CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-395

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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Addendum to Clinical Review: Review of Clinical Study Report C123, "An Open-Label Study of the Use of Topical Lidocaine (2.5%)/Prilocaine (2.5%) Cream as Pre-Treatment for NGX-4010 in subjects with Postherpetic Neuralgia

NDA #	**:** 22-395
Drug Name (generic)	**:** Qutenza (Capsaicin Patch 8%)
Sponsor	**:** NeurogesX
Indication	**:** Dermal patch for the prolonged reduction of neuropathic pain associated with post herpetic neuralgia
Type of Submission	**:** NDA amendment
Date of Submission	**:** 30th July 2009
Date Received	**:** 30th July 2009
Date of Review	**:** 1st October, 2009
Reviewer	**:** Neville A Gibbs, M.D, MPH
Project Manager	**:** Tanya Clayton

Background

NDA 22-395, capsaicin patch 8% (Qutenza) for the indication of the prolonged reduction of neuropathic pain, was submitted on October 13, 2008.

At the time of filing, it was determined that the applicant used an unapproved local anesthetic prior in all of the clinical trials. The anesthetic was used to improve the tolerability of the study drug. This issue was conveyed to the sponsor in a teleconference with the Division on May 6, 2009.

On May 19, 2009, the sponsor submitted a draft protocol for clinical study C123- "An Open-Label Study of the Use of Topical Lidocaine (2.5%/Prilocaine (2.5%) Cream as Pre-Treatment for NGX-4010 in subjects with Postherpetic Neuralgia (PHN). The Agency did not object to the study design.

On July 30, 2009, NeurogesX submitted the results of this study. This addendum includes a review of the protocol and the results of the study. NeurogesX successfully demonstrated that patients were able to wear the capsaicin patch for the recommended 60 minutes duration following pretreatment with an approved topical local anesthetic agent.

TITLE OF STUDY: AN OPEN-LABEL STUDY OF THE USE OF TOPICAL LIDOCAINE (2.5%)/PRILOCAINE (2.5%) CREAM AS PRE-TREATMENT FOR NGX-4010 IN SUBJECTS WITH POSTHERPETIC NEURALGIA (PHN)

Primary Objective: The primary objective of this study was to have been to evaluate the tolerability of NGX-4010 when using lidocaine (2.5%)/prilocaine (2.5%) cream as a pre-treatment, in patients with PHN.

Study Design:
This study was designed to have been an open-label multi-center evaluation of the tolerability of treatment with NGX-4010 in conjunction with pre-patch topical application of a lidocaine 2.5%/prilocaine 2.5% anesthetic cream.

Eligible subjects were to have been diagnosed with PHN with a level of pain at an intensity level deemed appropriate for open-label treatment with NGX-4010, as judged by the Investigator. Painful areas of up to a maximum of 1000 cm^2 were to have been pre-treated with lidocaine (2.5%)/prilocaine (2.5%) cream for 60 minutes followed by a single, 60-minute application of NGX-4010. Subjects may have been be on chronic pain medication regimens, but currently were not to have been using any topical pain medications on the affected areas, such as non-steroidal anti-inflammatory drugs, menthol, and methyl salicylate, local anesthetics including Lidoderm® (lidocaine patch 5%), steroids or capsaicin.

Subjects were to have been seen for study-required evaluations at the Screening Visit, Day 0, and Day 7 (Termination Visit), a total of three visits.

A Screening Visit was to have been performed, usually on Day -7 (± 2 days). Baseline Numeric Pain Rating Scale (NPRS) scores were to have been recorded by subjects in a take-home diary each evening beginning on the day of the Screening Visit (usually on Day -7) through the evening before the Study Patch Application Visit (Day -1). Scores were to have been based on an 11-point scale (0 = no pain, 10 = worst possible pain) to assess average pain in the past 24 hours.

Inclusion Criteria:
To be included in the clinical trial, subjects must have met all of the following inclusion criteria:

1. Between 18 and 90 years of age, inclusive.
2. Be in good health.
3. Prior diagnosis of PHN with pain persisting at least 3 months following shingles vesicle crusting.
4. Pain due to PHN that, in the opinion of the investigator, was to have been of an appropriate severity for treatment with NGX-4010. The subject should have completed at least 3 NPRS scores.
5. Intact, unbroken skin over the painful area(s) to be treated.
6. Female subjects with child-bearing potential must have a negative serum beta hCG pregnancy test, to be performed at the Screening Visit.

7. All subjects must be willing to use effective methods of birth control and/or refrain from participating in a conception process during the study and for 30 days following study termination.
8. Be willing and able to comply with protocol requirements for the duration of study participation. (Such requirements include, but are not limited to: attending all study visits, refraining from elective surgery or extensive travel during study participation.)
9. Subjects must sign an informed consent form for this study approved by the IRB.

Exclusion Criteria:
Subjects were to have been excluded from the clinical trial if they met any of the following criteria:

1. Receipt of NGX-4010 open label or blinded study patches within 12 weeks of the Study Patch Application Visit (Day 0).
2. Concomitant opioid medication, unless orally or transdermally administered and not exceeding a total daily dose of morphine 60 mg/day, or equivalent. Parenteral opioid use was to have been excluded, regardless of dose.
3. Unavailability of an effective pain medication strategy for the subject, such as unwillingness to use opioid analgesics during study treatment, or high tolerance to opioids precluding the ability to relieve treatment-associated discomfort with oxycodone or other analgesic, as judged by the Investigator.
4. Active substance abuse or history of chronic substance abuse within the past year, or prior chronic substance abuse (including alcoholism) judged likely to recur during the study period by the investigator.
5. Recent use (within 7 days preceding the Study Patch Application Visit [Day 0]) of any topically applied pain medication, such as non-steroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics (including Lidoderm®), steroids or capsaicin products on the painful areas.
6. Current or use within the past 30 days of any investigational agent
7. Patients treated with class I (such as tocainide and mexiletine) or III anti-arrhythmic drugs.
8. Significant pain of an etiology other than PHN, for example, compression-related neuropathies (e.g., spinal stenosis), fibromyalgia or arthritis. Subjects must not have significant ongoing pain from other cause(s) that may interfere with judging PHN related pain.
9. Neuropathic pain areas located only on the face, above the hairline of the scalp, and/or in proximity to mucous membranes.
10. Patients with congenital or idiopathic methemoglobinemia
11. Patients with glucose-6-phosphate dehydrogenase deficiencies
12. Uncontrolled (systolic blood pressure $\geq$ 175 mmHg or diastolic blood pressure $\geq$105 mmHg) or unstable hypertension.
13. Clinically significant cardiovascular disease defined as cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, current arrhythmia, coronary artery disease, any heart surgery including coronary

artery bypass graft surgery or percutaneous coronary angioplasty/stent placement, or valvular heart disease within the past 6 months.
14. Clinically significant abnormal ECG at screening.
15. Clinically significant abnormal labs at screening.
16. Significant ongoing or untreated abnormalities in cardiac, renal, hepatic, or pulmonary function.
17. Active malignancy or past history of malignancy during the past 5 years (history of squamous cell carcinoma or basal cell carcinoma of the skin are exempted from the exclusion criteria except if they occurred in the area of treatment).
18. Any implanted medical device (spinal cord stimulator, intrathecal pump or peripheral nerve stimulator) for the treatment of neuropathic pain.
19. Hypersensitivity to capsaicin (i.e., chili peppers or Over-the-Counter (OTC) capsaicin products), or any components of the capsaicin patch, Cleansing Gel, oxycodone, hydrocodone, or adhesives.
20. Patients with a known history of sensitivity to local anesthetics (including lidocaine and prilocaine) of the amide type or to any other component of the product.
21. Evidence of cognitive impairment including dementia that may interfere with subject's ability to complete daily pain diaries requiring recall of average pain level in the past 24 hours.

Treatment:
This study was to have been an open-label study where all study subjects received lidocaine (2.5%)/prilocaine (2.5%) cream for 60 minutes followed by a single, 60-minute application of NGX-4010.

Permitted Concomitant Medication
Subjects should not have used any *topically applied pain medications*, such as non-steroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics including Lidoderm® (lidocaine patch 5%), steroids or capsaicin products on or near the affected areas where study drug will be applied within 7 days preceding the Study Patch Application Visit (Day 0). Concomitant use of any topical pain medication on or near the affected areas where the study drug is applied was not to have been permitted during study participation.

Rescue medication:
An immediate-release opioid-based oral pain medication, such as oxycodone hydrochloride oral solution 1 mg/mL concentration was to have been be administered in the clinic during study patch application visits, as needed, to relieve treatment-associated discomfort or pain in the area treated. An adequate quantity of this medication was to have been obtained for each subject prior to the beginning of investigational treatment so that it could be readily administered, as needed, for pain relief during and following the treatment procedure while the subject was in the clinic. An initial dose of oxycodone (e.g., 5–10 mg) was to have been administered at the onset of treatment-associated discomfort, followed by repeat doses, as needed, according to the Investigator's clinical judgment. The total dosage of opioid-based medication administered, and the time of the

first and the last doses, was to have been recorded in the subject's source documentation and on the appropriate CRF (e.g., Pain Medications Log CRF).
The Investigator was to have prescribed a short-term regimen of an opioid-based pain medication in tablet form, such as hydrocodone/acetaminophen 5 mg/500 mg to be used as needed following completion of the study patch application visit up to and through Day 5 for the relief of treatment-associated discomfort or pain in the area treated.

Outcome Measures:

Tolerability Variables

- Duration of patch application
- Subjects completing at least 90% of the intended patch application duration
- NPRS scores on the day of treatment
- Pain medication use for treatment-related discomfort on the day of treatment

Safety Variables

- Adverse events (AEs), serious adverse events (SAEs) and treatment-emergent adverse events
- The proportion of subjects who prematurely terminate from the study due to an AE
- Vital signs on day of screening, on the day of treatment and at termination
- Dermal assessment ratings on day of screening, on the day of treatment and at termination
- Concomitant medications

Primary Endpoint:

The primary endpoint was to have been the mean duration of patch application.
A two-sided 95% confidence interval was to have been constructed around the estimated mean.

Secondary Endpoints:

Secondary endpoints were to have included the following:

1. Mean change in NPRS scores from pre-treatment values to subsequent time points on the day of treatment.
2. Proportion of subjects using a immediate-release opioid-based analgesic medication for treatment-associated pain during and following patch application on the day of treatment.
3. The proportion of subjects completing at least 90% of the intended patch application duration.

Safety:

Safety and tolerability assessments included:
(1) AE monitoring
(2) Evaluation of vital signs
(3) Evaluation of physical examination and medical history
(4) Dermal assessments
(5) Medication for treatment-related discomfort use

(6) Concomitant pain medication use.

Study Visit Schedule (Table 1):

Study Procedures	Screening Visit (Day −7 ± 2 days)	Study Patch Application Visit[b] (Day 0)	Unscheduled Visit	Termination or Early Term. Visit (Day 7 ± 2 days)
Informed Consent	X			
Medical History	X	X		
Concomitant Medications	X	X	X	X
Physical Exam	X			X
Vital Signs	X	X[d]	X	X
Clinical Laboratory Tests (Hematology, Chemistry)	X			
Pregnancy Test	X[a]			
12-lead Electrocardiogram	X			
Dermal Assessment	X	X[e]		X
Estimate Treatment Area	X			
Identify Painful Area(s)		X		
Average pain for past 24 hours Pain Ratings (NPRS)	X			
Pain Now NPRS Score	X	X[d]		
Topical Anesthetic/Patch Application		X		
Provide Pain Medication		X		
Adverse Events		X	X	X
Telephone Contact		X[c]		
Dispense and/or Collect paper diaries and review NPRS scores	X[g]	X[f,g]		X[f]
Dispense Pain Medication for Treatment-related Discomfort Diary		X		
Collect Pain Medication for Treatment-related Discomfort Diary			X	X

a) At study entry, serum beta hCG pregnancy test (if applicable) drawn at Screening Visit. To be performed through the study-specified central laboratory or in accordance with the local laboratory.

b) See Protocol Section 6.4 for details of Study Patch Application and related procedures. c) Within 72 hours after Study Patch Application

d) Vital Signs and NPRS Pain Now scores are assessed on Day 0 at the following timepoints: 5 minutes before topical anesthetic application, 15 minutes after topical anesthetic application (NPRS only), 30 minutes after topical anesthetic application 55 minutes after topical anesthetic application, 25 minutes after patch application, 5 minutes before patch removal, 5 minutes post patch removal, 25 minutes post patch removal, 55 minutes post patch removal, and 1 hour and 25 minutes post-patch removal.

e) Dermal Assessments are assessed on Day 0 at the following timepoints: Prior to any procedures, 5 minutes before topical anesthetic application, 5 minutes after topical anesthetic removal, 5 minutes post patch removal, 25 minutes post patch removal, 55 minutes post patch removal, and 1 hour and 25 minutes post-patch removal.

f) NPRS Pain Now Diary to be dispensed to subject before leaving the Day 0 visit for recording of "pain now" on the evening of Day 0 and to be collected at the termination visit.

g) Take-Home NPRS "Average pain for past 24 hours" diary to be dispensed at Screening Visit and collected at Day 0 Visit.

Statistical Analysis Plan and Definition of Analyzed Study Populations:
The population included all subjects who received study patch application. All tolerability and safety analyses were conducted on this population.

Demographics and other baseline characteristics were descriptively summarized using frequency distributions (n, %) for categorical variables and standard statistical summaries for continuous variables (n, mean, standard deviation, median, minimum, maximum).

A two-sided 95% confidence interval was constructed around the estimated mean duration of patch application. Descriptive summaries of "Pain now" NPRS scores were generated for each assessment time point throughout the study.

Analysis of Primary Tolerability Endpoint
The primary endpoint was to have been the mean duration of patch application duration. A two-sided 95% confidence interval will be constructed around the estimated mean. All subjects who receive study patch application will be included in the analysis.

Analysis of Secondary Tolerability Endpoint NPRS scores
Descriptive summaries of "Pain now" NPRS scores will be generated for each assessment time point throughout the study. NPRS scores on the day of treatment and changes in NPRS scores from the pre-topical anesthetic time point will be summarized.

Use of Pain Medication for Treatment-Related Discomfort
The number and proportion of subjects requiring pain medication for treatment-related discomfort on the day of treatment will be summarized.

Proportion of subjects completing at least 90% of the intended patch application duration
An exact two-sided 95% confidence interval will be constructed around the estimated proportion. All subjects who receive study patch application were to have been included in the analysis.

NPRS scores on the day of treatment and changes in NPRS scores from the pre-topical anesthetic time point were summarized.

The number and proportion of subjects requiring pain medication for treatment-related discomfort on the day of treatment as well as the daily dose were summarized.

An exact two-sided 95% confidence interval was constructed around the estimated proportion of subjects completing at least 90% of the patch application.

Protocol Amendments:
There were no protocol amendments for this safety and tolerability study.

Protocol deviation and violations:
There were four minor protocol deviation events that occurred in three subjects. Three subjects received topical anesthetic for more than 110% of the assigned duration (or more than 66 minutes). Additionally, one of these three subjects also used medication (Percocet 5/325 on Day 6, (beyond Day 5) for treatment related discomfort.
These minor deviations do not affect the final result or the conclusion from the study.

RESULTS
A total of 25 subjects were enrolled into the study and 24 received study drug treatment. One subject (# 038-6003) never received treatment with NGX-4010 due to an increase in blood pressure that occurred during treatment with the topical anesthetic.

