

ORIGINAL ARTICLE

Tolerability of the capsaicin 8% patch following pretreatment with lidocaine or tramadol in patients with peripheral neuropathic pain: A multicentre, randomized, assessor-blinded study

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Conflicts of interest

T.S.J. has received honoraria for participation in advisory boards or speakers' bureaus for Astellas, Pfizer and Grunenthal. K.H. has received honoraria for oral presentations and participation in advisory boards from Astellas Pharma, AstraZeneca, Eli Lilly, MSD, Pfizer and Takeda Nycomed. J.F. has acted as a senior consultant and lecturer for Astellas Pharma Europe Ltd. P.V. has no conflicts of interest. E.E. is a consultant for Astellas Pharma Europe Ltd. T.S. and S.M. are employed by Astellas Pharma Europe Ltd.

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Abstract

Background: Application of the capsaicin 8% patch is associated with treatment-related discomfort. Consequently, pretreatment for 60 min with anaesthetic cream is recommended; however, this may be uncomfortable and time consuming.

Methods: We conducted a multicentre, randomized (1:1), assessor-blinded study in patients with peripheral neuropathic pain to assess tolerability of the capsaicin patch following topical lidocaine (4%) or oral tramadol (50 mg) pretreatment. The primary endpoint was the proportion of patients tolerating capsaicin patch application (ability to receive $\geq 90\%$ of a 60-min application). Numeric Pain Rating Scale (NPRS) scores were assessed before, during and after treatment.

Results: Overall, 122 patients were included (61 per arm). The capsaicin patch was tolerated by 121 patients. Tolerability of the capsaicin patch was similar following pretreatment with lidocaine and tramadol. Following patch application, pain levels increased up to 55 min (change from baseline of 1.3 for lidocaine and 1.4 for tramadol). After patch removal, tramadol-treated patients experienced greater pain relief up to the end of day 1; in the evening, mean changes in NPRS scores from baseline were 0 for lidocaine and -1 for tramadol. Proportions of patients reporting increases of ≥ 2 NPRS points or $>33\%$ from baseline at one or more time point(s) on the day of treatment were similar between arms. Adverse event incidence was comparable between arms.

Conclusions: Capsaicin 8% patch tolerability was similar in the two arms, with comparable results for most secondary endpoints. Tramadol given 30 min before patch application should be considered as an alternative pretreatment option in patients receiving capsaicin patch treatment.

1. Introduction

Treatment of neuropathic pain (NP) is still unsatisfactory, with more than two-thirds of patients attaining insufficient pain relief (Attal et al., 2010;

Dworkin et al., 2010; Finnerup et al., 2010). In addition, most of the currently used systemic analgesics have important central nervous system side effects, such as dizziness, somnolence and other cognitive symptoms, which limit their use in many patients

What's already known about this topic?

- Application of topical capsaicin, a treatment for peripheral neuropathic pain conditions associated with allodynia, can cause painful discomfort.
- Therefore, a 60-min application of local anaesthetic cream before capsaicin 8% patch treatment was originally recommended.

What does this study add?

- Oral analgesic pretreatment may reduce overall capsaicin patch treatment time and potential unpleasantness associated with applying a topical agent to an allodynic area.
- Based on LIFT data showing similar tolerability to capsaicin patch regardless of pretreatment method, the European Medicines Agency has issued a type II variation stating: treatment area may be pretreated with a topical anaesthetic or an oral analgesic may be given prior to patch application.

(Finnerup et al., 2010). Consequently, there is a great need for compounds that do not cause such systemic side effects. Topical application of high-dose capsaicin represents such a potential alternative treatment (McCormack, 2010; Anand and Bley, 2011).

