Tolerability of Treatment with NGX-4010 (Qutenza®) in Conjunction with Pre-Patch Topical Application of a Lidocaine 2.5%/Prilocaine 2.5% Anesthetic Cream

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BACKGROUND

- NGX-4010 (Qutenza®) is a high-concentration capsaicin dermal patch (capsaicin, 8%) that has recently been approved by the FDA for the management of neuropathic pain associated with postherpetic neuralgia (PHN).
- Capsaicin activates transient receptor potential vanilloid 1 receptor (TRPV1) ligand-gated cation channels on nociceptive nerve fibers, causing depolarization, action potential initiation, and the transmission of pain signals to the spinal cord. Following continued capsaicin exposure, TRPV1-containing sensory axons become defunctionalized, inhibiting pain transmission [1, 2].
- Before NGX-4010 treatment, a topical anesthetic is applied to reduce discomfort [3].
- This study evaluated the tolerability of a 60-minute treatment with NGX-4010 following a 60-minute pretreatment with lidocaine (2.5%)/prilocaine (2.5%) cream. Previous studies used a 4% lidocaine (LMX4®/ELA-Max®) cream.
- Lidocaine (2.5%)/prilocaine (2.5%) eutectic mixtures (e.g. EMLA®) are effective, commonly used topical anesthetics that are FDA approved to provide local analgesia on intact skin. There is strong scientific evidence for the comparability of activity of LMX4/ELA-Max and EMLA [4-8].

MATERIALS AND METHODS

- A total of 24 patients with PHN were enrolled and treated in this open-label, multicenter, 1-week study.
- Patients had their painful area(s) pre-treated with a thick layer of lidocaine (2.5%)/prilocaine (2.5%) cream (1–2 g/10 cm^2) for 60 minutes prior to study patch application to offset treatment-related discomfort or pain resulting from capsaicin.
- A protective covering (Tegaderm™ Film, 3M Health Care, Neuss, Germany) was placed over the treatment area to keep the cream in place and to prevent it from drying out.
- Following the local anesthetic pre-treatment and removal, NGX-4010 was applied to the painful area(s) for 60 minutes.
- For relief of treatment-related discomfort, subjects were permitted to use an approved rapid-onset, opioid-based oral pain medication as needed while in the clinic.
- Additional opioid-based oral pain medication, such as hydrocodone bitartrate/acetaminophen, 5/500 mg, was permitted as needed for up to 5 days following the treatment procedure.
- Safety and tolerability were assessed by adverse events (AEs), vital signs, physical examinations, "Pain Now" Numeric Pain Rating Scale (NPRS) scores, dermal assessments (0- to 7-point scoring system) and medication use for treatment-related discomfort.
- The primary endpoint was the duration of patch application.

RESULTS

DISPOSITION, DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 25 patients were enrolled into the study and 24 received NGX-4010 treatment. One patient never received treatment with NGX-4010 due to an increase in blood pressure that occurred during treatment with the topical anesthetic.
- Patient characteristics are shown in **Table 1**.

Table 1: Demographics and Baseline Characteristics

	NGX-4010 (n = 24)
Age (years), Mean ± SD	66.9 ± 11.8
Male, n (%)	13 (54%)
Ethnicity, n (%)	
Not Hispanic or Latino	24 (100%)
Race	
White	23 (96%)
African American	1 (4%)
Duration of PHN Pain (years), Mean ± SD	5.5 ± 4.3
Baseline Pain Level, Mean ± SD	5.5 ± 1.7

SD = standard deviation

SAFETY AND TOLERABILTY

- No patients had early patch removal (defined as removal at < 54 minutes).
- The mean application duration was 60.2 minutes.

Table 2: "Pain Now" NPRS Score on the Day of Treatment

Change from before topical anesthetic application	Lidocaine/Prilocaine (n=24)
Before topical anesthetic application, mean (SD)	4.71 (1.73)
15 min. after topical anesthetic application, mean (SD)	-1.04 (1.46)
30 min. after topical anesthetic application, mean (SD)	-2.04 (1.85)
55 min. after topical anesthetic application, mean (SD)	-2.79 (2.26)
25 min. after patch application, mean (SD)	1.00 (3.22)
55 min. after patch application, mean (SD)	3.00 (2.86)
Within 5 min. after patch removal, mean (SD)	1.38 (2.81)
25 min. after patch removal, mean (SD)	1.46 (3.28)
55 min. after patch removal, mean (SD)	1.38 (3.17)
85 min. after patch removal, mean (SD)	0.71 (3.28)
Evening of the treatment day, mean (SD)	0.71 (2.63)

SD = standard deviation

- On the treatment day, mean NPRS scores decreased after anesthetic application and increased during patch application (**Table 2**).
- The largest mean increase in NPRS score from the pre-anesthetic time point was 3.00 at 55 minutes after patch application.
- Within 5 minutes after patch removal, pain scores declined and at 85 minutes returned to close to pre-anesthetic treatment values (+0.71) after patch removal.
- At the evening of the day of treatment, NPRS scores remained close to pre- anesthetic treatment values (+0.71).
- On day 0, 83% of subjects reported an increase from pre- anesthetic treatment values in mean NPRS score of 2 or more.
- AEs were mostly mild or moderate with application site pain and erythema being the most common (**Table 3**).

Table 3: Treatment Emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term, n (%)	NGX-4010 (n = 24)
Number of Subjects Reporting One or More Treatment-Emergent AEs	24 (100%)
General Disorders and Administration Site Conditions	24 (100%)
Application Site Edema	4 (17%)
Application Site Erythema	24 (100%)
Application Site Pain	22 (92%)
Application Site Pruritus	1 (4%)
Pain	1 (4%)
Investigations	1 (4%)
Blood Pressure Increased	1 (4%)
Musculoskeletal and Connective Tissue Disorders	2 (8%)
Back Pain	2 (8%)
Muscular weakness	1 (4%)
Reproductive System and Breast Disorders	1 (4%)
Breast mass	1 (4%)
Skin and Subcutaneous Tissue Disorders	3 (13%)
Erythema	1 (4%)
Rash papular	2 (8%)

Note: Counts indicate the numbers of subjects reporting one or more AEs that mapped to the MedDRA (Version 10.1) system organ class. At each level of summarization, subjects were only counted once, under the greatest severity.

- About half the patients used oral analgesics for treatment-related discomfort on the treatment day.
- Immediately prior to topical anesthetic application on the treatment day and at termination (day 7), all subjects had a dermal assessment score of 0 (no evidence of irritation).
- On the treatment day, 88% of subjects reported a dermal assessment score of 2 within 5 minutes after patch removal (definite erythema, readily visible, minimal edema or minimal papular response).
- Dermal assessment scores decreased over time and at 85 minutes after patch removal the proportion of subjects reporting dermal assessment scores of 2 was 63%.
- No subjects reported a dermal assessment score above 2 at any time point on the day of treatment.

CONCLUSIONS

- Application of NGX-4010 following lidocaine (2.5%)/prilocaine (2.5%) was generally well tolerated.
- Treatment-related pain was similar to that seen in other studies with NGX-4010 following 4% lidocaine [9-11], adequately managed with cooling measures or short acting opioids and did not result in early patch removal.

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