DISPOSITION

Eighty eight percent of subjects (88%; 22 subjects) completed the 1-week study. A total of 3 subjects (12%) withdrew from the study prematurely. This included the 1 subject who was enrolled but did not receive NGX-4010 treatment. Reasons for premature termination, in order of overall frequency, included “other” (2 subjects: scheduling conflict between subject and site and unexpected surgery of husband) and “adverse events” (1 subject, increased blood pressure).

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS (SAFETY POPULATION)

The average age of subjects enrolled in the study was approximately 67 years. Most subjects were white (96%) and all were non-Hispanic. Slightly more male subjects were treated (54%). The average duration of PHN pain was 5.5 years and the average pain level at screening was 4.3.

TABLE 2: DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF SAFETY POPULATION

Race	
White	23 (96%)
African American	1 (4%)
Other	0
Height (cm)	
Mean ± SD	170.6 ± 10.3
Weight (kg)	
Mean ± SD	84.0 ± 17.9
Duration of PHN Pain (years)	
Mean ± SD	5.5 ± 4.3
Min, Max	1.0, 19.3
Pain Level at Screening	
Mean ± SD	4.3 ± 2.2
Baseline Pain Level	
Mean ± SD	5.5 ± 1.7

	NGX-4010 (n = 24)
Age (years)	
Mean ± SD	66.9 ± 11.8
Min, Max	39, 83
Age Group [years; n (%)]	
≤ 50	3 (13%)
51-60	3 (13%)
61-70	9 (38%)
71-80	5 (21%)
> 80	4 (17%)
Gender, n (%)	
Male	13 (54%)
Female	11 (46%)
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	24 (100%)

Source: Table 14.1.3 - Study report body- p41/73

RESULTS

PRIMARY
The mean duration of patch application, (the primary endpoint) was 60.2 minutes and all subjects completed at least 90% of the intended patch application duration.

Four subjects received NGX-4010 treatment for slightly more than 60 minutes:
- 3 subjects for 61 minutes and one subject for 63 minutes.
- One subject had the patch removed at 59 minutes.
- All other subjects had application durations of 60 minutes.

(See Table 3 noted below).

SECONDARY

Secondary endpoints included the following:
1. Mean change in NPRS scores from pre-treatment values to subsequent time points on the day of treatment. On the treatment day, mean NPRS scores decreased after topical anesthetic application and increased during patch application with the largest mean increase in NPRS score from the pre-anesthetic time point of 3.0 at 55 minutes after patch application and returning to close to pre-anesthetic treatment values (+ 0.7) at 85 minutes after patch removal.

2. Proportion of subjects using a immediate-release opioid-based analgesic medication for treatment-associated pain during and following patch application on the day of treatment.
One-half of subjects (50%) used medication for treatment-related discomfort on the day of treatment and 54% of subjects used medication for treatment-related discomfort on at least one day during Days 0-7.

3. The proportion of subjects completing at least 90% of the intended patch application duration. All subjects completed at least 90% of the intended patch application duration.

(See Table 3 noted below)

TABLE 3: SUMMARY OF TREATMENT ADMINISTRATION

		NGX-4010
Surface Area Treated (cm^2)	N	24
	Mean	407.3
	Standard Deviation	300.7
	Standard Error	61.4
	Median	395
	Min, Max	59, 1000
Duration (min) of Topical Anesthetic	N	24
	Mean	60.9
	Standard Deviation	3.0
	Standard Error	0.6
	Median	60
	Min, Max	56, 72
Duration (min) of Patch Application	N	24
	Mean	60.2
	Standard Deviation	0.7
	Standard Error	0.1
	95% Confidence Interval	59.90, 60.51
	Median	60
	Min, Max	59, 63
Duration (<54 or >=54 min) of Patch Application	N	24
	>= 54 minutes	24 (100.0%)
	95% Exact Confidence Interval	85.75, 100.0

Source: p 58 of 73 Study C123

Treatment Emergent Adverse Events

All subjects experienced treatment emergent AEs which were primarily due to capsaicin-related application site events. Most of the AEs were mild or moderate in severity. Only three subjects (4.2%) reported severe AEs, all severe application site pain.

(See Table 4 noted below).

No SAE's or deaths were reported.

Table 4: Summary of Treatment Emergent Adverse Events by MedDRA Term

System Organ Class	Preferred Term	Mild	Moderate	Severe	Total
Number of Subjects Receiving Study Drug					24 (100.0%)
Number of Subjects Reporting One or More Events		6 (25.0%)	14 (58.3%)	4 (16.7%)	24 (100.0%)
General disorders and administration site conditions		6 (25.0%)	15 (62.5%)	3 (12.5%)	24 (100.0%)
	Application site erythema	9 (37.5%)	15 (62.5%)	0 (0.0%)	24 (100.0%)
	Application site oedema	3 (12.5%)	1 (4.2%)	0 (0.0%)	4 (16.7%)
	Application site pain	4 (16.7%)	15 (62.5%)	3 (12.5%)	22 (91.7%)
	Application site pruritus	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
	Pain	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Investigations		1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
	Blood pressure increased	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Musculoskeletal and connective tissue disorders		1 (4.2%)	0 (0.0%)	1 (4.2%)	2 (8.3%)
	Back pain	1 (4.2%)	0 (0.0%)	1 (4.2%)	2 (8.3%)
	Muscular weakness	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Reproductive system and breast disorders		0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.2%)
	Breast mass	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.2%)
Skin and subcutaneous tissue disorders		3 (12.5%)	0 (0.0%)	0 (0.0%)	3 (12.5%)
	Erythema	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
	Rash papular	2 (8.3%)	0 (0.0%)	0 (0.0%)	2 (8.3%)

NOTE: Adverse events with onset date on or after treatment administration date are included.
NOTE: Counts indicate the numbers of subjects reporting one or more adverse events that map to the MedDRA 10.1 System Organ Class. At each level of summarization (System Organ Class or Event), subjects are only counted once, under the greatest severity.
ae1.sas

Source: p 61/73 C123 Study Report

SUMMARY OF VITAL SIGNS ON THE DAY OF TREATMENT

Changes in blood pressure associated with treatment-related changes in pain were observed on the day of treatment. Mean systolic and diastolic blood pressures temporarily increased after patch application. See Table 5 and 6. Mean increases in blood pressure at all timepoints were <11.9 mmHg for systolic (Table 5) and <4.2 mmHg for diastolic blood pressures (Table 6).

Mean blood pressure increases reached a maximum around 55 minutes after patch application and diminished in magnitude during the period after patch removal.

An AE related to abnormal blood pressure (blood pressure increased) was reported in one subject on the day of treatment that resolved the same day. The event was considered mild and probably related to treatment.

TABLE 5: CHANGES IN SYSTOLIC BLOOD PRESSURE

	N	Mean	SD	95% CI	Minimum	Median	Maximum
Before Topical Anesthetic Application	24	127.3	14.4	121.2, 133.4	98	127	163
30 min After Topical Anesthetic Application	24	127.9	17.7	120.4, 135.3	100	127	161
55 min After Topical Anesthetic Application	24	128.5	17.6	121.1, 136.0	90	128	172
25 min After Patch Application	24	132.1	18.0	124.5, 139.7	90	130	180
55 min After Patch Application	24	139.1	20.5	130.5, 147.8	102	133	184
Within 5 min After Patch Removal	24	138.5	21.5	129.4, 147.5	100	132	179
25 min After Patch Removal	24	137.0	20.7	128.2, 145.8	90	132	175
55 min After Patch Removal	24	131.0	19.6	122.7, 139.2	90	130	170
1 hr 25 min After Patch Removal	24	132.5	18.9	124.5, 140.5	104	130	168
Change from Before Topical Anesthetic Application							
Before Topical Anesthetic Application	24	0.0	0.0	0.0, 0.0	0	0	0
30 min After Topical Anesthetic Application	24	0.5	12.1	-4.6, 5.6	-21	1	40
55 min After Topical Anesthetic Application	24	1.2	11.6	-3.7, 6.1	-19	-1	35
25 min After Patch Application	24	4.8	14.0	-1.1, 10.7	-16	4	45
55 min After Patch Application	24	11.8	15.4	5.3, 18.3	-12	6	49
Within 5 min After Patch Removal	24	11.1	16.3	4.3, 18.0	-10	6	58
25 min After Patch Removal	24	9.7	16.0	2.9, 16.4	-14	13	54
55 min After Patch Removal	24	3.6	13.8	-2.2, 9.4	-28	2	41
1 hr 25 min After Patch Removal	24	5.2	14.5	-0.9, 11.3	-17	4	42

Source: p 66/73 C123 Study Report

TABLE 6: CHANGES IN DIASTOLIC BLOOD PRESSURE ON DAY OF TREATMENT

	N	Mean	SD	95% CI	Minimum	Median	Maximum
Before Topical Anesthetic Application	24	75.3	9.0	71.5, 79.1	55	73	97
30 min After Topical Anesthetic Application	24	75.7	9.5	71.7, 79.7	60	77	97
55 min After Topical Anesthetic Application	24	74.2	7.5	71.0, 77.4	62	76	87
25 min After Patch Application	24	77.0	8.5	73.4, 80.5	59	79	94
55 min After Patch Application	24	79.4	9.3	75.4, 83.3	60	80	95
Within 5 min After Patch Removal	24	79.3	10.7	74.8, 83.9	62	80	104
25 min After Patch Removal	24	77.6	10.1	73.3, 81.8	56	80	104
55 min After Patch Removal	24	74.8	11.0	70.1, 79.4	48	78	90
1 hr 25 min After Patch Removal	24	75.5	8.4	71.9, 79.0	60	76	90
Change from Before Topical Anesthetic Application							
Before Topical Anesthetic Application	24	0.0	0.0	0.0, 0.0	0	0	0
30 min After Topical Anesthetic Application	24	0.4	6.6	-2.4, 3.2	-10	0	19
55 min After Topical Anesthetic Application	24	-1.1	7.5	-4.3, 2.1	-16	-2	21
25 min After Patch Application	24	1.7	7.8	-1.6, 5.0	-16	3	16
55 min After Patch Application	24	4.1	8.6	0.4, 7.7	-12	4	26
Within 5 min After Patch Removal	24	4.0	6.7	1.2, 6.9	-10	4	14
25 min After Patch Removal	24	2.3	11.1	-2.4, 7.0	-18	2	31
55 min After Patch Removal	24	-0.5	12.0	-5.6, 4.5	-21	0	33
1 hr 25 min After Patch Removal	24	0.2	10.4	-4.2, 4.5	-12	-1	32

Source p 67/73 of C123 Study Report

No changes in heart or respiratory rate were observed on the day of treatment (Tables 7 and 8 below).

TABLE 7: CHANGES IN HEART RATE ON DAY OF TREATMENT

	N	Mean	SD	95% CI	Minimum	Median	Maximum
Before Topical Anesthetic Application	24	74.2	11.7	69.2, 79.1	48	72	94
30 min After Topical Anesthetic Application	24	74.5	10.8	69.9, 79.0	46	74	96
55 min After Topical Anesthetic Application	24	73.4	12.0	68.3, 78.5	44	72	94
25 min After Patch Application	24	72.8	11.4	67.9, 77.6	48	73	98
55 min After Patch Application	24	73.4	12.4	68.2, 78.7	48	72	96
Within 5 min After Patch Removal	24	71.6	13.2	66.0, 77.2	44	70	96
25 min After Patch Removal	24	72.2	12.3	67.0, 77.4	50	71	96
55 min After Patch Removal	24	70.9	13.0	65.4, 76.4	46	70	94
1 hr 25 min After Patch Removal	24	71.8	14.0	65.9, 77.8	44	69	96
Change from Before Topical Anesthetic Application							
Before Topical Anesthetic Application	24	0.0	0.0	0.0, 0.0	0	0	0
30 min After Topical Anesthetic Application	24	0.3	6.5	-2.5, 3.0	-13	0	16
55 min After Topical Anesthetic Application	24	-0.8	7.1	-3.8, 2.3	-14	-1	16
25 min After Patch Application	24	-1.4	7.5	-4.6, 1.7	-13	-1	16
55 min After Patch Application	24	-0.8	6.3	-3.4, 1.9	-14	0	12
Within 5 min After Patch Removal	24	-2.6	6.5	-5.3, 0.2	-18	-3	6
25 min After Patch Removal	24	-2.0	6.8	-4.8, 0.9	-16	0	8
55 min After Patch Removal	24	-3.3	7.0	-6.3, -0.3	-18	-3	8
1 hr 25 min After Patch Removal	24	-2.3	6.8	-5.2, 0.5	-15	-2	12

Source: p 68/73 C123 Study Report

TABLE 8: SHOWING: CHANGES IN RESPIRATORY RATE ON DAY OF TREATMENT

	N	Mean	SD	95% CI	Minimum	Median	Maximum
Before Topical Anesthetic Application	24	16.3	2.0	15.5, 17.2	14	16	22
30 min After Topical Anesthetic Application	24	16.1	2.6	15.0, 17.2	12	16	24
55 min After Topical Anesthetic Application	24	16.4	3.0	15.1, 17.6	12	16	24
25 min After Patch Application	24	17.0	2.8	15.8, 18.2	14	16	24
55 min After Patch Application	24	16.8	2.7	15.7, 18.0	12	16	22
Within 5 min After Patch Removal	24	17.7	4.1	15.9, 19.4	14	16	32
25 min After Patch Removal	24	16.9	2.8	15.7, 18.1	12	16	24
55 min After Patch Removal	24	16.6	2.9	15.4, 17.9	12	16	24
1 hr 25 min After Patch Removal	24	16.5	2.8	15.3, 17.7	12	16	24
Change from Before Topical Anesthetic Application							
Before Topical Anesthetic Application	24	0.0	0.0	0.0, 0.0	0	0	0
30 min After Topical Anesthetic Application	24	-0.2	0.8	-0.6, 0.1	-2	0	2
55 min After Topical Anesthetic Application	24	0.0	1.1	-0.4, 0.5	-2	0	2
25 min After Patch Application	24	0.7	1.3	0.1, 1.2	-2	0	4
55 min After Patch Application	24	0.5	1.8	-0.3, 1.3	-4	0	4
Within 5 min After Patch Removal	24	1.3	3.4	-0.1, 2.8	-2	0	16
25 min After Patch Removal	24	0.6	1.6	-0.1, 1.3	-4	0	4
55 min After Patch Removal	24	0.3	1.2	-0.2, 0.8	-2	0	2
1 hr 25 min After Patch Removal	24	0.2	1.2	-0.3, 0.7	-4	0	2

Source: p 69/73 C123 Study Report

CONCLUSION AND DISCUSSION:

The primary endpoint was the mean duration of patch application and secondary endpoints included the mean change in NPRS scores from pre-treatment values to subsequent time points on the day of treatment, the proportion of subjects using an immediate-relase opioid-based analgesic medication for treatment-associated pain during and following patch application and the proportion of subjects completing at least 90% of the intended patch application duration.

The mean duration of patch application was 60.2 minutes and all subjects completed at least 90% of the intended patch application duration.

This study showed that the safety and tolerability of pretreatment with lidocaine (2.5%)/prilocaine (2.5%) cream appeared qualitatively similar to the 4% lidocaine cream used during the Qutenza development program. The study was single arm so the lidocaine/prilocaine data were compared to the 4% lidocaine data from the clinical development program.