Capsaicin activates a ligand-gated, non-selective cation channel – the transient receptor potential vanilloid 1 receptor – expressed by a population of C and A δ nociceptors (Szallasi and Blumberg, 1999). These receptors are activated by heat, low pH and certain endogenous agonists (Anand and Bley, 2011) and subsequently initiate depolarization of fibres by influx of sodium and calcium ions into the cell. Following application of capsaicin, a number of changes may occur, including prolonged changes such as a more persistent increase in intracellular calcium, resulting in what has been termed 'dysfunctionalization' (Holzer, 2008; Anand and Bley, 2011). The exact mechanisms behind this dysfunctionalization are unknown, but it is speculated to involve microtubules and mitochondrial dysfunction as well as a reduction/retraction of epidermal nerve fibres (Kennedy et al., 2010). The principle of exposing neuropathic skin to a high concentration of topical capsaicin is now used in clinical practice (McCormack, 2010). Recently, a dermal application of capsaicin (8% w/w) (QUTENZATM, Astellas Pharma Europe B.V., Leiden, Netherlands) has been licensed in Europe for the management of peripheral NP (PNP) in non-diabetic adults (McCormack, 2010). Prolonged pain reduction following application of this capsaicin

8% patch was observed in patients with post-herpetic neuralgia (PHN) and painful human immunodeficiency virus-associated neuropathy in phase III studies (Backonja et al., 2008; Simpson et al., 2008; Irving et al., 2011).

Application of capsaicin is usually associated with local erythema and treatment-associated discomfort including pain. To reduce this discomfort, it was originally recommended that a local anaesthetic cream should be applied to the skin for 60 min before patch application (McCormack, 2010); however, this practice has several limitations. Firstly, local application of an anaesthetic cream may be uncomfortable when applied to patients with PNP due to nerve injury, in whom touch-evoked allodynia is commonly experienced (Jensen et al., 2009). Secondly, application of anaesthetic for 60 min before capsaicin treatment is time consuming for both patients and healthcare providers. Finally, the efficacy of local anaesthetic creams in reducing discomfort during capsaicin application has been questioned (The Capsaicin Study Group, 1991; Wallace and Pappagallo, 2011).

To address these limitations, we conducted a multicentre, randomized, assessor-blinded study to investigate the tolerability of the capsaicin 8% patch when applied after pretreatment with either topical lidocaine or oral tramadol. This was the first study to investigate the administration of an oral analgesic prior to application of the capsaicin 8% patch. The aim of the study was not to determine efficacy or other pharmacological parameters.

2. Methods

2.1 Study design

The LIFT study (registered at clinicaltrials.gov; NCT01416116) was a multicentre (Belgium, Czech Republic, Denmark, Great Britain, Ireland, Norway and Slovakia), randomized, assessor-blinded study conducted between July 2011 and April 2012. Patients were enrolled by the investigators, then randomly allocated, using randomization numbers and envelopes by staff at the study site, to one of two treatment arms in a 1:1 ratio. Subjects in arm 1 received application of topical anaesthetic cream (lidocaine 4%) to the area of pain, 70 min before patch application, for 60 min; those in arm 2 were administered oral tramadol 50 mg, 30 min before patch application. At the treatment visit, patients received their assigned pretreatment, followed by a 60-min application of the capsaicin 8% patch. After patch removal, patients were monitored for at least 2 h and then discharged (Fig. 1).

The study was conducted according to the principles of the Declaration of Helsinki, International Conference on

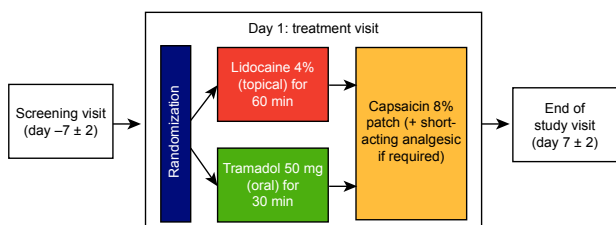


Figure 1 Study design.

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and local ethical and legal requirements. All patients provided written informed consent.

