(10.58)	44.9	(12.00)
	Median (Min-Max)	48.0	(10-59)	45.8	(8-59)
Week 8	n	262		246	
	Mean (SD)	50.8	(9.30)	46.0	(12.09)
	Median (Min-Max)	54.4	(20-59)	48.0	(8-59)
Week 8 (BOCF)	n	281		275	
	Mean (SD)	50.5	(9.49)	45.3	(12.56)
	Median (Min-Max)	54.4	(18-59)	48.0	(8-59)
MOS-Sleep	Index I (6 items)				
Baseline	n	276		273	
	Mean (SD)	46.1	(10.94)	45.7	(10.03)
	Median (Min-Max)	46.3	(14-65)	46.3	(19-65)
Week 4	n	268		239	
	Mean (SD)	50.2	(10.34)	51.0	(8.90)
	Median (Min-Max)	50.5	(23-65)	56.8	(21-65)

Supplemental Table 1 con't. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		PREGABALIN (n = 277)	
Week 8	n	262		245	
	Mean (SD)	51.3	(10.35)	50.9	(10.24)
	Median (Min-Max)	52.6	(23-65)	52.6	(21-65)
Week 8 (BOCF)	n	281		274	
	Mean (SD)	50.9	(10.54)	50.1	(10.48)
	Median (Min-Max)	52.6	(19-65)	52.6	(19-65)
MOS-Sleep	Index II (9 items)				
Baseline	n	276		273	
	Mean (SD)	46.3	(10.57)	45.7	(9.82)
	Median (Min-Max)	46.3	(20-66)	44.9	(20-66)
Week 4	n	268		239	
	Mean (SD)	50.5	(10.12)	51.2	(8.61)
	Median (Min-Max)	51.9	(25-66)	51.9	(22-66)
Week 8	n	262		245	
	Mean (SD)	51.7	10.07	51.0	10.15
	Median (Min-Max)	53.3	(22-66)	53.3	(22-66)
Week 8 (BOCF)	n	281		274	
	Mean (SD)	51.3	10.24	50.2	10.40
	Median (Min-Max)	51.9	(21-66)	51.9	(20-66)
EQ-5D-5L	EQ-UI: n (%)				
Mobility (walking about)					
Baseline	n	276		272	
	No problems	126	(45.7%)	86	(31.6%)
	Slight problems	63	(22.8%)	75	(27.6%)
	Moderate problems	49	(17.8%)	65	(23.9%)
	Severe problems	38	(13.8%)	44	(16.2%)
	Unable	0		2	(0.7%)
Week 8	n	262		245	
	No problems	160	(61.1%)	121	(49.4%)
	Slight problems	46	(17.6%)	70	(28.6%)
	Moderate problems	38	(14.5%)	39	(15.9%)
	Severe problems	17	(6.5%)	14	(5.7%)
	Unable	1	(0.4%)	1	(0.4%)
Week 8 (BOCF)	n	281		274	
	No problems	168	(59.8%)	126	(46.0%)
	Slight problems	49	(17.4%)	78	(28.5%)
	Moderate problems	43	(15.3%)	46	(16.8%)
	Severe problems	20	(7.1%)	21	(7.7%)
	Unable	1	(0.4%)	3	(1.1%)

Supplemental Table 1 con't. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		PREGABALIN (n = 277)	
Self-Care (washing or dressing)					
Baseline	n	276		272	
	No problems	174	(63.0%)	155	(57.0%)
	Slight problems	51	(18.5%)	53	(19.5%)
	Moderate problems	39	(14.1%)	53	(19.5%)
	Severe problems	11	(4.0%)	10	(3.7%)
	Unable	1	(0.4%)	1	(0.4%)
Week 8	n	262		245	
	No problems	198	(75.6%)	176	(71.8%)
	Slight problems	39	(14.9%)	47	(19.2%)
	Moderate problems	21	(8.0%)	18	(7.3%)
	Severe problems	3	(1.1%)	3	(1.2%)
	Unable	1	(0.4%)	1	(0.4%)
Week 8 (BOCF)	n	281		274	
	No problems	210	(74.7%)	182	(66.4%)
	Slight problems	45	(16.0%)	59	(21.5%)
	Moderate problems	22	(7.8%)	27	(9.9%)
	Severe problems	3	(1.1%)	5	(1.8%)
	Unable	1	(0.4%)	1	(0.4%)
Usual activity					
Baseline	n	276		272	
	No problems	99	(35.9%)	93	(34.2%)
	Slight problems	88	(31.9%)	72	(26.5%)
	Moderate problems	62	(22.5%)	81	(29.8%)
	Severe problems	23	(8.3%)	20	(7.4%)
	Unable	4	(1.4%)	6	(2.2%)
Week 8	n	262		245	
	No problems	146	(55.7%)	135	(55.1%)
	Slight problems	75	(28.6%)	69	(28.2%)
	Moderate problems	27	(10.3%)	32	(13.1%)
	Severe problems	14	(5.3%)	6	(2.4%)
	Unable	0		3	(1.2%)
Week 8 (BOCF)	n	281		274	
	No problems	151	(53.7%)	139	(50.7%)
	Slight problems	80	(28.5%)	81	(29.6%)
	Moderate problems	35	(12.5%)	40	(14.6%)
	Severe problems	15	(5.3%)	11	(4.0%)
	Unable	0		3	(1.1%)