Similar to previous NGX-4010 studies where topical 4% lidocaine was used prior to patch application:

- Mean NPRS scores decreased after topical anesthetic application and increased during patch application.
- The largest mean increase in NPRS score was 3.0 from the pre-anesthetic time point at 55 minutes after patch application.
- NPRS scores fell within 5 minutes after patch removal and returned to close to pre-anesthetic treatment values (+ 0.7) at 85 minutes after patch removal.
- At the evening of the day of patch application treatment, NPRS scores remained close to pre- anesthetic treatment values (+ 0.7)
- About half of the subjects used medication for treatment-related discomfort and pain
- Use of rescue medications rapidly decreased after Day 0
- The incidence of treatment-emergent AEs and treatment-related AE's was similar to previous studies with NGX-4010 and primarily due to capsaicin-related application site events.
- Changes in blood pressure associated with treatment-related changes in pain were observed on the day of treatment.
- Mean systolic and diastolic blood pressures temporarily increased after patch application and the increases were similar to those observed in previous studies.

The use of lidocaine (2.5%)/prilocaine (2.5%) cream was not associated with a greater increase in dermal irritation compared to 4% lidocaine cream when used prior to NGX-4010 treatment.

The maximum dermal assessment score in any subject was 2. Similarly, in previous studies, minimal dermal irritation was observed after lidociane (4%) cream removal that subsequently increased with NGX-4010 treatment.

In conclusion, this study demonstrates that an FDA approved topical anesthetic cream can be used as a pretreatment for NGX-4010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	NGX-4010 (CAPSAICIN PATCH 8%)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NEVILLE A GIBBS
10/15/2009

ROBERT B SHIBUYA
10/15/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	22395
Submission Code	0000
Letter Date	13th October, 2008
Stamp Date	13th October, 2008
PDUFA Goal Date	16th August, 2009
Reviewer Name	Neville A Gibbs, MD, MPH
Review Completion Date	June 16th 2009
Established Name	Capsaicin Patch 8%
(Proposed) Trade Name	Qutenza
Therapeutic Class	TRPV cation channel agonist
Applicant	NeurogesX
Priority Designation	S
Formulation	Patch application
Dosing Regimen	Capsaicin (640 mcg/cm^2)
Indication	Dermal patch for the prolonged reduction of neuropathic pain associated with post herpetic neuralgia
Intended Population	Neuropathic pain associated with postherpetic neuralgia

Table of Contents

1) RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

The data submitted in this New Drug Application support the approval of Qutenza, identified as "NGX-4010" during development, which is a dermal patch containing 8% capsaicin, for the indication of the treatment of the prolonged reduction of neuropathic pain associated with post herpetic neuralgia. The product is designed to be used either a single time or at ≥3 month intervals and it to be administered by a health care professional.

This recommendation is based on the review of the efficacy and safety data submitted by the Applicant, NeurogesX, for this population of adult study participants with moderate to severe post herpetic neuralgia (PHN) pain, who were more than six months post vesicular crusting.

The effectiveness of NGX-4010 was demonstrated primarily in two adequate and controlled Phase 3 clinical trials, Studies C116 and C117. These studies had nearly identical enrollment criteria, patients with moderate to severe postherpetic neuralgia pain (PHN). The observed treatment effect was consistent across gender, race and age.

The review of the safety data found NGX-4010 to have an acceptable safety profile for its intended use in patients with PHN. A total of 1696 patients were treated with NGX-4010 (including 429 patients who were treated more than once with NGX-4010). Adverse events were monitorable and self-limited. The adverse events (AEs) included, most prominently, application site reactions and transient elevations in blood pressure that occurred around the time of dosing.

1.2 Risk Benefit Assessment

NGX-4010 was found to be effective in treating pain in subjects with moderate to severe pain due to PHN, who were at least six months post vesicular crusting where most had used prescription medicine for their painful PHN. The patients studied in the NGX-4010 development program had substantial disease with regard to the duration of pain post healing of the lesions. It is important to note that the mean and median duration of PHN disease in the NGX-4010 study population was approximately four years and two years respectively compared to the commonly reported duration of disease in the literature of 3 months.

Longitudinal PHN studies demonstrate that pain associated with shingles resolve when skin lesions heal. (Thyregood et al;Pain 128 (2007). Most cases of PHN resolve within 3 months. Only about 10% of cases of shingles develop persistent pain after the skin lesions heal.
The study population in the pivotal studies largely consisted of post-shingles patients whose pain failed to resolve long (2-4 years) after skin lesions healed. The rarity of such long standing PHN cases should be kept in mind when generalizing the results of the pivotal trials to the general treatment PHN population.

The adverse events associated with use of the product are predominantly local and include application site pain and erythema although elevations in blood pressure around the time of dosing were also observed. The elevation of blood pressure and, to a lesser extent, heart rate and respiratory rate appears to be related to increased sympathetic outflow because of pain. These adverse events are self-limited and monitorable.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendations for other Post Marketing Study Commitments

The Applicant used LMX4, an unapproved, marketed drug, to affect local anesthesia to make the application of NGX-4010 tolerable. A study to assess whether an approved local anesthetic (EMLA cream) can affect sufficient anesthesia is pending at this time. Presuming that the Applicant can demonstrate comparable tolerability with EMLA, no further studies to address this issue should be necessary.

The Applicant was not advised of the necessity of conducting special dermatology studies (photoallergenicity and photosensitivity, cumulative irritation, and sensitization) during product development. During this review cycle, the Applicant was contacted and asked to conduct these studies as a postmarketing commitment. The Applicant was also given the opportunity to submit a rationale why such studies were not necessary. The Applicant did so. An opinion regarding the acceptability of the Applicant's rationale was requested of the Division of Dermatolology and Dental Products (DDDP). The official DDDP consult is pending at this time. However, in informal communications, DDDP has indicated that, provided that the product is labeled appropriately, the special dermatology studies may be waived.

2) INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

NGX-4010 (capsaicin patch 8%) is a dermal patch containing a high-concentration of capsaicin that is intended to be used for the management of neuropathic pain associated with postherpetic neuralgia (PHN). The patch contains 640 mcg/cm^2 of capsaicin so each patch contains a total of 179 mg of capsaicin. The capsaicin molecule is currently marketed in low concentration (~0.025%) topical formulations. All of those products are over-the-counter, monograph products. Therefore, NGX-4010 is considered a New Molecular Entity.

Capsaicin, the active pharmaceutical ingredient in the patch, is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1). TRPV1 is a ligand-gated, non-selective cation channel preferentially expressed on small diameter sensory neurons, especially those nociceptors which specialize in the detection of painful or noxious sensations.

NGX-4010 is to be applied to the painful area, following application of a topical anesthetic, by a physician or a health care professional. The patch is left on for one hour and subsequently removed. After removal of the patch, a cleansing gel is applied to the treatment area, left on for approximately one minute and then removed with a dry wipe. Treatment with NGX-4010 may be repeated every three months as warranted by the return of pain.

Following exposure to capsaicin, cutaneous nociceptors can become less sensitive to a variety of stimuli, including further capsaicin exposure or thermal stimuli. Reduced spontaneous and evoked painful sensations may also result from capsaicin exposures; these effects of capsaicin are frequently referred to as 'defunctionalization' and are the rationale for the development of various capsaicin formulations for the management of chronic pain syndromes.

Sensations from non-TRPV1-expressing cutaneous nerves remain unaltered, including the ability to detect mechanical and vibratory stimuli.

Pharmacologic class for capsaicin: As noted previously, NGX-4010 is a TRPV cation channel agonist. This product is differentiated from other capsaicin-containing products by the high concentration of purified drug in the patch. According to the Applicant, the use of a high concentration of capsaicin is necessary to deliver sufficient capsaicin to rapidly defunctionalize the tips of cutaneous sensory nerves expressing TRPV1.

A single 60-minute NGX-4010 treatment procedure delivers a dose of approximately 6.45 mg to the skin.

Clinical studies with the NGX-4010 cutaneous patch show that little to no systemic absorption of capsaicin occurs; therefore, the potential for drug-drug interactions is very low.

2.2 Tables of Currently Available Treatments for Proposed Indications

Other approved products for the treatment of post herpetic neuralgia (PHN) include:

1) Neurontin® (gabapentin), an antiepileptic drug that is taken orally two to three times per day

2) Lyrica® (pregabalin)- a precursor of gabapentin, is also taken orally three times a day.

Both Neurontin® and Lyrica® have CNS-related side effects such as somnolence and dizziness and require dose-titration and three times daily dosing, which frequently limits its use in subjects.

3) Lidoderm® a topical lidocaine preparation is applied to the affected area for 16 hours and removed for 8 hours. Reapplication is required during each 24 hour period

Clinicians have used a variety of other orally administered anticonvulsants and antidepressants off-label, either singly or combined in treating PHN.

- Antiepileptic agents used off-label in the treatment of PHN includes Tegretol, Keppra, Topamax, Zonegran, and Lamictal; these anticonvulsants are fraught with adverse effects.

- Antidepressants, such as amitriptyline or nortriptyline are also frequently used off-label in treating PHN; however these agents cause weight gain, constipation & sleepiness, and their use is not recommended in elderly persons, greater than 65 years of age, in whom the condition of PHN tends to occur.

- Clinicians also over-the-counter (OTC) low dose, topically applied capsaicin cream 0.025% for the treatment of PHN. This OTC agent causes more pain before the pain in the painful area subsides, and requires three times daily application; such a regimen can be inconvenient and cumbersome.

2.3 Availability of Proposed Active Ingredient in the United States
A variety of low dose capsaicin creams, lotions and patches containing capsaicin in the range of 0.025% to 0.1% by weight are sold in the USA are listed in Table 2.3.1. These products are available without the requirement of a prescription, for the treatment of neuropathic and musculoskeletal pain. Clinical studies of these low-concentration medications, usually involving three to five daily topical applications for period of two to six weeks, have suggested beneficial effects for the treatment of many disorders, including postherpetic neuralgia, diabetic neuropathy, osteoarthritis and even psoriasis.

TABLE 2.3.1: SHOWING EXAMPLES OF PRODUCTS CONTAINING CAPSAICIN AS THE ACTIVE INGREDIENT

TRADE NAME	MARKETING AUTHORIZATION HOLDER IN THE USA	INDICATIONS	FORMULATION	CAPSAICIN DOSE STRENGTH (% W/W)
Zostrix/ Zostrix HP	Health Care Products, a division of HI-TECH Pharmacal Products. (USA)	Arthritis, shingles, psoriasis and diabetic neuropathy	Topical cream	Zostrix – 0.025 Zostrix HP – 0.075
Capzacin-P/ Capzacin-HP Capsaicin	Chattem Labs (USA)	Arthritis	Topical cream Topical Analgesic liquid	Capzasin-P 0.035 Capzasin-HP 0.1 Capsaicin 0.15
TheraPatch Pain Relief Patch with Capsaicin, 2 × 3 Patch	LecTec Consumer, (USA)	Muscle and joint pain	Topical patch	Not specified
TheraPatch Warm Capsaicin, Penetrating Pain Relief Patch	LecTec Corporation (USA)	Muscle and joint pain	Muscle and joint pain	0.09

SOURCE: FDA compilation of information supplied by Sponsor; p12/116 of Nonclinical Overview

These low-concentration capsaicin-based products often result in contamination of the patient's clothing, bedding, contact lenses, etc. and each application is associated with a burning sensation, poor patient compliance with these products is often cited as a likely contributor to limited efficacy [Paice et al., 2000].

2.4 Important Safety Issues With Consideration to Related Drugs
As previously noted, the low concentration capsaicin products are associated with mild, self-limited burning and pain upon application. The products are not associated with any systemic toxicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission
NGX-4010 was studied under IND 63,354. Initially, review of the IND was the responsibility of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products (DAAODP).

At a Pre-IND meeting held with DAAODP on 26th June 2001, the following were discussed

- Measurement of capsaicin blood levels should be done to determine whether there is systemic exposure.
- The sponsor was advised of the Division's position that neuropathic pain of differing etiologies must be assumed to have a different pathophysiology and consequently each etiology of neuropathic pain is a distinct entity. Thus, the Agency would require two adequate and well-controlled studies to support a finding of effectiveness.
- The capsaicin dose and exposure times were also discussed.

At the End-of-Phase 1 Meeting held on 6th March, 2003, the Division and the sponsor achieved concurrence on the following:

- The design of the pivotal studies
- The choice of efficacy and safety endpoints, and
- The choice of control product to be used in the development of NGX-4010.

A teleconference was held with the sponsor on 10th February 2004, and the sponsor was informed that, prior to approval:

- The FDA required studies to determine whether re-growth of cutaneous nerve occurred after the high dose capsaicin patch was applied, and that
- The safety database was to include 300 or more patients to support safety of repeated applications.

The End-of-Phase 2 Meeting held on 9th November 2004. The Division and the sponsor reached agreement on the following:

- The design of Phase 3 PHN pivotal studies
- The 60 minute time duration of patch application of NGX-4010
- Concurrence on the use of low-dose capsaicin patch, rather than an inert patch as a control, so as not to break the blind, and
- The need to perform ECG's at Weeks 4 & 8 in the pivotal trials.

(b) (4)

.

At the Pre-NDA Meeting held on 6th March 2008, the sponsor met with the Division to discuss the content and format of their NDA submission.
The following items were discussed:

- Agreement on the organization & the presentation of the ISE and ISS data and the proposed analyses.
- Separation of healthy volunteer studies from the neuropathic pain studies
- The content, structure and format of the efficacy datasets and the acceptability of SDTM data sets
- The need to obtain "buy in" from DDMAC and DMETS/OSE regarding acceptability of the proposed trade name
- (b) (4)

The applicant submitted their NDA application on October 13th 2008.

Pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360bb), the Applicant's request for orphan-drug designation status was granted on May 22nd 2009 for "management of neuropathic pain in patients with post herpetic neuralgia"

On February 3, 2009, the Applicant and the Review Division (DAARP) held a teleconference to discuss the requirements for provocative special dermal safety studies.
The Applicant's minutes of the conference stated the following.

- Issues regarding special dermal safety studies had not been discussed prior to filing; had these issues been discussed, the absence of these studies would have constituted a filing issue.
- DAARP stated that given that capsaicin is a monographed drug (although not at this high concentration) and that there were no novel excipients in the product formulation, the Applicant should conduct these studies as soon as possible
- The Division advised the sponsor that they would not be required to be complete these studies prior to the NDA action date and the provocative studies would be a post-marketing commitment (PMC).
- The Applicant agreed to either initiate these studies and to submit the results as a PMC, or to provide rationale on why these studies were not necessary.

On April 7th 2009, the applicant submitted a waiver request providing the scientific rationale for waiving all the provocative dermatologic safety studies. The Division sought the opinion of the Division of Dermatologic and Dental Products as to whether these studies should be waived. Informally, DDDP has notified us that the special studies may be waived, provided that the labeling appropriately addresses these issues.

2.6 Other Relevant Background Information

Not applicable.

3) ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

In general, the data quality and integrity were adequate. The integrity of analyses shown in the Integrated Summary of Safety and Integrated Summary of Efficacy was adequate and corresponded to the attached source tables. Random datasets were audited with their corresponding tables and the integrity of data was found to be satisfactory.

The Division of Scientific Investigation (DSI) inspected four study sites.

The inspections covered studies performed in C116 and C117.

The following Clinical Investigator/Site #'s were inspected by DSI:

1) Dr. Cynthia Bell
(Formerly Francis, Philip M. Jr); Site # 9

2) L Michael Minehart, MD; Site # 73

3) Edwin D Dunteman, MD, M.S.; Site #129

4) Marvin D. Tark, MD; Site # 70

The study sites for inspection were selected based primarily on sites with the largest number of study participants, and on the highest between-group difference in change in average pain. At the time of the finalization of this review, the results of these inspections are pending.