2.2 Patient population

As per the LIFT study protocol, eligible patients were naïve to treatment with the capsaicin 8% patch, aged 18–90 years, in good health (as judged by the investigator) and had a documented diagnosis of PNP due to: (1) PHN, with pain persisting for ≥ 3 months after shingles vesicle crusting, or (2) NP caused by peripheral nerve injury (PNI) including post-surgical NP and post-traumatic PNP, with pain persisting for ≥ 3 months following the event. A Numeric Pain Rating Scale (NPRS) score of ≥ 4 for 'Average Pain' both at the screening visit and the treatment visit (prior to the patch application) was also required. Intact, non-irritated, dry skin over the painful area(s) to be treated was an additional requirement for study entry.

Patients were excluded for the following reasons: significant ongoing or recurrent pain of aetiology other than PHN or PNI; pain due to complex regional pain syndrome (type I); NP areas located only on the face, above the hairline of the scalp, on the feet and/or in proximity to mucous membranes; past/current type I or II diabetes mellitus; active malignancy or treatment for malignancy during the past year (including radiotherapy, chemotherapy and biological or hormonal therapies); and clinically significant cardiovascular disease within 6 months prior to the treatment visit. Patients with a history of squamous cell carcinoma or a basal cell carcinoma not involving the area to be treated were not excluded. Use of monoamine oxidase inhibitors and carbamazepine were not permitted within 14 days prior to study entry. Use of any topical pain medications (such as non-steroidal anti-inflammatory drugs, menthol, methyl salicylate, local anaesthetics including lidocaine patch 5%, steroids or capsaicin products), on or near the affected areas where study treatment was to be applied, and opioids (including tramadol) was not permitted within 7 days preceding the treatment visit. During the course of the study, the following medications and procedures were not permitted: opioids (except short-acting oral opioids during the period from the treatment visit to day 6 for relief from treatment-associated discomfort), carbamazepine, monoamine oxidase inhibitors, any local/topical

pain therapy or systemic non-pharmacological pain treatment. The investigators were not permitted to change stable pre-study analgesic doses.

2.3 Assessments

Following patch application, a physician blinded to study pretreatment assessed adverse events (AEs), including treatment-related pain, and decided whether to apply cooling measures and/or administer medications for application-associated discomfort. Patients and nurses/investigators who administered pretreatment and the capsaicin 8% patch were not blinded to the pretreatment.

Patients were assessed by investigators on three separate occasions during the course of the study: at the screening visit, 7 days before the procedure; at the treatment visit, on the day of the procedure; and at the end of study visit, 7 days after the procedure. Baseline NPRS 'Pain Now' scores were assessed 75 min before patch application at the treatment visit.

Demographic information, medical history and vital signs (blood pressure and pulse rate) were recorded. Physical examination and laboratory tests (haematology and biochemistry tests, urinalysis) were also performed, as well as pregnancy tests if applicable. Treatment area(s) were identified based on the presence of spontaneous and evoked pain as determined by a sensory examination performed by the investigator.

The primary endpoint was the proportion of patients who tolerated capsaicin 8% patch treatment. Tolerance was defined as the ability to undergo at least 90% (54 min) of the intended 60-min patch application duration. Secondary endpoints included the mean duration of patch application; the mean change in NPRS 'Pain Now' score from baseline; the proportion of patients reporting an increase of ≥ 2 points on the NPRS 'Pain Now' score from baseline to post-baseline time points up to the evening of the treatment visit; the proportion of patients reporting a clinically significant increase in pain ($>33\%$ increase in at least one post-application NPRS 'Pain Now' score) from baseline to any post-baseline time points up to the evening of the treatment visit; the proportion of patients reporting a clinically significant increase in pain ($>33\%$ increase in at least one post-application NPRS 'Average Pain' score) from baseline to subsequent time points in the evening of the treatment visit, days 2 and 3; patient-reported tolerability [assessed using a 10-point numerical scale ranging from 0 (comfortable) to 10 (unbearable)] on the treatment visit (120 min after patch removal) and at the end of study visit; and the proportion of patients using medications for application-associated discomfort and cooling measures on the treatment visit and within 5 days of patch application. Change in size of the painful area was also assessed at the treatment visit and end of study visit.