Supplemental Table 1 con't. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		PREGABALIN (n = 277)	
Pain/Discomfort					
Baseline	n	276		272	
	No problems	4	(1.4%)	4	(1.5%)
	Slight problems	36	(13.0%)	23	(8.5%)
	Moderate problems	151	(54.7%)	142	(52.2%)
	Severe problems	84	(30.4%)	100	(36.8%)
	Unable	1	(0.4%)	3	(1.1%)
Week 8	n	262		245	
	No problems	58	(22.1%)	42	(17.1%)
	Slight problems	111	(42.4%)	100	(40.8%)
	Moderate problems	63	(24.0%)	76	(31.0%)
	Severe problems	27	(10.3%)	24	(9.8%)
	Unable	3	(1.1%)	3	(1.2%)
Week 8 (BOCF)	n	281		274	
	No problems	58	(20.6%)	42	(15.3%)
	Slight problems	116	(41.3%)	102	(37.2%)
	Moderate problems	73	(26.0%)	89	(32.5%)
	Severe problems	31	(11.0%)	37	(13.5%)
	Unable	3	(1.1%)	4	(1.5%)
Anxiety/Depression					
Baseline	n	276		272	
	No problems	137	(49.6%)	122	(44.9%)
	Slight problems	87	(31.5%)	72	(26.5%)
	Moderate problems	44	(15.9%)	61	(22.4%)
	Severe problems	6	(2.2%)	13	(4.8%)
	Unable	2	(0.7%)	4	(1.5%)
Week 8	n	262		245	
	No problems	174	(66.4%)	148	(60.4%)
	Slight problems	51	(19.5%)	64	(26.1%)
	Moderate problems	27	(10.3%)	20	(8.2%)
	Severe problems	7	(2.7%)	10	(4.1%)
	Unable	3	(1.1%)	3	(1.2%)
Week 8 (BOCF)	n	281		274	
	No problems	187	(66.5%)	156	(56.9%)
	Slight problems	56	(19.9%)	72	(26.3%)
	Moderate problems	28	(10.0%)	29	(10.6%)
	Severe problems	7	(2.5%)	12	(4.4%)
	Unable	3	(1.1%)	5	(1.8%)
EQ-5D-5L	EQ-VAS				
Baseline	n	276		272	
	Mean (SD)	61.4	(17.50)	58.5	(17.42)
	Median (Min-Max)	61.0	(0-98)	60.0	(10-92)

Supplemental Table 1 con't. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		PREGABALIN (n = 277)	
Week 8	n	262		245	
	Mean (SD)	71.8	(18.86)	68.6	(19.92)
	Median (Min-Max)	75.0	(11-100)	73.0	(0-100)
Week 8 (BOCF)	n	281		274	
	Mean (SD)	71.1	(19.28)	66.5	(20.79)
	Median (Min-Max)	75.0	(0-100)	70.0	(0-100)
TSQM					
Effectiveness					
Week 4	n	268		239	
	Mean (SD)	57.7	(24.59)	57.8	(20.15)
	Median (Min-Max)	61.1	(0-100)	61.1	(0-100)
Week 8	n	262		245	
	Mean (SD)	62.0	(25.65)	58.4	(23.27)
	Median (Min-Max)	66.7	(0-100)	61.1	(0-100)
Week 8 (LOCF)	n	278		263	
	Mean (SD)	61.5	(25.57)	57.5	(23.14)
	Median (Min-Max)	66.7	(0-100)	61.1	(0-100)
Side effects					
Week 4	n	268		239	
	Mean (SD)	95.6	(13.81)	80.3	(27.3)
	Median (Min-Max)	100	(13-100)	100.0	(0-100)
Week 8	n	262		245	
	Mean (SD)	97.3	(11.20)	77.8	(30.35)
	Median (Min-Max)	100.0	(19-100)	100.0	(0-100)
Week 8 (LOCF)	n	278		263	
	Mean (SD)	97.0	(12.27)	76.3	(31.19)
	Median (Min-Max)	100.0	(13-100)	100.0	(0-100)
Convenience					
Week 4	n	268		239	
	Mean (SD)	71.7	(20.08)	74.5	(16.24)
	Median (Min-Max)	72.2	(17-100)	72.2	(0-100)
Week 8	n	262		245	
	Mean (SD)	72.9	(20.72)	74.1	(17.14)
	Median (Min-Max)	72.2	(0-100)	77.8	(11-100)
Week 8 (LOCF)	n	278		263	
	Mean (SD)	72.8	(20.52)	73.6	(17.46)
	Median (Min-Max)	72.2	(0-100)	72.2	(11-100)
Global satisfaction					
Week 4	n	268		239	
	Mean (SD)	60.7	(27.06)	58.5	(22.53)
	Median (Min-Max)	64.3	(0-100)	64.3	(0-100)

Supplemental Table 1 con't. *Patient-Reported outcome scores for HCCP vs. pregabalin.*

		HCCP (n = 282)		**PREGABALIN (n = 277)**	
Week 8	n	262		245	
	Mean (SD)	63.3	(28.94)	56.9	(27.17)
	Median (Min-Max)	71.4	(0-100)	64.3	(0-100)
Week 8 (LOCF)	n	278		263	
	Mean (SD)	62.6	(29.02)	56.1	(26.90)
	Median (Min-Max)	71.4	(0-100)	64.3	(0-100)

BOCF: Baseline Observation Carried Forward; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels; EQ-UI: EuroQol-Utility Index; EQ-VAS: EuroQol-Visual Analog Scale; HCCP: High-Concentration Capsaicin 179 mg Patch; LOCF: Last Observation Carried Forward; Max: Maximum; Min: Minimum; MOS-Cog: Medical Outcomes Study Cognitive Functioning scale; MOS-Sleep: Medical Outcomes Study Sleep scale; n: Number of Patients; PGIC: Patient Global Impression of Change; TSQM: Treatment Satisfaction Questionnaire for Medication; SD: Standard Deviation.