3.2 Compliance with Good Clinical Practices
Each of the clinical trials was certified as being conducted under acceptable ethical standards in accordance with the Declaration of Helsinki and with the approval of the appropriate Ethics Committee.

3.3 Financial Disclosures

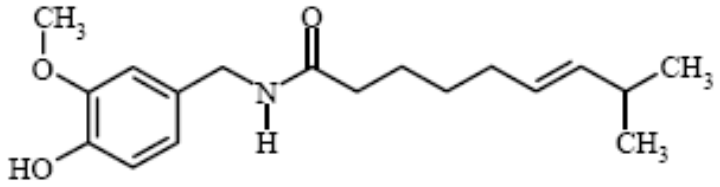
All clinical investigators have certified that they have not entered into any financial arrangement with the sponsor whereby the value of compensation to the clinical investigators could have reasonably affected the outcome of the study. The clinical investigators have also certified that they did not have any proprietary interest in the product in the product. The investigators have also certified that they were not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4) SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Capsaicin is the trans isomer of a molecule derived from chili pepper plants of the genus Capsicum. It is a selective agonist of the transient receptor potential vanilloid 1 (TRVP1).

The chemical formula is as follows:



No novel excipients are used in the formulation. The CMC review does not identify any deficiencies or issues that will affect the approvability of this product.

Further details of the chemistry, manufacturing and controls of this product can be obtained from the review of Dr Theodore Carver.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The single-dose toxicology studies of NGX-4010 in rats and dogs did not produce any test article-related changes in the toxicity parameters measured in the study at dosing regimens relevant to clinical dosing.

The repeated-dose toxicology studies of NGX-4010 in rats and minipig also indicated that topical capsaicin did not produce any test article-related changes in the toxicity parameters measured in the study at dosing regimens relevant to clinical dosing.

Absorption/Distribution/Metabolism/Excretion (ADME) studies were conducted in both rats and pigs following ^{14}C-capsaicin topical patch application. All studies showed transfer of capsaicin from the patch into the skin. The initial rat study indicated that 70% capsaicin had been transferred to the skin or other tissues and that radioactivity was present in blood and plasma samples from 0.5 hours until the end of the 72-hour test period. A subsequent rat study indicated that limited radioactivity appeared to have been absorbed, based on radioactivity levels

remaining in the patch and low amounts measured in excreta. These differences were attributed to the differences in the patches because they were manufactured on study site for each study by scientist.

Data from the pig study were more consistent with the second rat study and showed limited (2% to 6%) dermal absorption of ^{14}C-capsaicin and measurable radioactivity in plasma was only found at 1 to 4 hours after administration. Taken together, these ADME studies may reflect a species difference in the transfer of capsaicin from the patch into the skin and the systemic circulation. Since the pig is considered to be the most predictive species for human percutaneous absorption limited systemic absorption of capsaicin from the patch is predicted in humans.

Capsaicin was highly bound to plasma proteins in all four species (human, dog, rabbit and rat) over the concentration range of 50 to 500 ng/mL. Binding was independent of the concentration in all species.

Biotransformation of capsaicin in human skin was slow and capsaicin was metabolized to vanillylamine and vanillic acid, although the majority of the sample radioactivity was associated with unchanged capsaicin.

Data collected from the cytochrome P450 inhibition. and induction studies, combined with the very low level of systemic exposure to capsaicin in humans (Cmax ≤4.64 ng/mL in PHN subjects following 60 minute NGX-4010 application), indicated that it is unlikely that capsaicin will either inhibit or induce *in vivo* the clearance of concomitantly administered drugs metabolized by any of the CYP enzymes evaluated.

Genetic Toxicity Testing

1) Bacterial Mutation Assay -negative
2) Mouse Lymphoma Assay- Mutagenic, in the presence or absence of metabolic enzymes Small colonies predominated indicating that the alterations were associated with large chromosomal deletions.
3) In vivo mouse micronucleus assay (oral doses 200, 400, 800 mg/kg males 200 mg/kg females) was negative
4) In vitro Chromosomal Aberration of human peripheral blood lymphocytes- negative (up to 123 µg/mL without metabolic activation, or 192 µg/mL with metabolic activation).

The result of the positive mouse lymphoma study should be reported in the label. Other genetic toxicity tests were negative. One reason for running a battery of genetic toxicity tests in the development of a new molecular entity is that no single test is optimal or definitive. Genetic toxicity is a surrogate for carcinogenicity for most drugs, and carcinogenicity in animals is a surrogate for human carcinogenicity. No single genetic toxicity test by itself is considered to be a perfect predictor by itself.

At the CAC Executive Committee Meeting held on April 14th 2009, the committee determined the carcinogenic study to be invalid, noting concerns with the conduct of the study, data collection, data summarization, data presentation, data analysis and interpretation of the study

data. The Committee recommended that DSI should investigate this study. However, because of the proposed manner of use of the product (mostly one-time and multiple-dose use limited to every three months), carcinogenicity studies were not required.

A full detailed report of Pharmacology and Toxicology associated with this compound can be seen in the report of Dr. Lawrence Leschin.

4.4 Clinical Pharmacology

The clinical pharmacology development of NGX-4010 divided into three major groups: In vitro studies, clinical pharmacology studies in healthy volunteers, and population pharmacokinetic studies in patients.

In Vitro Studies using Human Cells or Tissues. (Section 4.4)

The following studies were performed:

a) Chromosomal aberration assay
b) Hepatic metabolism
c) Skin metabolism
d) Identification of cytochrome P450 enzymes involved in capsaicin metabolism
e) Plasma protein binding
f) CYP inhibition and induction in liver microsomes and primary human hepatocytes
g) Delivery kinetics of capsaicin from NGX-4010

Study VAL-07-002-R was an *in-vitro* mass balance study conducted to inform the delivery kinetics of capsaicin from NGX-4010 over various potential application times.

The objective of this study, using heat-separated human epidermis and diffusion cells, was to determine amount of capsaicin present at various timepoints in (and on) the skin, buffer solution and used patch.

This study showed that only a small percentage (approximately 0.9% or less) of the total capsaicin in the NGX-4010 topical patch was transferred from the patch into the skin during a 60 minute application time, with no quantifiable levels of capsaicin present in the receptor solution.

The extent of *in vitro* capsaicin delivery from NGX-4010 was approximately linear with the patch application time, therefore, during clinical use it is expected that the delivered dose of capsaicin will be directly related to the duration of exposure to NGX-4010.

These data show that NGX-4010 is a topical patch, not a transdermal patch. Accordingly, the calculation of safety margins for human clinical exposure of capsaicin should take into account the important distinction between drug contained in NGX-4010 and the fraction/dose delivered into the skin.

Finally, although the drug delivery from the low-concentration patch is about 29-fold less than from NGX-4010, this finding underscores the fact that the control patch cannot be conceived of as a truly inert placebo, and that some degree of pharmacological activity of the low-concentration control patches cannot be excluded.

Therefore, based on the maximum recommended treatment area of approximately 1,120 cm^2 for the NGX-4010 topical patch, the dose of capsaicin delivered to the skin is predicted to be approximately 6.45 mg. Accordingly, the maximum estimated capsaicin exposure is of the order of 92 mcg/kg (for a 70 kg human) per treatment.

Further information on the clinical pharmacokinetics and pharmacodynamics of NGX-4010 can be obtained from the report of Dr David Lee.

Clinical Pharmacology Studies in healthy volunteers

Studies were conducted in healthy volunteers to assess the effects of NGX-4010 on epidermal nerve fiber density and quantitative sensory testing. These studies will be discussed in detail in Section 7.4.5. Briefly, the studies showed a decline in both intraepidermal nerve fiber density and sensation that largely normalized by 12-weeks and completely returned to baseline by 24-weeks post-dose.

Population pharmacokinetics

A population pharmacokinetic analysis performed on a total of 96 PHN subjects in 3 clinical studies (C108, C111, and C116) receiving NGX-4010 for 60 or 90 minutes were evaluated for determination of capsaicin levels and its metabolites, M1, M2, and M3, in plasma. Of these, 30 subjects (19 males and 11 females) displayed quantifiable levels of capsaicin at 1 or more time points.

Pharmacokinetic data in humans showed transient, low (< 5 ng/mL) systemic exposure to capsaicin in about one third of PHN patients following 60-minute applications of NGX-4010.

The highest plasma concentration of capsaicin detected was 4.64 ng/mL and occurred immediately after NGX-4010 removal. Most quantifiable levels were observed at the time of NGX-4010 removal and were below the limit of quantitation 3 to 6 hours after NGX-4010 removal.

The population PK analysis indicated that capsaicin levels in plasma:

- Peaked around 20 minutes after NGX-4010 removal and
- Declined very rapidly, with a mean elimination half-life of about 130 minutes.
- Mean AUC and C_{max} values of capsaicin following a single 60-minute application were 5.71 ng•h/mL and 1.48 ng/mL, respectively,
- Mean population AUC and C_{max} values of capsaicin were 6.99 ng•h/mL and 1.88 ng/mL, respectively (for combined 60 and 90-minute treatment groups).

- Capsaicin drug levels in plasma peaked at about 80 minutes after patch application and declined very rapidly, with a population mean overall elimination half-life of 2.18 hours, corresponding to approximately 130 minutes.

No detectable levels of metabolites were detected in any subject at any time point.

Considering the infrequent dosing of NGX-4010, combined with the low systemic exposure and the very rapid elimination half-life, administration of NGX-4010 is likely to result in capsaicin-mediated systemic effects or drug-drug interactions.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Clinical Studies

Of the 14 studies completed for the NGX-4010 clinical development program, six studies were conducted to assess the efficacy (as well as the safety and tolerability) of NGX-4010 in patients with PHN.

Twelve clinical studies, listed below in Table 5.1.1 were conducted in patients. In addition to the 12 studies conducted in patients with peripheral neuropathic pain, two studies were conducted in healthy volunteers (Studies C101 and C115).

The six studies conducted in PHN subjects have been divided into the following groupings for analysis purposes:
(1) Controlled Studies (C117, C116 [Pivotal studies] and C110, C108, and C102 [Supportive studies)

And

(2) Open-label and Repeat-treatment Studies (C118, the open-label portion of C108, C106 [open-label extension of C102], and C111).

TABLE 5.1.1: DEMONSTRATING THE CLINICAL STUDIES PERFORMED IN THE NGX-4010 DEVELOPMENTAL PROGRAM (ALL DISEASE INDICATIONS)

PHN	HIV-AN	Mixed population (PHN/ HIV-AN/PDN or PHN/HIV-AN)
Pivotal Phase 3 double-blind studies Study C116 Study C117 **Supportive double-blind studies** Study C102 Study C108 Study C110 **Open-label study** Study C106 (extension of C102)	**Pivotal Phase 3 double-blind studies** Study C107 Study C119 **Supportive double-blind study** Study C112[a] **Open-label study** Study C109	**Open-label study** Study C111 Study C118

[a] Study C112 was terminated after 5 subjects were enrolled. These subjects remained in the study for 12 weeks.

SOURCE: Overview of Clinical Studies with NGX-4010 p 11/69 C123Protocol _13 May 2009_v1 0.pdf

The tables below (Summary Table 5.1.2) summarize the main design features of the clinical studies evaluating the efficacy and safety of NGX 4010 in subjects with PHN.

The current application is submitted for the indication *prolonged reduction of neuropathic pain associated with PHN;* (b) (4) .

SUMMARY TABLE 5.1.2: CLINICAL STUDIES EVALUATING EFFICACY OF NGX-4010 IN SUBJECTS WITH PHN
PIVOTAL STUDIES RELEVANT TO EFFICACY AND SAFETY

STUDY #	PHASE Disease	DESIGN Duration of Study	N Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
PIVOTAL CONTROLLED STUDIES					
C116	3 PHN	Rand 1:1 DB, PC 12 weeks	N= 206 + 196 Active : control 60 mins	Clinical effectiveness & safety/tol	Pivotal- for determination of efficacy
C117	3 PHN	Rand 1:1 DB, PC 12 weeks	N= 212+204 Active : control 60 mins	Clinical effectiveness & safety/tol	Pivotal-for determination of efficacy

Source: FDA Compilation based on information submitted by the Applicant

SUPPORTIVE CONTROLLED STUDIES RELEVANT TO SAFETY AND EFFICACY

STUDY	PHASE Disease	DESIGN Duration Of Study	N Duration of Application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
C110	3 PHN	Rand 2:1 allocation ratio DB, PC 12 weeks	N= 155 Active: Control = 102 : 53 60 min	Clinical effectiveness & safety/ tolerability	Only pivotal study enrolling subjects 3 months post vesicular crusting
C108 (Dose-ranging Study)	2/3	Rand 3:3:3 to 1:1:1; PC, DB 12weeks	Active 30 mins (n= 72) 60 mins (n= 77) 90 mins (n= 73) Control 30 mins (n= 23) 60 mins (n= 29) 90 mins (n= 25)	Dose-ranging Clinical effectiveness & safety/tol @ 3 different application durations	Assessed efficacy in multiple durations of patch application
C102	PHN	Rand 2:1, PC, DB Eligible to continue Study # 106	N= 36 (DB phase) N= 6 (OL phase) Duration= 4 weeks.	Pilot study	To explore the need for short-term local anesthesia and analgesic medication during and after application of NGX-4010.
	2 PHN	Foll by OL extension Phase Study #118 x 40 wks, w q12 wkly applic	90-60-30 mins	Feasibility, Tolerance, safety & efficacy	Supportive of pivotal trials, BUT trial Only 4 weeks duration

REPEAT TREATMENT STUDIES IN PHN SUBJECTS

STUDY #	PHASE / Disease	DESIGN / Duration of Study	N / Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
REPEAT TREATMENT STUDIES IN PHN SUBJECTS					
C106 (OL extension of C102)	Phase 2 PHN	OL extension of Study 102	N = 24 60 mins	OL extension of C102	Provided an OL extension to Study 102. Offered 6 week between subsequent re-treatment
C118 (enrolled subjects who completed Studies C116/C110, & C108)	2 PHN & HIV	OL extension study, single arm, safety & efficacy Up to one year	N= 106 PHN(n= 54) HIV (n= 52) 60 mins	Enrolled subjects who completed Studies C116/C110, & C108)	OL extension provides data for analysis following repeated treatment & development of tolerance
C108 12 week DB, Foll by 40 week OL portion	2/3	40 week OL portion	N= 222 (DB) N=77 (OL) 30-60-90 mins	OL extension	OL extension provides data for analysis following repeated Rx, & development of tolerance Systemic lidocaine blood levels performed

# C111 (Mixed disease population study)	2 PHN, HIV-AN and PDN	OL, Rand to LMX4, Topicaine & Betacaine Pre Rx	N=117 LMX (n=39) Topicaine(n=38) Betacaine(n=40) 60 or 90 mins	For determination of optimal pre-patch application 4% lidocaine product	Data for determination of optimal pre-patch 4% lidocaine product i.e LMX4 vs EMLA vs lido/prilo 2.5/2.5

HEALTHY VOLUNTEER STUDIES

STUDY #	PHASE / Disease	DESIGN	N / Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
HEALTHY VOLUNTEER STUDIES					
C101			N =20 30, 60 & 120 mins	1) To determine exposure time to induce sig loss of immunoreactivity of cap-sensitive cut nociceptors @ 7 days 2) Compare immunohistochemical changes a/w cap patch @ 3 diff exposure times 3) Compare change in cut nerve fiber function as measured by QST prior to and 7 days after capsaicin exosure 4) Compare intensity of pain a/w high and low conc capsaicin patch.	- QST testing

STUDY #	PHASE Disease	DESIGN Duration of Study	N Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
C115	1		N=36	1) Assess ENFD on skin biopsy between treated and untreated area 2) Assess difference bet patch & control for thermal detection threshold 3) Assess difference in pain and tactile threshold All @ 1, 12 & 24 weeks	Results of study show that NGX-4010 reduces ENFD. Changes were associated with small changes in sensory function. The effects were transient with full recovery of epidermal innervation and sensory function with 12 to 24 weeks after treatment.
	Healthy		24 weeks		

SOURCE: FDA Compilation based on information provided by the Sponsor

5.2 Review Strategy

The efficacy of NGX-4010 was primarily supported by two Phase 3 Studies: Studies C116 and C117, conducted in patients with PHN. The efficacy of these adequate and well-controlled pivotal trials was reviewed individually, and is reviewed in detail in Section 5.3 of this review. The two pivotal trials were not combined for the purposes of efficacy analysis.