Safety assessments included the incidence of AEs and serious AEs. Pretreatment-emergent AEs were defined as events that started or worsened in severity from administration of the pretreatment until the start of application of the capsaicin 8% patch. Capsaicin patch-emergent AEs were

defined as AEs that started or worsened in severity during or after application of the capsaicin 8% patch until the end of the study visit. Skin areas on which patches were placed were examined before administration of any pretreatment (baseline: 80–90 min prior to patch application) and 5 and 55 min after patch removal. The area was rated using a dermal assessment score (0- to 7-point scale, where 0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible; minimal oedema or minimal papular response; 3 = erythema and papules; 4 = definite oedema; 5 = erythema, oedema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond test site).

2.4 Statistical analysis

The sample size for this study was based on clinical judgement to adequately assess the tolerability of the capsaicin 8% patch. With a sample size of 60 patients per arm, based on an expected 95% of patients tolerating the treatment, a two-sided 95% confidence interval for a single proportion using the large sample, normal approximation extended 5.5% from the observed result. All data were analysed for the total population, by treatment arm and by visit/time point when applicable, unless otherwise stated. For continuous variables, descriptive statistics included the number of subjects, mean, standard deviation (SD), median, minimum, maximum, 25% percentile and 75% percentile. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of subjects with no missing data (i.e., total values will equal 100%). When needed, 95% binomial confidence intervals were added. All data processing, summarization and analyses were performed using SAS® software (version 8.2 or higher on UNIX; SAS Institute, Cary, NC, USA).

3. Results

A total of 122 patients were enrolled into the study with 61 randomly allocated to each arm. Fol-

lowing pretreatment, all randomly assigned patients were treated with the capsaicin 8% patch. Overall, 121 patients (99.2%) completed the study. A summary of patient demographics and baseline characteristics is presented in Table 1. The two pretreatment arms were generally well balanced, although patients pretreated with lidocaine had longer mean disease duration than those pretreated with tramadol.

All patients were considered pretreatment compliant. The mean duration of exposure to lidocaine pretreatment was 60.7 min, and the mean time between the start of pretreatment and capsaicin 8% patch application was 71.3 and 32.0 min for lidocaine and tramadol administration, respectively. Patients in the lidocaine arm were treated with a mean (SD; range) of 1.24 (0.97; 0.03–4) capsaicin 8% patches, whereas patients in the tramadol arm were treated with a mean (SD; range) of 1.25 (0.90; 0.05–4) patches. The capsaicin 8% patch was most frequently applied to the torso (45.7%), followed by the legs (25.6%), arms (14.7%), hands (10.9%), feet (1.6%), and head and neck (1.6%) (Fig. 2). Some patients received treatment to more than one area. Two patients, one each from the lidocaine and tramadol arms, were treated on the foot, and received capsaicin 8% patch applications for 35 and 60 min, respectively. These patients were considered to be in violation of the protocol.

3.1 Tolerability of capsaicin 8% patch treatment

In total, 121 of 122 subjects (99.2%) tolerated treatment with the capsaicin 8% patch. Similar proportions of patients tolerated capsaicin 8% patch treatment in the two arms (98.4% and 100.0% for lidocaine and tramadol, respectively) with overlapping 95% confidence intervals. One patient in the lidocaine treatment

Table 1 Demographic and baseline characteristics.

Characteristic	Lidocaine (n = 61)	Tramadol (n = 61)	Total (n = 122)
Female, n (%)	37 (60.7)	33 (54.1)	70 (57.4)
White, n (%)	59 (96.7)	60 (98.4)	119 (97.5)
Mean (SD) age, years	57.1 (15.9)	53.6 (16.7)	55.3 (16.4)
Mean (SD) weight, kg	81.5 (18.1)	78.1 (15.8)	79.8 (17.0)
Mean (SD) height, cm	167.4 (9.6)	169.5 (10.4)	168.5 (10.1)
Mean (SD) duration of PNP, years	4.9 (5.8)	3.4 (3.7)	4.2 (4.9)
Type of PNP, n (%)			
Post-herpetic neuralgia	13 (21.3)	15 (24.6)	28 (23.0)
Peripheral nerve injury	48 (78.7)	46 (75.4)	94 (77.0)
Post-surgical	32 (66.7)	37 (80.4)	69 (73.4)
Post-traumatic	16 (33.3)	9 (19.6)	25 (26.6)
Mean (SD) NPRS 'Pain Now' score	6.1 (1.6)	5.8 (1.8)	6.0 (1.7)

NPRS, Numeric Pain Rating Scale, recorded 75 min before patch application; PNP, peripheral neuropathic pain; SD, standard deviation.

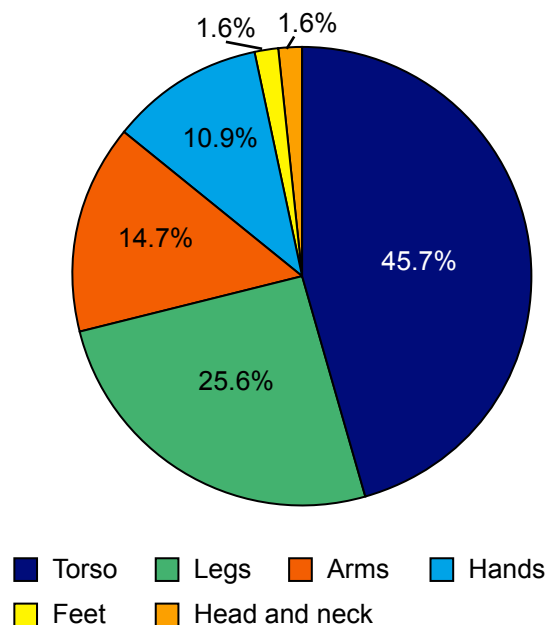


Figure 2 Body areas treated with the capsaicin 8% patch in all patients. Some patients received treatment to more than one area.

arm did not tolerate treatment, discontinuing patch application after 15 min because of erythema and application-site pain. Among patients treated in a per protocol body location ($n = 120$), the mean duration of capsaicin 8% patch application was 60.0 and 60.3 min in the lidocaine and tramadol arms, respectively.

Comparable pain levels, as assessed by the NPRS 'Pain Now' score, were observed at baseline for both treatment arms (Table 1). Mean changes in NPRS 'Pain Now' score from baseline are shown in Fig. 3. Pain relief before patch application was observed in both treatment arms and was greater for the lidocaine

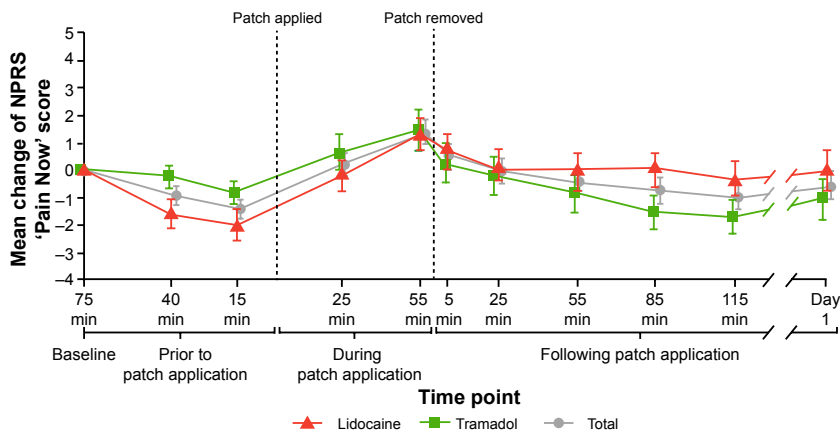


Figure 3 Mean change from baseline in NPRS 'Pain Now' score. Baseline is assessment recorded 75 min before patch application; if missing, the last non-missing value is used instead. The 95% confidence interval of the mean was calculated using normal approximation. Day 1 (evening) is not on scale. NPRS, Numerical Pain Rating Scale.