Efficacy reviews of the Studies C116 and C117 were jointly conducted by the statistical reviewer, Ms. Kate Meaker and me. A detailed description of all analyses (including responder analysis and findings can be found in Section 6 of this report and in Ms. Meaker's review.

The applicant is seeking an indication for "the prolonged treatment of postherpetic neuralgia" (PHN); therefore, analysis of safety was based on data from the pooled placebo-controlled

studies conducted in post herpetic neuralgia (PHN) study participants, and was performed by me. (See Section 7 of this report).

5.3 Discussion of Individual Studies

The objectives, study design, inclusion and exclusion criteria, permitted and disallowed concomitant medication and rescue medications, primary efficacy endpoints, safety measures, visit schedule, statistical analysis plan and definition of analyzed populations were essentially identical in both pivotal studies. The protocol for Study C116 will be described in detail here.

INDIVIDUAL STUDY REPORT C116

Title of study: A Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia (PHN)

Primary objective: The primary objectives of this study were to have been to assess the efficacy, safety, and tolerability of a single 60 minute application of NGX-4010, a high-concentration capsaicin patch (640 mcg/cm^2), compared to a low-concentration capsaicin Control patch (3.2 mcg/cm^2), in subjects with postherpetic neuralgia (PHN).

Study Design: This study was to have been a randomized, double-blind, controlled, multicenter evaluation of the efficacy, safety and tolerability of NGX-4010 for the treatment of PHN.

The protocol specified that duration of participation in this study was to have been 12-weeks, in addition to 14 or more days for Screening. Generally, within 2 weeks after Screening, subjects were to have been scheduled for the Study Patch Application Visit (Day 0). At this visit, subjects were to have received a single 60-minute application with a topical local anesthetic on their painful area(s), (the total application area could not exceed a maximum total surface area of 1000 cm^2) prior to placement of patch(es) containing study drug.

After removal of the local anesthetic, subjects were to have received a single 60-minute treatment with either NGX-4010 or Control (low-concentration capsaicin, 3.2 mcg/cm^2) patch(es) over the affected areas. After treatment, the patch(es) were to have been removed and the treatment area(s) were to have been cleansed with a supplied cleansing gel. Subjects were to have been monitored for at least 2 hours following treatment before being discharged and were to have been asked to return for Follow-Up Visits at 4, 8, and 12 (Termination Visit) weeks after treatment.

Efficacy was to have been assessed daily throughout the study using Numeric Pain Rating Scale (NPRS) scores and by periodic assessments of the modified Brief Pain Inventory (BPI) Short Form, Short-Form McGill Pain Questionnaire (SF-MPQ), Short Form-36 version 2 Heath Survey (SF-36v2), Patient Global Impression of Change (PGIC), and Self-Assessment of Treatment (SAT).

Safety and tolerability were to have been assessed by continuous monitoring of adverse events (AE's) and periodic assessments of clinical laboratory parameters, vital signs, physical examinations, electrocardiograms (ECG's), dermal assessments, targeted neurological/sensory assessments, rescue medication and concomitant medication usage. In addition, at selected sites, plasma samples were to have been obtained before and after treatment for analysis of capsaicin and capsaicin metabolites.

Subjects were to have been randomly assigned to receive NGX-4010 or Control patches, according to a 1:1 allocation scheme.

All treated subjects were to have been included in the Safety and Intent-to-Treat (ITT) analyses.

Main Inclusion and Exclusion criteria:

Inclusion criteria
Subjects were eligible for inclusion in the study if they met all of the following Inclusion Criteria:

1. Between 18 and 90 years of age, inclusive.

2. In good health.

3. A diagnosis of PHN made by the primary treating physician or Investigator, and was at least 6 months since shingles vesicle crusting.

4. Average NPRS scores for PHN-associated pain during Screening period of 3 to 9, inclusive.

The sum of the subject's daily NPRS scores for Day -14 to Day -4 (inclusive) must not have been less than 33 or greater than 99 to be eligible for the study. If any of the subject's scores were missing, then the subject was not eligible. Pain scores were recorded in the evening as whole numbers using an 11-point scale (0 = no pain, 10 = worst possible pain).

5. Intact, unbroken skin over the painful area(s) to be treated.

6. If taking chronic pain medications, were on a stable (not as needed [PRN]) regimen for at least 21 days prior to the Study Patch Application Visit (Day 0), and were willing to maintain medications at same stable dose(s) and schedule throughout the study (see Section 9.4.7).

7. Female subjects with child-bearing potential must have had a negative serum beta human chorionic gonadotropin (hCG) pregnancy test, performed within 7 days of the Study Patch Application Visit (Day 0).

Serum beta hCG pregnancy testing was performed at the Screening Visit when both of the following criteria were met: age below 60 years and menses during the preceding year.

8. Willing to use effective methods of birth control and/or refrain from participating in a conception process during the study and for 30 days following experimental drug exposure. A conception process was defined as an attempt to become pregnant or to impregnate, sperm donation, or in vitro fertilization.

9. Willing and able to comply with protocol requirements for the duration of study participation. Requirements included, but were not limited to: completing a daily pain diary, attending all study visits, and refraining from elective surgery and extensive travel during study participation.

10. Signed informed consent form for this study approved by the IRB.

Exclusion Criteria
Subjects were excluded from the study if they met any of the following Exclusion Criteria:

1. Concomitant opioid medication use, unless orally or transdermally administered and not exceeding a total daily dose of morphine 60 mg/day, or equivalent. Parenteral opioid use was excluded, regardless of dose.

2. Unavailability of an effective rescue medication strategy for the subject, such as unwillingness to use opioid analgesics during treatment or high tolerance to opioids precluding the ability to relieve treatment-associated discomfort with Roxicodone®, as judged by the Investigator.

3. Active substance abuse or history of chronic substance abuse within the past year, or prior chronic substance abuse (including alcoholism) judged likely to recur during the study period by the Investigator.

4. Recent use (within 21 days preceding the Study Patch Application Visit) of any topically applied pain medication, such as non-steroidal anti-inflammatory drugs (NSAIDs), menthol, methyl salicylate, local anesthetics (including Lidoderm®), steroids, or capsaicin products on the painful areas.

5. Participation in a previous NeurogesX clinical trial in which subject received NGX-4010 (either blinded or open-label study treatment).

6. Current use of any investigational drug, or Class 1 anti-arrhythmic drugs (e.g., tocainide and mexiletine).

7. Diabetes mellitus, unless well-controlled as evidenced by a hemoglobin A1C (HbA1C) level less than or equal to 9% performed through the study-specified central laboratory.

8. Hypertension, unless adequately controlled by medication.

9. Significant pain of an etiology other than PHN, for example, compression-related neuropathies (e.g., spinal stenosis), fibromyalgia, or arthritis. Subjects must not have had significant ongoing pain from other cause(s) that may have interfered with judging PHN-related pain.

10. Painful PHN areas located only on the face, above the hairline of the scalp, and/or in proximity to mucous membranes. (Investigational treatment with NGX-4010 is not allowed in these areas.)

11. Any implanted medical device (spinal cord stimulator, intrathecal pump, or peripheral nerve stimulator) for the treatment of neuropathic pain.

12. Hypersensitivity to capsaicin (i.e., chili peppers or over-the-counter [OTC] capsaicin products), local anesthetics, oxycodone hydrochloride (e.g., Roxicodone®), hydrocodone (Vicodin®), or adhesives.

13. Significant ongoing or untreated abnormalities in cardiac, renal, hepatic, or pulmonary function that may interfere either with the ability to complete the study or the evaluation of AEs.

14. Recent history of a significant medical-surgical intervention, in the judgment of the Investigator. Examples included but were not limited to: major elective or nonelective non-cardiac surgery within the past 3 months, cardiac surgery or percutaneous angioplasty/stent placement within the past 6 months, or receipt of immunosuppressive chemotherapy for malignancy within the past 3 months, relative to date of the Study Patch Application Visit (Day 0).

15. Evidence of cognitive impairment, including dementia that may interfere with subject's ability to complete daily pain diaries requiring subject's recall of average PHN pain level in the past 24 hours.

Treatment:
Treatment was to have consisted of a single 60-minute application of high concentration Capsaicin 640 mcg/cm^2 or low concentration capsaicin 3.2 mcg/cm^2 control patch. There was no true placebo because of concerns regarding blinding.

Permitted Concomitant medication:
The use of *topical* NSAID's, local anesthetics, steroids, and capsaicin-containing preparations was to have been prohibited within 21 days prior to starting the study, and throughout the duration of the study.

Subjects were to have been permitted to use (*non-topical*) pain-control medications, including opioid analgesics if they were on a stable/fixed regimen for at least 21 days prior to treatment, and maintained the stable dose throughout the study.

Changes in concomitant medication use were *not* to have been permitted during the study.

In order to offset the potential pain associated with capsaicin patch administration, all subjects in all studies were to have had their painful areas pre-treated with a topical local anesthetic cream (4% w/w lidocaine) for 60 minutes prior to study patch application.

Rescue medication:

All subjects were to have been permitted to use rescue medication during and up to 5 days after patch application treatment for treatment-related discomfort. Additionally a rapid onset, opioid-based oral pain medication such as oxycodone hydrochloride (HCL) oral solution (1mg/mL; eg Roxicodone) was to have been administered as needed while subject was in the clinic.

An opioid-containing *oral pain medication* such as hydrocodone bitartrate/acetaminophen (5/500 mg prn eg, Vicodin) was to have been permitted post treatment through Day 5).

Rescue medications were defined as one or more of the following:
Roxicodone®, Oxycontin®, OxyIR®, Oxyfast®, oxycodone, Percocet®, Oxycodone/acetaminophen, Vicodin®, Vicodin ES®, Lortab®, hydrocodone, or hydrocodone bitartrate/acetaminophen.

Outcome measures:

Primary Efficacy Endpoint:
The primary efficacy endpoint was to have been: The change in "average pain for the past 24 hours" as measured by NPRS scores from Baseline to Weeks 2–8.

Secondary Efficacy Endpoints:
The secondary efficacy variables were to have included the following:

1) Percent change in "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2–12
2) Proportion of subjects achieving a 30% and 50% decrease in their "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2–8
3) Proportion of subjects achieving a 30% and 50% decrease in their "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2–12.
4) Percent change in "average pain for the past 24 hours" NPRS scores from
5) Baseline to Weeks 2–4
6) Proportion of subjects achieving a 30% and 50% decrease in their "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2–4
7) Weekly percent change from Baseline in "average pain for the past 24 hours" NPRS scores;
8) Weekly proportion of subjects achieving a 30% and 50% decrease from Baseline in their "average pain for the past 24 hours" NPRS scores;
9) Onset and duration of efficacy
10) Proportion of subjects with changes in concomitant pain medication usage from Baseline to Weeks 2–8 and Weeks 2–12
11) Change in BPI from Baseline
12) Change in SF-MPQ from Baseline
13) Change in SF-36v2 from Baseline
14) PGIC at Weeks 4, 8, and 12/Termination
15) SAT at Termination.

Safety Measures:
Safety and tolerability assessment were to have included:

1) AE monitoring
2) Clinical laboratory tests
3) Evaluation of vital signs and physical examination
4) Electrocardiograms (ECGs)
5) Dermal assessments
6) Targeted neurological/sensory assessments
7) Duration of patch application
8) Change in NPRS pain scores on the day of treatment
9) Change in NPRS scores in the evening on the day of treatment
10) Pain increase during the first 3 study days (Days 0–2) following treatment
11) Rescue pain medication use during Days 0–5.

TABLE 5.3.1 : Schedule of study events, Study 116

APPENDIX 1: STUDY SCHEDULE

Study Procedures	Screening Visit (Day –14 to Day –21)	Study Patch Application Visit (Day 0)	Interim Visit (Week 4 ± 4 days)	Interim Visit (Week 8 ± 4 days)	Unscheduled Visit	Termination or Early Term. Visit (Week 12 ± 4 days)
Informed Consent	X					
Medical History	X					
Concomitant Medications	X	X	X	X	X	X
Physical Exam	X					X
Vital Signs	X	X	X	X	X	X
Clinical Laboratory Tests[a]	X[a]					X[a]
Serum Pregnancy Test[b]	X[b]					X[b]
Dermal Assessment	X	X	X			
Neurological/Sensory Exam	X			X		X
Measure Painful Area(s)	X	X				
Measure Allodynia	X			X		X
Pain Ratings (NPRS)	X	X	X	X		X
ECG	X					X
Topical Lidocaine (Anesthetic)/ Patch Application[c]		X[c]				
Provide Rescue Medication		X				
Adverse Events		X	X	X	X	X
Telephone Contacts[d]	X	X	X	X		
Diary Collection[e]		X	X	X	X	X
Subject Questionnaires[f]	NPRS, BPI, SF-MPQ, SF-36v2™ and BDI-II	NPRS	NPRS, PGIC, and CGIC	NPRS, BPI, SF-MPQ, PGIC, CGIC, and SF-36v2™		NPRS, BPI, SF-MPQ, PGIC, CGIC and SAT

Legend:

[a] Refer to the study specified central laboratory manual for identification of laboratory tests conducted at the corresponding study visit.

[b] At study entry, serum beta hCG pregnancy test (if applicable) drawn within 7 days of the Study Patch Application Visit (Day 0) to be performed through the study-specified central laboratory. At Termination Visit, urine pregnancy test (if applicable) performed using urine test kit provided by the study-specified central laboratory.

[c] See Protocol Section 6.4 for details of investigational treatment and related procedures.

[d] Intervals for Telephone Contacts: Screening Period: once per week; Post-Treatment Week 1: once within 72 hours after the Study Patch Application Visit; Post-Treatment Weeks 2 to 12: once per month.

[e] Diary pages completed since the most recent study visit will be collected and stored with the subject's source document record..

[f] NPRS (Numeric Pain Rating Scale); BPI (Brief Pain Inventory); PGIC (Patient Global Impression of Change); CGIC (Clinical Global Impression of Change); SF-MPQ (Short-Form McGill Pain Questionnaire; SAT (Self-Assessment of Treatment); SF-36v2™ (Short Form 36 Health Survey); BDI-II.

Source: p 36/598 Study C116

PROTOCOL AMENDMENTS for Study C116 (9th March 2005):
The protocol was amended to include the following key protocol changes and the rationale for these changes:

- Stratified randomization by gender, as data from earlier trials were suggested that gender may be a predictor of response to NGX-4010. Stratifying for gender removes the potential for biased results in case of imbalance in the gender proportions in the treatment groups).

- The inclusion criterion regarding upper age limit was to have been changed from 80 to 90 years. Based on the demographics observed in previous trials of NGX-4010 in PHN, an age limit of 80 years would exclude approximately 20% of potential subjects.

- Two exclusion criteria were to have been added to exclude subjects with recent significant medical conditions/procedures prior to study entry, or with cognitive impairment that may interfere with subject's ability to complete the study.

- Addition of fasting lipid panel and high sensitivity C-reactive protein measurement to laboratory assessments to be performed at the screening visit. These tests were thought to help to further characterize the population enrolled with respect to potential risk for cardiovascular events.

- Statistical secondary endpoints were to have been updated to include *the proportion of subjects reaching 50% decrease from baseline in their "average pain for the past 24 hours" NPRS scores*. This additional descriptive assessment was added to the proportion reaching 30% decrease from baseline during Weeks 2 to 4 and 2 to 12 respectively, and thought to be of clinical interest.

- The potential risks of NGX-4010 were to have been updated to reflect the information in the current Investigator's Brochure (Edition 8).

- Administrative changes and edits to increase clarity.

STATISTICAL ANALYSIS PLAN AND DEFINITION OF STUDY POPULATIONS TO BE ANALYZED:

The Safety Population was to have included all subjects in the study who were randomized and who received study drug.

The ITT Population was to have included all subjects enrolled in the study who were randomized, received study drug, and had at least 3 days of non-missing "average pain for the past 24 hours" NPRS scores for the calculation of Baseline NPRS score.

The PP Population included all subjects in the ITT Population who did not have any major protocol violations.

Demographic and Baseline characteristics were to have included the following:
Age, gender, ethnic origin, height, weight, Beck's Depression Inventory® [BDI®-II] score, pain level at the Screening Visit, pain history, size of painful area, dermal assessment score, time of day pain was worst, and concomitant pain medication use for subjects in the NGX-4010 and Control groups were compared using either Student's t-test or Fisher's Exact test.

All statistical tests were to have been two-sided and performed at a significance level of 0.05.

Day 0 was to be defined as the day of treatment administration. Study Day # is defined as [day of event] - [day of treatment]. Therefore the day after treatment administration was to be defined as Day 1, and the day before treatment administration is defined as Day -1. All references to weeks or days in this plan are in relation to Day 0.

Calculation of Baseline NPRS Scores - The study protocol allows certain changes of concomitant pain medications up to the day of the screening visit and stipulates that, if such changes are made, the screening period of two weeks should be prolonged by one additional week in order to ensure a reliable baseline period.

The baseline NPRS score was to be the average of all NPRS scores from Day − 14 through Day − 1. No imputation for missing values will be performed.

Calculation of Mean NPRS Scores - For each subject, the mean NPRS score for Weeks 2 to n, was to have been computed as the average of the NPRS scores from day 8 to day 7*n.

Percent Change from Baseline for NPRS Scores from Weeks 2 to n (n > 2)
Was to have been defined as:
(Mean NPRS score for Weeks 2 to n - Baseline score) x 100) / Baseline Score,
where n is any number greater than 2.

Imputation of Missing NPRS Scores
A Last Observation Carried Forward (LOCF) approach was to have been used to impute any missing post-treatment NPRS score:

- If the NPRS score is missing on any of days 0 to 8, the baseline score will be imputed for that day.
- If the NPRS score is missing on day 8 and one or more consecutive days, then the baseline score will be imputed for those days. If the NPRS score is missing for any day past day 8, then the latest available non-missing score collected before that day will be imputed for that missing value.
- If all post-treatment NPRS scores are missing (including Day 0) then the baseline score is imputed for all missing scores.

Sensitivity Analyses for Missing Data
The primary analysis will be repeated for the percent change from baseline for "Average pain for Past 24 Hours" NPRS scores averaged over Weeks 2 to 8 and Weeks 2 to 12 where no imputation has been performed for missing scores.

Also, the aforementioned analyses will be performed using different imputation methods, i.e. baseline observation carried forward (BOCF) and the area under the curve (AUC) approach (i.e. linear interpolation method will be used to impute missing value(s) between two observed values, baseline value will be used to impute missing value(s) after the last observed value) .

An analysis of the percent change from baseline for "Average pain for Past 24 Hours" NPRS scores averaged over Weeks 2 to 8 and Weeks 2 to 12 using a gender stratified ANCOVA model with baseline pain score as the only covariate will also be performed. These analyses are not intended to replace the primary analysis and are viewed as exploratory/sensitivity analysis only.

RESULTS:

DISPOSITION
In Study C116, a total of 402 subjects entered the study; 206 subjects were enrolled in the NGX-4010 group and 196 subjects were enrolled in the Control group. Ninety-one percent (91%) of subjects in each treatment group completed the 12-week study.

The reasons for premature termination were similar between treatment groups.
The most common overall reason for premature termination was "unsatisfactory therapeutic response" (10 [5%] subjects in the NGX-4010 group and 9 [5%] subjects in the Control group). One (<1%) subject in the NGX-4010 treatment group terminated the study prematurely due to an AE.

These results of disposition are summarized in Table 5.3.2 (below).

TABLE 5.3.2: SUBJECT DISPOSITION BY TREATMENT GROUP FOR STUDY C116

	NGX-4010, n (%)	Control, n (%)
Total Randomized	402	
	206	196
Completed	187 (91%)	178 (91%)
Discontinuations n (%)	20 (9%)	18 (9%)
Total		
Adverse events	1 (0.4)	0
Unsatisfactory therapeutic response	10 (<1)	9 (2)
Protocol Deviation		
Non compliance	1 (0.5)	1 (0.5)
Lost to follow up	3 (1)	2 (1)
Death	1 (<1)	0
Other	4 (2)	6 (3)

SOURCE: C116, Study report body, p59/598

PROTOCOL DEVIATIONS AND VIOLATIONS

The Applicant classified the protocol violations as major and minor violations. The proportion of study subjects in Study C116 who had at least one major violation was 16 % or (66/402), while the proportion with minor violations was 41 %.

The major violations included the following:

- PHN onset < 6 months prior to onset of study

Baseline average pain score was not in the moderate to severe range as stipulated in the protocol

- Baseline concomitant pain medications increased or decreased by the patient during the study or on study medication changes

The minor violations included the following:

- Missed follow up visits
- Occasional missed screening laboratory tests or ECG's
- Incorrect patient stratification to appropriate cardiovascular risk group at randomization

TABLE 5.3.3: PROTOCOL VIOLATIONS, STUDY C116

Subjects with each Deviation, n (%)	NGX-4010 (n = 206)	Control (n = 196)	Total (n = 402)
Total Subjects with at Least 1 Protocol Deviation	114 (55%)	107 (55%)	221 (55%)
Subjects with Study Visits Outside the Visit Window	64 (31%)	59 (30%)	123 (31%)
Subjects with Missed Lab Draw	37 (18%)	29 (15%)	66 (16%)
Subjects with Missed ECG	25 (12%)	25 (13%)	50 (12%)
Subjects with Missed Study Visits	19 (9%)	21 (11%)	40 (10%)
Subjects with Improper Concomitant Medication Usage	20 (10%)	22 (11%)	42 (10%)
Subjects with Missing Diary Pain Scores	7 (3%)	10 (5%)	17 (4%)
Subjects with an Entry Criteria Deviation	7 (3%)	6 (3%)	13 (3%)
Subjects with Baseline Pain Medication Change	1 (< 1%)	2 (1%)	3 (< 1%)
Subjects with PHN Onset Less Than 180 Days	1 (< 1%)	2 (1%)	3 (< 1%)
Subjects with Randomization Issues[a]	2 (1%)	0	2 (< 1%)
Subjects with Baseline Diary Pain Scores not Between 3 and 9	0	2 (1%)	2 (< 1%)
Subjects with Patch Application Duration < 80% or ≥ 125%	0	1 (< 1%)	1 (< 1%)

Source: Clinical Study Report body (C116), page 60/598

Table 5.3.3 shows that the proportion and nature of the protocol violations were balanced between the groups. As such, the protocol violations did not affect the outcome of the study.

DEMOGRAPHICS:

The average age of subjects enrolled in the study was 71 years. Most subjects were White (92%). Gender distribution was fairly equal, with slightly more female subjects enrolled (53%). No significant differences between NGX-4010 and Control groups were noted for any demographic characteristics. (See Table 5.34).

TABLE 5.3.4: SHOWING THE DEMOGRAPHICS OF THE SUBJECTS RANDOMIZED TO NGX-4010 AND CONTROL ARM

	NGX-4010	CONTROL
N	206	196
Males, n (%)	99 (48.1)	91 (46.4)
Females, n (%)	107 (51.9)	105 (53.6)
Age, (years)		
Mean (SD)	71.5 (11.5)	70.8 (11.7)
Median	73	73
Min, Max	21,94	21,90
< 65	48 (23.3)	52 (26.5)
≥ 65	158 (76.7)	144 (73.5)
< 75	111(53.9)	113 (57.7)
≥ 75	95 (46.1)	83 (42.3)
< 40	3 (1.5)	2 (1.0)
41-50	6 (2.9)	9 (4.6)
51-60	24 (11.7)	25 (12.8)
61-70	50 (24.3)	43 (21.9)
71-80	79 (38.3)	78 (39.8)
≥ 81	44 (21.4)	39 (19.9)
Caucasian/Black/Asian/Other, n (%)		
Asian	5 (2.4)	2 (1.0)
Black	7 (3.4)	6 (3.1)
Caucasian	188 (91.3)	181 (92.3)
Other	6 (2.9)	7 (3.6)

SOURCE: Study report body C116; p 63/598

BASELINE CHARACTERISTICS:
The average duration of PHN pain was similar between the 2 treatment groups; 4.1 years in the NGX-4010 group and 3.7 years in the Control group.

For all subjects, the average pain level at Screening was 4.75 and the average pain level reported during the Baseline period was 5.9, with no statistically significant differences between groups. A similar proportion of subjects in the NGX-4010 (68%) and Control (64%) groups were receiving some form of concomitant pain treatment at Baseline.

More subjects in the NGX-4010 group were using concomitant opioid, non-SSRI antidepressant, and/or anticonvulsant pain medications at Baseline compared to the Control group (50% vs. 38%); a difference that was statistically significant ($p = 0.0209$).

The variation between groups was largely due to more subjects in the NGX-4010 group using anticonvulsant medications (NGX-4010 = 38%; Control = 25%). Planned analyses of primary and selected secondary efficacy variables performed on subsets of the ITT

Population based on concomitant pain medication usage and medication class examined the potential for bias due to this imbalance in number of subjects using concomitant pain medications.
The mean treatment area was 329.8 cm^2 for the NGX-4010 group and 349.2 cm^2 for the Control group ($p = 0.375$).
The baseline characteristics of the treatment population are summarized in Table 5.3.5

TABLE 5.3.5: BASELINE CHARACTERISTICS OF THE TREATMENT POPULATION

	NGX-4010	CONTROL
BASELINE PAIN LEVEL		
Mean (SD)	6.0 (1.6)	5.8 (1.5)
Median	6.1	5.9
Min, Max	3.0, 8.9	2.9, 9.1
TREATMENT AREA SIZE (cm^2)		
≤ 250	88 (42.7)	77 (39.3)
> 250 to ≤ 500	78 (37.9)	75 (38.3)
> 500 to ≤ 750	28 (13.6)	33 (16.8)
> 750	12 (5.8)	11 (5.6)
DURATION OF PHN (years), n (%)		
Mean	4.0 (4.3)	3.7 (4.9)
Median	2.5	2.1
Min, Max	0.5, 25.4	0.4, 28.7
< 6 months	2 (1.0)	2 (1.0)
$\geq$ 6 to <12 months	33 (16.0)	52 (26.5)
$\geq$ 12 to < 24 months	55 (26.7)	43 (21.9)
$\geq$ 2 years to < 5 years	65 (31.6)	60 (30.6)
$\geq$ 5 years	51 (24.8)	39 (19.9)
TAKING CONCOMITANT NEUROPATHIC PAIN MEDICATIONS, n (%)		
No	104 (50.5)	121 (61.76)
Yes	102 (49.5)	75 (38.3)
- Opioids Only	12 (5.8)	11 (5.6)
- Anti-Convulsants Only	78 (38)	50 (25)
- AntiDepressants Only	12 (5.8)	9 (4.6)
- Opioids & Anti-Convulsants	17 (8.3)	9 (4.6)
- Opioids & Anti-Depressants	0 (0)	5 (2.6)
- Anti-Convulsants & Anti-Depressants	9 (4.4)	6(3.1)
- All Three	7(3.4)	4(2)
Taking "other" concomitant pain medication	66(32)	69(35.2)
Taking any treatment (concomitant pain medication and/or Other)	140 (68)	126 (64.3)

SOURCE: p 64/598 of C116 –study report body

The patients who were randomized to C116 all had clinically meaningful disease, in that they:

- Experienced moderate pain with baseline scores of 3 to 9 on an 11 point NPRS system

- Had long standing zoster disease – six months post vesicular crusting (by inclusion), with a mean and median duration of disease four and two years respectively (baseline characteristics of treatment population)
- One-half of patient population was taking concomitant pain medication at baseline

There are important implications when one considers the natural history post herpetic neuralgia.

Longitudinal PHN studies demonstrate that pain associated with shingles usually resolve when the skin lesions heal, which is usually within three months. [Thyregood et al; Pain 128(2007)] The group of study participants tested in the development of NGX-4010 undoubtedly had severe longstanding PHN disease, which is a rare disease outcome. Most patients, (more than 90% of post shingles subjects) tend not to follow this chronic course, with persistent pain despite medical treatments.
The rarity of such long standing 'clinically meaningful' PHN should be kept in mind when generalizing the results of the pivotal trials to the general treatment PHN population.

EFFICACY RESULTS - (Applicant's analysis)

Primary Efficacy Endpoint:

The primary objective of this study was to asses the efficacy of a single 60-minute application of NGX-4010 over 12-weeks in subjects with PHN; the primary efficacy variable was the percent change in "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2–8.

Following a single 60-minute application, the NGX-4010 group demonstrated a − 29.6% change in pain during Weeks 2–8, a result that was statistically superior to the Control group (− 19.9%; p = 0.001) as noted in Table5.3.3 below. The effect of treatment was maintained beyond the 8 week primary assessment period, with the superiority of NGX-4010 treatment compared to Control also demonstrated over the entire study period of 12 weeks (NGX-4010 − 29.9%, Control − 20.4%; p = 0.0016)

TABLE 5.3.6: PRIMARY EFFICACY ANALYSIS (BASELINE PAIN VERSUS THE AVERAGE OF WEEKS 2-8) (ITT POPULATION)

NPRS Scores	NGX-4010 (n = 206)	Control (n = 196)
Baseline		
Mean (SE)	6.0 (0.11)	5.8 (0.11)
95% CI	5.73, 6.18	5.63, 6.05
Actual (Weeks 2–8),		
LS Mean (SE)	4.2 (0.12)	4.7 (0.12)
Change from Baseline		
LS Mean (SE)	−1.7 (0.12)	−1.2 (0.12)
95% CI	−1.94, −1.46	−1.42, −0.92
p-value[a]	0.0024	
Percent Change from Baseline		
LS Mean (SE)	−29.6 (2.04)	−19.9 (2.10)
95% CI	−33.63, −25.59	−24.02, −15.78
p-value[a]	0.0010	

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day –14 to Day –1. The Baseline score was imputed for any missing scores on Days 0-8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.