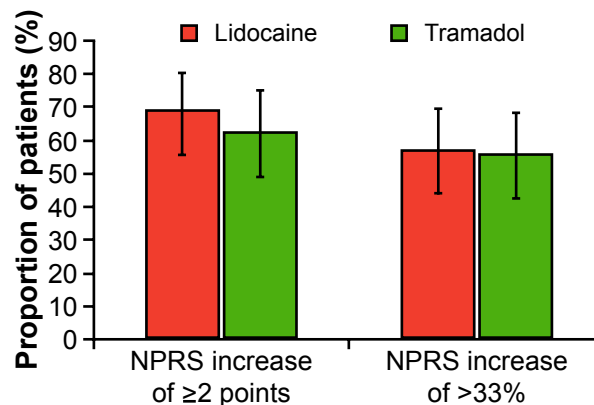


Figure 4 Proportion of patients with an increase in NPRS 'Pain Now' scores from baseline at any time up to the evening of the day of the treatment visit. Error bars indicate 95% confidence intervals. NPRS, Numerical Pain Rating Scale.

arm (administered 70 min before patch application) compared with the tramadol arm (administered 30 min before patch application). Levels of pain increased for both treatment arms up to 55 min after patch application (5 min prior to patch removal), with a mean change from baseline of 1.3 and 1.4 for lidocaine and tramadol, respectively. Following patch removal, patients in the tramadol arm experienced greater pain relief up to the end of the treatment visit versus those in the lidocaine arm. In the evening of the day of the treatment visit, the mean change from baseline for NPRS 'Pain Now' score was 0 and -1 for the lidocaine and tramadol arms, respectively.

A similar proportion of patients receiving lidocaine reported an increase of ≥ 2 points from baseline in the NPRS 'Pain Now' score for at least one time point to the evening of the treatment visit compared with tramadol-treated patients (Fig. 4). The proportion of

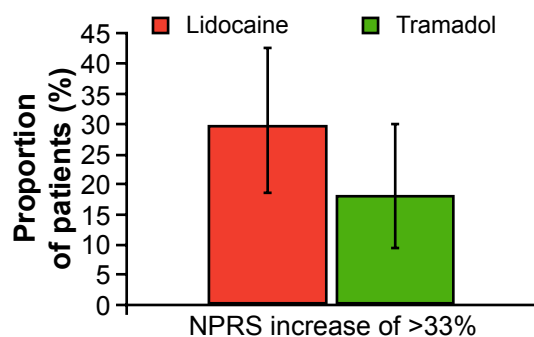


Figure 5 Proportion of patients with >33% increase in NPRS 'Average Pain' scores from baseline at any time up to day 3. Error bars indicate 95% confidence intervals. NPRS, Numerical Pain Rating Scale.

patients reporting an increase of >33% in NPRS 'Pain Now' score from baseline for at least one time point to the evening of the treatment visit was similar between treatment arms (Fig. 4). The proportion of patients reporting an increase of >33% in NPRS 'Average Pain' score from baseline to at least one subsequent time point up to day 3 was similar in the lidocaine and the tramadol arms (Fig. 5).

Decreases in mean patient-rated tolerability scores (indicating improvements in tolerability) were observed in both arms between the treatment visit and end of study visit. At the treatment visit (120 min after patch removal), scores were 5.5 and 4.8 in the lidocaine and tramadol arms, respectively, decreasing to 5.1 and 4.2, respectively, by the end of study visit. There were no major differences in tolerability scores between the lidocaine and tramadol treatment arms when patients were considered by type of NP (data not shown). The difference in mean change from baseline in NPRS 'Pain Now' score between the tramadol and lidocaine treatment arms was slightly numerically larger in patients with PHN compared with those with PNI; however, no formal statistical analysis was performed.

The proportions of patients using cooling measures and medications for application-associated discomfort were comparable between treatment arms (Table 2).

3.2 Safety

Changes in vital signs noted during and shortly after treatment with the capsaicin 8% patch were comparable between the treatment arms.

Pretreatment-emergent AEs were experienced by two subjects (vertigo and nausea), both in the tramadol arm. No treatment was required and both patients fully recovered. The proportion of patients reporting

Table 2 Use of cooling measures and medication for application-associated discomfort.

No. of patients receiving treatment (%) (95% CI)	Lidocaine (n = 61)	Tramadol (n = 61)
Day of treatment visit		
Medication for application-associated discomfort	19 (31.2) (19.9–44.3)	16 (26.2) (15.8–39.1)
Cooling measures	48 (78.7) (66.3–88.1)	42 (68.9) (55.7–80.1)
Within 5 days following patch application		
Medication for application-associated discomfort	21 (34.4) (22.7–47.7)	19 (31.2) (19.9–44.3)
Cooling measures	48 (78.7) (66.3–88.1)	43 (70.5) (57.4–81.5)

CI, confidence interval.

capsaicin patch-emergent AEs was similar between arms (Table 3). Overall, 86.9% and 78.7% of patients in the lidocaine and tramadol arms, respectively, reported capsaicin patch-emergent AEs possibly or probably related to capsaicin 8% patch treatment. The majority of capsaicin patch-emergent AEs were mild or moderate in intensity. Two patients experienced capsaicin patch-emergent serious AEs; one patient in the lidocaine arm experienced hypertension and one patient in the tramadol arm was treated off label with a 60-min application of the capsaicin 8% patch to the foot. No deaths were reported during the study.

Overall, the dermal assessment score was comparable for the two arms at every time point assessed. At 90–80 min before patch application, a dermal assessment score of 0 (no evidence of irritation) was reported by the majority of patients [115 (94.3%)], while a score of 1 (minimal erythema, barely perceptible) was reported by seven patients (5.7%). At 5 and 55 min after patch removal, more patients reported higher dermal assessment scores. At 5 min, the scores reported were 0 in eight patients (6.6%), 1 in 33 patients (27.0%) and 2 (definite erythema, readily visible; minimal oedema or minimal papular response) in 75 patients (61.5%).

Table 3 Capsaicin patch-emergent adverse events occurring in ≥5% of patients.

Adverse event, n (%)	Lidocaine (n = 61)	Tramadol (n = 61)
Any adverse event	54 (88.5)	49 (80.3)
Application-site pain	37 (60.7)	34 (55.7)
Erythema	20 (32.8)	19 (31.1)
Application-site erythema	13 (21.3)	10 (16.4)
Pain	8 (13.1)	5 (8.2)
Nausea	4 (6.6)	3 (4.9)

3.3 Change in size of painful area

At screening the mean (SD) size of the painful area was similar in the lidocaine and tramadol arms: 257.0 (215.7) versus 251.3 (194.9) cm². Between the treatment visit and end of study visit, greater reductions in the mean (SD) size of the painful area were observed in the tramadol versus the lidocaine arms: 38.4% [treatment visit = 267.5 (188.0) compared with end of study = 164.8 (193.6) cm²] versus 21.6% [treatment visit = 276.4 (222.5) compared with end of study = 216.6 (215.8) cm²].

4. Discussion

Treatment with the capsaicin 8% patch is effective in reducing symptoms of PNP in non-diabetic adults (Backonja et al., 2008; Simpson et al., 2008; Backonja et al., 2010; Irving et al., 2011). The application of the patch, however, may result in treatment-related discomfort. Consequently, to enable patients to tolerate the procedure, a 60-min pretreatment with a local anaesthetic cream prior to application of the capsaicin 8% patch was originally recommended (McCormack, 2010). However, pretreatment itself can aggravate allodynia and lengthens the treatment procedure.