[a] P-value was computed using gender-stratified ANCOVA to test for a difference between the NGX-4010 and Control groups, with Baseline pain level, pre-L.M.X.4® pain score, and percent change in pain score after L.M.X.4® treatment as covariates.

Source: Table 14.2.1

Source: p 66/598 of C116 –study report body

The sponsor analyzed the endpoint by averaging the pain scores over Weeks 2 through Week 8, and determining the percent change from baseline difference.
This analysis conceptually approximates an “area under the curve” analysis.

The appropriate efficacy endpoint for this indication is a landmark analysis, whereby the pain intensity at baseline and at end-of-study are compared. For the indication of PHN, the accepted post-therapy point is 8 weeks. Ms. Meaker conducted that analysis and found significant differences favoring NGX-4010. (Please see Section 6 of this review for details).

Secondary Efficacy Results (Applicant's analysis)

1) Change in "Average Pain for the Past 24 Hours" NPRS Scores from Baseline to Weeks 2–12 (ITT Population)

The mean percent change in NPRS scores from Baseline to Weeks 2–12 was greater for the NGX-4010 group (-29.9%) compared to the Control group (-20.4%); a difference that was statistically significant (p = 0.0016). Statistically significant greater reduction in mean NPRS scores from Baseline to Weeks 2–12 was also observed in the NGX-4010 group (p = 0.0032). See Table 5.3.7 noted below.

TABLE 5.3.7: CHANGE IN "AVERAGE PAIN FOR THE PAST 24 HOURS" NPRS SCORES FROM BASELINE TO WEEKS 2–12 (ITT POPULATION)

NPRS Scores	NGX-4010 (n = 206)	Control (n = 196)
Baseline		
Mean (SE)	6.0 (0.11)	5.8 (0.11)
95% CI	5.73, 6.18	5.63, 6.05
Actual (Weeks 2–12)		
LS Mean (SE)	4.2 (0.12)	4.7 (0.13)
Change from Baseline		
LS Mean (SE)	−1.7 (0.12)	−1.2 (0.13)
95% CI	−1.96, −1.48	−1.44, −0.94
p-value[a]	0.0032	
Percent Change from Baseline		
LS Mean (SE)	−29.9 (2.09)	−20.4 (2.14)
95% CI	−34.00, −25.79	−24.61, −16.19
p-value[a]	0.0016	

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0–8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.

[a] P-value was computed using gender-stratified ANCOVA to test for a difference between the NGX-4010 and Control groups, with Baseline pain level, pre-L.M.X.4® pain score, and percent change in pain score after L.M.X.4® treatment as covariates.

Source: Table 14.2.2

Source: p 67/598 csr-c116-study-report-body

2) PROPORTION OF RESPONDERS DURING WEEK 2 -8

Responders were defined as subjects who achieved a mean percent decrease from Baseline of ≥30% in "average pain for the past 24 hours" NPRS scores. A summary of the proportion of responders during Weeks 2–8 is presented in Table 5.3.8 noted below.

A greater proportion of NGX-4010 subjects (42%) compared to Control subjects (32%) were considered responders; the difference was statistically significant (p = 0.0343).

A greater proportion of NGX-4010 subjects (26%) compared to control subjects (21% achieved a mean percent decrease from baseline ≥ 50%. However this difference was not statistically significant.

TABLE 5.3.8: PROPORTION OF RESPONDERS FROM BASELINE TO WEEKS 2–8 (ITT POPULATION)

Subjects, n (%)	NGX-4010 (n = 206)	Control (n = 196)
≥ 30% Decrease from Baseline		
Yes	86 (42%)	63 (32%)
No	120 (58%)	133 (68%)
p-value[a]	0.0343	
≥ 50% Decrease from Baseline		
Yes	50 (24%)	39 (20%)
No	156 (76%)	157 (80%)
p-value[a]	0.249	

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0–8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.

[a] P-value was computed using logistic regression to test for a difference between the NGX-4010 and Control groups, with Baseline pain and gender as covariates.

Source: Table 14.2.2

Source: p 68/598 csr-C116 study-report-body

2) PROPORTION OF RESPONDERS DURING WEEK 2 -12

Table 5.3.9, below shows the applicant's analysis of the results of the proportion of responders during Week 2-12.

TABLE 5.3.9: PROPORTION OF RESPONDERS DURING WEEK 2-12 (ITT POPULATION)

Subjects, n (%)	NGX-4010 (n = 206)	Control (n = 196)
≥ 30% Decrease from Baseline		
Yes	90 (44%)	68 (35%)
No	116 (56%)	128 (65%)
p-value[a]	0.0487	
≥ 50% Decrease from Baseline		
Yes	54 (26%)	41 (21%)
No	152 (74%)	155 (79%)
p-value[a]	0.180	

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0–8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.

[a] P-value was computed using logistic regression to test for a difference between the NGX-4010 and Control groups, with Baseline pain and gender as covariates.

Source: Table 14.2.2

Source: p 69/598 csr-C116 study-report-body

The 2-12 week responder analysis supports the notion that NGX-4010 is effective.

3) CUMULATIVE DISTRIBUTION OF MEAN PERCENT CHANGE IN "AVERAGE PAIN FOR THE PAST 24 HOURS" NPRS SCORES FROM BASELINE TO WEEKS 2–8

The cumulative distribution of the percent change in NPRS scores from Baseline to Weeks 2–8 was calculated (Table 5.3.10) and a graphical display was produced (Figure 5.3.10) to demonstrate a more comprehensive representation of treatment effect. A greater proportion of NGX-4010 subjects (83%) than Control subjects (71%) reported decreases in pain from Baseline during Weeks 2–8. The proportion of subjects reporting a decrease in pain was greater for the NGX-4010 group compared to the Control group at all levels of response. Although the difference between groups is narrowed at the ≥ 50% level, larger differences were observed at higher levels of treatment response, with more than twice the number of NGX-4010 subjects compared to Control

TABLE 5.3.10: SHOWING APPLICANT'S ANALYSIS OF RESULTS OF THE CUMULATIVE DISTRIBUTION OF MEAN PERCENT CHANGE IN NPRS SCORES FROM BASELINE TO WEEKS 2–8 (ITT POPULATION)

Percent Change from Baseline, n (%)	NGX-4010 (n = 206)	Control (n = 196)
Any Increase	27 (13%)	49 (25%)
No Change	9 (4%)	8 (4%)
> 0% Decrease	170 (83%)	139 (71%)
≥ 10% Decrease	137 (67%)	105 (54%)
≥ 20% Decrease	112 (54%)	78 (40%)
≥ 30% Decrease	86 (42%)	63 (32%)
≥ 40% Decrease	72 (35%)	51 (26%)
≥ 50% Decrease	50 (24%)	39 (20%)
≥ 60% Decrease	39 (19%)	24 (12%)
≥ 70% Decrease	25 (12%)	12 (6%)
≥ 80% Decrease	16 (8%)	6 (3%)
≥ 90% Decrease	9 (4%)	1 (< 1%)
100% Decrease	2 (1%)	0

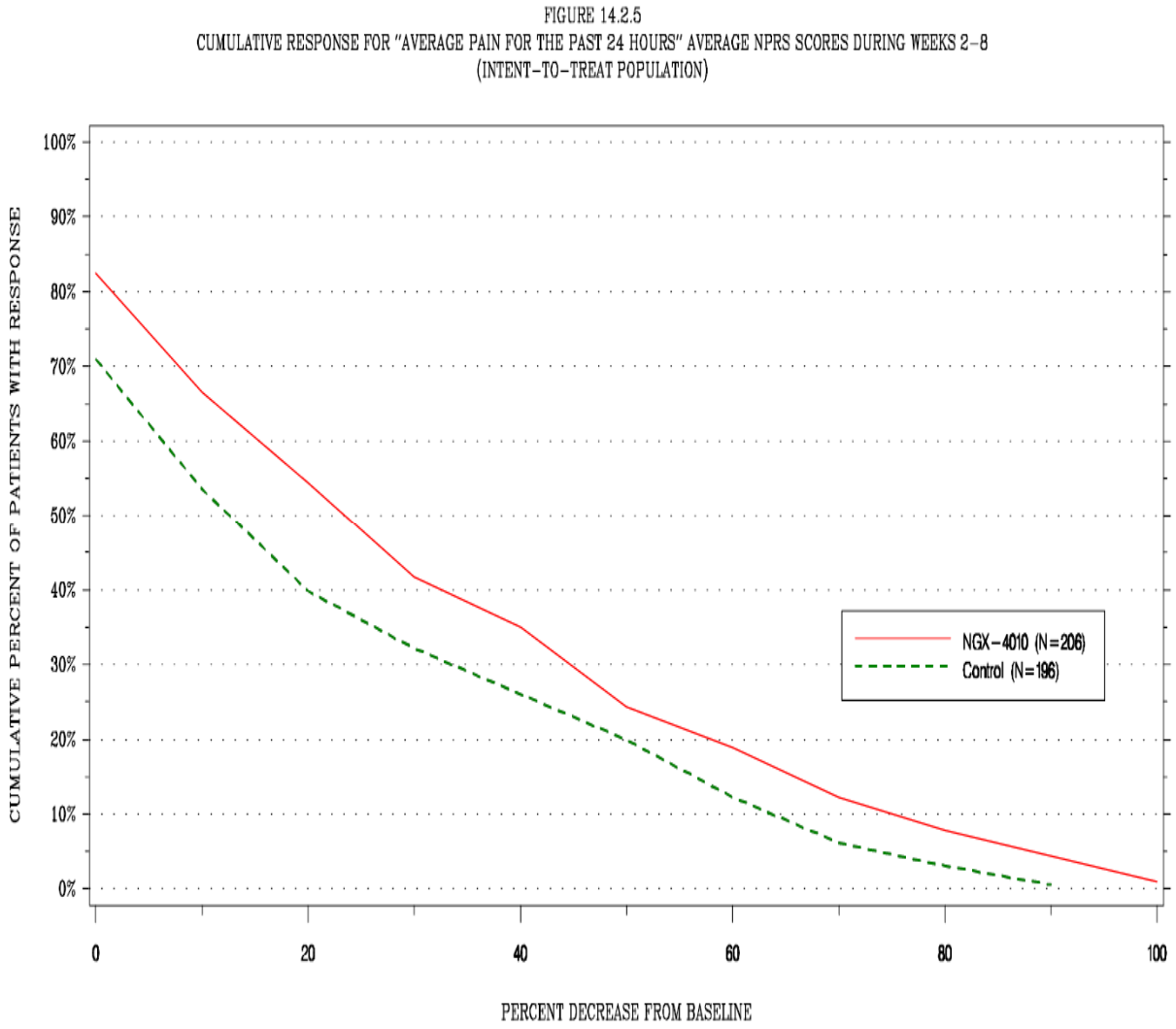
Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0–8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.
Source: Table 14.2.4

Source: p70/598 –csrC116 -study -report –body

The proportion of subjects reporting a decrease in pain was greater for the NGX-4010 group compared to the Control group at all levels of response. Although the difference between groups is smaller at the ≥ 50% level, larger differences were observed at higher levels of treatment response, with more than twice the number of NGX-4010 subjects compared to Control subjects experiencing mean decreases in pain from Baseline of ≥ 70% (25 vs.12 subjects), ≥ 80% (16 vs. 6 subjects), and ≥ 90% (9 vs. 1 subjects).

This is shown in the figure 5.3.11 below, where the cumulative percent of patients with response is plotted against the percent decrease from baseline. For subjects experiencing a worsening of their pain, nearly twice as many control subjects (25%) as NGX-4010 subjects (13%) reported an increase ion mean percent change from baseline to Weeks 2-8.

FIGURE 5.3.11: SHOWING RESULT OF THE CUMULATIVE RESPONSE FOR "AVERAGE PAIN FOR THE PAST 24 HOURS" AVERAGE NPRS SCORES DURING WEEK 2-8 (ITT POPULATION)



5) CUMULATIVE DISTRIBUTION OF MEAN PERCENT CHANGE IN "AVERAGE PAIN FOR THE PAST 24 HOURS" NPRS SCORES FROM BASELINE TO WEEKS 2–12

A summary of the cumulative distribution of the percent change in NPRS scores from Baseline to Weeks 2–12 is presented in Table 5.3.12 and a graphical display is provided in Figure 5.3.12

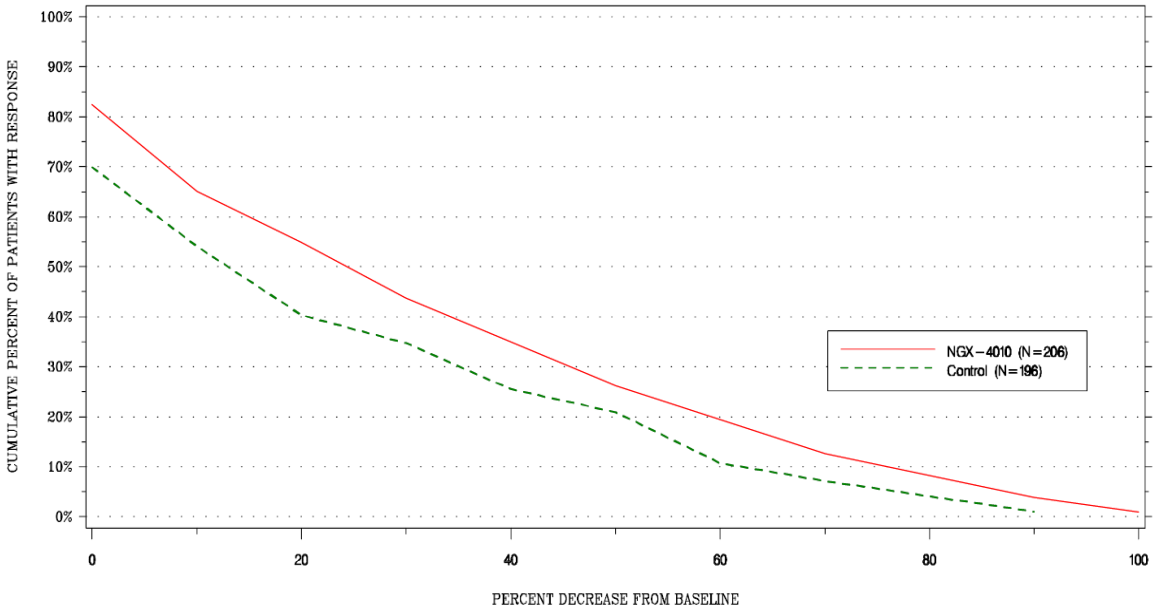
TABLE 5.3.12: SHOWING APPLICANT'S RESULT OF THE CUMULATIVE DISTRIBUTION OF MEAN PERCENT CHANGE IN NPRS SCORES BASELINE TO WEEK 2-12 (ITT POPPULATION)

Percent Change from Baseline, n (%)	NGX-4010 (n = 206)	Control (n = 196)
Any Increase	30 (15%)	52 (27%)
No Change	6 (3%)	7 (4%)
> 0% Decrease	170 (83%)	137 (70%)
≥ 10% Decrease	134 (65%)	106 (54%)
≥ 20% Decrease	113 (55%)	79 (40%)
≥ 30% Decrease	90 (44%)	68 (35%)
≥ 40% Decrease	72 (35%)	50 (26%)
≥ 50% Decrease	54 (26%)	41 (21%)
≥ 60% Decrease	40 (19%)	21 (11%)
≥ 70% Decrease	26 (13%)	14 (7%)
≥ 80% Decrease	17 (8%)	8 (4%)
≥ 90% Decrease	8 (4%)	2 (1%)
100% Decrease	2 (1%)	0