The LIFT study was designed to evaluate the tolerability and safety of treatment with the capsaicin 8% patch in patients with PNP following pretreatment with either topical lidocaine or oral tramadol. The study met its primary tolerability endpoint, with similar proportions of patients in each arm tolerating treatment with the capsaicin 8% patch. Of the 122 patients enrolled, only one did not tolerate capsaicin 8% patch treatment following pretreatment with lidocaine.

Overall, secondary tolerability endpoint outcomes were also comparable between treatment arms. During capsaicin 8% patch application, pain levels increased to the same extent in patients in both treatment arms, peaking at 55 min after application (5 min before patch removal). Following removal of the capsaicin 8% patch, patients pretreated with tramadol experienced slightly greater pain relief, as shown by a difference in NPRS 'Pain Now' scores in the evening of the day of the treatment visit. In patients who had received pretreatment with tramadol, an NPRS 'Pain Now' score of approximately 1 point below baseline was observed, whereas no reduction from baseline was observed at this time point in those pretreated with lidocaine. Relief from NP was observed in patients treated with the capsaicin 8% patch after lidocaine and tramadol pretreatment; however, this relief was initially more pronounced in the lidocaine

arm (up to 55 min after patch application). This is possibly related to the difference in onset of a topical anaesthetic effect versus a systemic analgesic effect. Moreover, lidocaine was administered 70 min before the capsaicin 8% patch application, whereas tramadol was administered 30 min beforehand.

The proportions of patients reporting an increase of ≥ 2 points or $>33\%$ on the NPRS 'Pain Now' score from baseline to time points up to the evening of the day of the treatment visit, and the proportions of patients reporting an increase of $>33\%$ in NPRS 'Average Pain' score from baseline to day 3 were comparable between treatment arms. In accordance with the reported durations of response of lidocaine and tramadol, a slightly higher proportion of patients pretreated with lidocaine required medication for application-associated discomfort and cooling measures compared with patients receiving tramadol. While outside the scope of this study, it would be interesting to investigate whether tolerability to the capsaicin 8% patch correlates with any patient baseline characteristics or the number of patches applied. It may also be relevant to see whether any such correlations are affected by the method of pretreatment.

Consistent with the results from previous capsaicin 8% patch studies (Backonja et al., 2008; Simpson et al., 2008; Simpson et al., 2010; Vanhove et al., 2010; Irving et al., 2011), treatment-emergent AEs were experienced by the majority of patients, with incidence rates comparable between the arms. The majority of capsaicin patch-emergent AEs were mild or moderate in intensity. One serious AE occurred in each treatment arm, and no deaths were reported during the study.

A possible limitation of the LIFT study is the lack of double blinding. However, as the aim of the study was not to assess capsaicin 8% patch efficacy, but to determine whether the two pretreatments were similarly efficacious in enabling tolerability, double blinding was not considered to be necessary. Further, use of a double-blind, double-dummy design involving administration of a placebo cream or tablet would add a confounder to the pretreatment experience of the patient. As both treatment arms received some form of pretreatment medication, patient bias was expected to be minimal. It is important to note that the investigators who assessed AEs, including treatment-related pain, and decided whether to apply medication for application-associated discomfort and cooling measures were blinded to pretreatment received.

Overall, these results indicate that capsaicin 8% patch treatment for PNP is equally well tolerated if patients are pretreated with either topical lidocaine

4% or oral tramadol 50 mg. Indeed, based on data from this study, the European Medicines Agency has approved a type II variation stating that the treatment area may be pretreated with a topical anaesthetic or the patient might be administered an oral analgesic prior to application of the capsaicin 8% patch to reduce potential application-related discomfort (Astellas Pharma Europe Ltd, SPC update 2013).

Author contributions

T.S.J., K.H., J.F. and P.V. conducted the study. S.M. managed the study. T.S.J., E.E., T.S. and S.M. analysed and interpreted the data. All authors discussed the results, participated in writing the manuscript and approved the final version.

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