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0–8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.
Source: Table 14.2.4

Source: p 71/598 csr-Study C116-study-report-body

FIGURE 5.3.12: SHOWING APPLICANT'S RESULT OF THE CUMULATIVE RESPONSE FOR "AVERAGE PAIN FOR THE PAST 24 HOURS' AVERAGE NPRS SCORES DURING WEEKS 2-12 (ITT POPULATION) STUDY C116

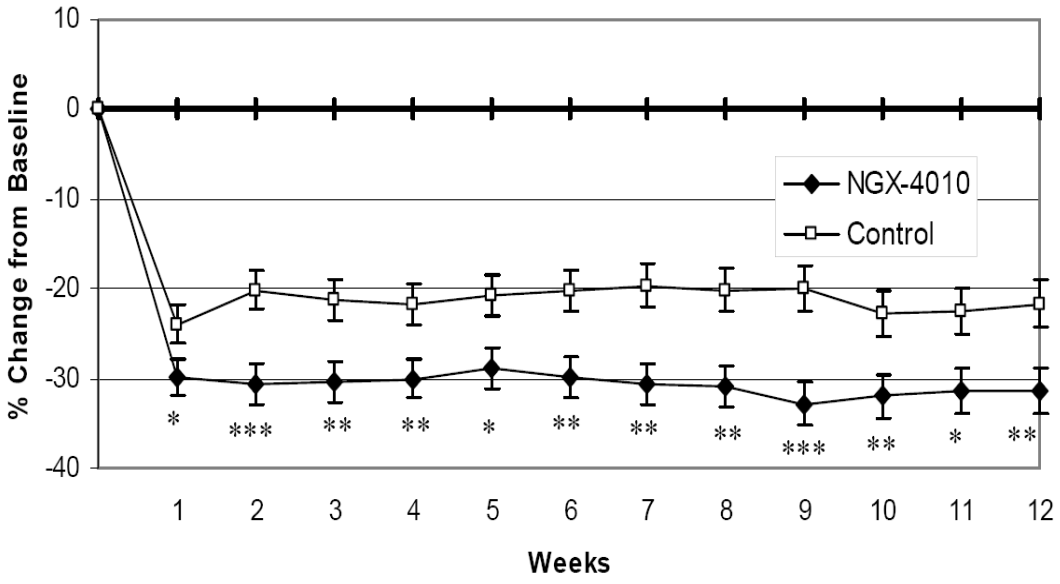


Source: p 72/598 csr-C116 study-report-body

6) WEEKLY CHANGE IN NPRS SCORES

A summary of the percent change in "average pain for the past 24 hours" NPRS scores from Baseline is presented by week in Figure 5.3.11 (shown below). The mean percent changes in NPRS scores from Baseline for the NGX-4010 and Control groups were maintained at Week 8 (− 30.9% and − 20.1%, respectively; p = 0.0015) and at Week 12 (− 31.4% and − 21.6%, respectively; p = 0.0099).

FIGURE 5.3.13: SHOWING THE APPLICANT'S RESULT OF THE PERCENT CHANGE IN "AVERAGE PAIN FOR THE PAST 24 HOURS NPRS SCORES BY WEEK (ITT POPULATION), IN THE CONTROL AND TREATMENT ARMS



Source: p 73/598 csr-C116 study-report-body

7) PROPORTION OF SUBJECTS WITH A 30% AND 50% OR GREATER DECREASE BY WEEK

A summary of the proportion of subjects achieving greater than 30% and greater than 50% decrease in their "average pain for the past 24 hours" NPRS scores for each week is presented in Table 5.3.14.

At each week, a greater proportion of NGX-4010 subjects (range = 43% to 48%) were considered responders (≥30% mean pain reduction) compared to Control subjects (range = 31% to 40%).

Similarly, at each week, a greater proportion of NGX-4010 subjects (range = 25% to 34%) experienced ≥ 50% mean pain reduction compared to Control subjects (range = 18% to 23%).

TABLE 5.3.14: SHOWING THE PROPORTION OF RESPONDERS BY WEEK (ITT POPULATION)

Proportion of Responders	NGX-4010		Control		p-value[a]
	N	n (%)	N	n (%)	
≥ 30% Decrease from Baseline					
Week 1	203	89 (44%)	189	75 (40%)	0.361
Week 2	202	89 (44%)	189	59 (31%)	0.0063
Week 3	202	88 (44%)	189	65 (34%)	0.0452
Week 4	202	90 (45%)	190	69 (36%)	0.077
Week 5	199	85 (43%)	186	68 (37%)	0.189
Week 6	198	87 (44%)	186	69 (37%)	0.140
Week 7	197	85 (43%)	185	65 (35%)	0.094
Week 8	196	90 (46%)	184	67 (36%)	0.050
Week 9	190	89 (47%)	180	64 (36%)	0.0202
Week 10	187	87 (47%)	177	65 (37%)	0.0373
Week 11	187	90 (48%)	177	70 (40%)	0.064
Week 12	185	85 (46%)	172	64 (37%)	0.060
≥ 50% Decrease from Baseline					
Week 1	203	51 (25%)	189	34 (18%)	0.080
Week 2	202	60 (30%)	189	36 (19%)	0.0141
Week 3	202	57 (28%)	189	40 (21%)	0.089
Week 4	202	54 (27%)	190	37 (19%)	0.072
Week 5	199	53 (27%)	186	39 (21%)	0.174
Week 6	198	57 (29%)	186	36 (19%)	0.0250
Week 7	197	63 (32%)	185	41 (22%)	0.0264
Week 8	196	59 (30%)	184	39 (21%)	0.0419
Week 9	190	65 (34%)	180	40 (22%)	0.0083
Week 10	187	59 (32%)	177	41 (23%)	0.053
Week 11	187	55 (29%)	177	37 (21%)	0.0430
Week 12	185	55 (30%)	172	40 (23%)	0.126

Note: Baseline pain level was defined as the mean of all available NPRS scores from Day −14 to Day −1. No imputation was performed for missing scores.

[a] P-value was computed using logistic regression to test for a difference between the NGX-4010 and Control groups, with Baseline pain and gender as covariates.

Source: Table 14.2.7

Source: p 75/598 csr-C116 study-report-body

SAFETY- Study C116

A complete discussion of the integrated safety for NGX-4010 is in Section 7 of this review. Briefly, in Study C116, the most common adverse events were related to the application site and included erythema and pain. There were no deaths, 16 SAE's, and one adverse discontinuation in the active study arm that led to study discontinuation.

CONCLUSIONS (Study C116)
The applicant showed that treatment with NGX-4010, a high-concentration capsaicin (640 mcg/cm^2) patch for 60 minutes was efficacious and provided a stable reduction in pain over a 8-week period in subjects suffering from PHN.

Most of the application site-related AE's in both treatment groups were mild or moderate in severity. A higher proportion of subjects in the NGX-4010 group experienced severe treatment-emergent and treatment related AE's, with the higher incidence in the NGX-4010 group being mostly due to application site-related events.

INDIVIDUAL STUDY REPORT- STUDY C117

The objectives, study design, inclusion and exclusion criteria, permitted and disallowed concomitant medication and rescue medications, primary efficacy endpoints, safety measures, visit schedule, statistical analysis plan and definition of analyzed populations were essentially identical in both pivotal studies. The protocol for Study C116 was described in detail, preceding. There were no substantive differences between the two studies, except for the following:

- Study C117 utilized the following secondary endpoints that were not used in Study C116
  - Absolute change in "average pain for the past 24 hours" NPRS scores from Baseline during Weeks 2 to 8 and Weeks 2 to 12
  - Proportion of subjects with a mean absolute reduction in "average pain for past 24 hours" NPRS score of 2 points or more from Baseline during Weeks 2 to 8 or Weeks 2 to 12
  - Clinical Global Impression of Change
- Study C116 utilized the weekly proportion of subjects with a $\geq$ 30% decrease and weekly proportion of subjects with a $\geq$ 50% decrease in " average pain for the past 24 hours" NPRS score from baseline

Although the results of the individual pivotal studies were different, the conclusions in Study C117 were supportive of the conclusions reached in Study C116.

The Results of Study C117 are discussed below:

RESULTS:

DISPOSITION

A total of 416 subjects received study treatment; 212 subjects in the NGX-4010 group and 204 subjects in the Control group. Two subjects randomized to the NGX-4010 group never received treatment, (one had an allergic reaction to the topical anesthetic pre-treatment and one subject was found not to meet entry criteria). Thirty eight subjects terminated the study prematurely; 20 subjects in the NGX−4010 group (including the two subjects who did not receive treatment) and 18 subjects in the Control group.

The overall reasons for premature termination were "lost to follow-up" (4 [2%] subjects in the NGX-4010 group and 5 [2%] subjects in the Control group), and "other" (8 [4%] subjects in the NGX-4010 group and 1 [<1%] subject in the Control group). Three subjects (1%) in each treatment group terminated prematurely due to an AE. Two subjects who were randomized to the NGX-4010 group never received study treatment; 1 subject due to an AE related to the topical anesthetic and 1 subject who did not meet study entry criteria. (See Table 5.3.15 noted below).

TABLE 5.3.15: SUBJECT DISPOSITION BY TREATMENT GROUP (C117)

	NGX- 4010, n (%)	Control, n (%)
Total Screened	416	
Randomized	212	204
Completed	194 (91)	186 (91)
Discontinuations n (%)	20 (9)	18 (9)
Total		
Adverse events	3 (1)	3 (1)
Unsatisfactory therapeutic response	1 (<1)	5 (2)
Protocol Deviation		
Non compliance	3	4 (2)
Lost to follow up	4 (2)	5 (2)
Death	1 (<1)	0
Other	8 (4)	1 (<1)

SOURCE: Study C117-study report body p62/584

PROTOCOL DEVIATIONS AND VIOLATIONS:

The study investigators reported the protocol violations for C117. They were classified as major and minor violations by the applicant. The proportion of study subjects in Study C117 who had at least one major violation was 20% or (82/416), while the proportion of minor violations was 12.5 %.

The major violations included the following:

- PHN onset < 6 months prior to onset of study
- Baseline average pain score was not in the moderate to severe range as stipulated in the protocol
- Baseline concomitant pain medications increased or decreased by the patient during the study or on study medication changes

The minor violations included the following:

- Missed follow up visits
- Occasional missed screening laboratory tests or ECG's
- Incorrect patient stratification to appropriate cardiovascular risk group at randomization

Table 5.3.16 shows that the proportion and nature of the protocol violations were balanced between the groups. As such, the protocol violations did not affect the outcome of the study.

TABLE 5.3.16: SHOWING MAJOR PROTOCOL VIOLATIONS IN C117

Subjects with each Deviation, n (%)	NGX-4010 (n = 212)	Control (n = 204)
Violations of entry criteria	15 (7%)	15 (7%)
Pain medication changes 14 days or less before treatment (Day 0)	1 (<1%)	1 (<1%)
Baseline average pain score outside the range of 3.0 to 9.0	3 (1%)	1 (<1%)
Less than 6 months between reported onset date of PHN and treatment day	5 (2%)	7 (3%)
Use of topical pain medication in the treatment area during the screening and post-treatment period	6 (3%)	6 (3%)
Deviations from therapeutic procedure	3 (1%)	0
Actual patch application less than 80% or more than 125% of assigned duration	3 (1%)	0
Deviations during the follow-up period	28 (13%)	24 (12%)
Less than 50% of on-study pain scores for the parameter "Average pain for the past 24 hours" between study days 8 and 56 (inclusive)	0	3 (1%)
On-study pain medication changes	28 (13%)	22 (11%)

Source: Table 14.1.4

Source: Clinical Study Report body (C117) p 63/584

DEMOGRAPHICS

In Study C117, the demographic characteristics of the NGX-4010 group (n = 212) were similar to the Control group (n = 204). The average age of subjects enrolled in the study was approximately 70 years. Most subjects were Caucasian (93% of NGX-4010 and 94% of Control subjects) and non-Hispanic (97% of NGX-4010 and 98% of Control subjects). Gender distribution was fairly equal, with slightly more female subjects enrolled overall (56% of NGX-4010 and 53% of Control subjects). See Table 5.3.17 noted below.

TABLE 5.3.17: SHOWING SUBJECT DEMOGRAPHICS BY TREATMENT GROUP

	NGX-4010	CONTROL
N	212	204
Males, n (%)	93 (43.9)	97 (47.5)
Females, n (%)	119 (56.1)	107 (52.5)
Age, (years)		
Mean (SD)	70.2 (12.3)	70.4 (12.9)
Median	73.0	73.0
Min, Max	34.0, 91.0	23, 91
< 65	64 (30.2)	56 (27.5)
≥ 65	148 (69.8)	148 (72.5)
< 75	114 (53.8)	110 (53.9)
≥ 75	98 (46.2)	94 (46.1)
≤ 40	5 (2.4)	7 (3.4)
41-50	13 (6.1)	10 (4.9)
51-60	22 (10.4)	17 (8.3)
61-70	54 (25.5)	49 (24.0)
71-80	72 (34)	77 (37.7)
≥ 81	46 (21.7)	44 (21.6)
Caucasian/Black/Asian/Other, n(%)		
Asian	3 (1.4)	2(1.0)
Black	6 (2.8)	8 (3.9)
Caucasian	197 (92.9)	191 (93.6)
Other	6 (2.8)	3 (1.5)

SOURCE: C117, Study report body p64/584

BASELINE CHARACTERISTICS
The mean and median baseline pain ranged from 5.7 to 5.8, and was similar in both treatment arms. The size of the treatment area was also similar between both treatment arms.

The mean and median duration of PHN disease was three and two years respectively and was similar in both treatment arms.

Approximately one-half of the treatment population was receiving concomitant treatment medication for PHN at study entry. See Table 5.3.18 noted below.

TABLE 5.3.18: SHOWING BASELINE CHARACTERISTICS OF STUDY POPULATION

	NGX-4010	CONTROL
BASELINE PAIN LEVEL		
Mean (SD)	5.7 (1.6)	5.8 (1.6)
Median	5.7	5.8
Min, Max	2.1, 9.2	2.8, 9.0
TREATMENT AREA SIZE (cm^2)		
< 250	95 (45.0)	98 (48)
> 250 to 500	72 (34.1)	65 (31.9)
> 500 to <750	33 (15.6)	29 (14.2)
> 750	11 (5.2)	12 (5.9)
DURATION OF PHN (years), n (%)		
Mean (SD)	3.1 (3.5)	3.3 (3.7)
Median	2.0	2.1
Min, Max	0.1, 26.4	0.3, 26.6
< 6 months	1 (0.5)	3 (1.5)
≥ 6 to <12 months	54 (25.5)	52 (25.5)
≥ 12 to < 24 months	48 (22.6)	43 (21.1)
≥ 2 years to < 5 years	75 (35.4)	66 (32.4)
≥ 5 years	34 (16.0)	40 (19.6)
TAKING CONCOMITANT NEUROPATHIC PAIN MEDICATION, n (%)		
No	95 (44.8)	88 (43.1)
Yes (Any)	117 (55.2)	116 (56.9)
o Opioids only	13 (6.1)	16 (7.8)
o Anticonvulsants only	42 (19.8)	53 (26.0)
o Anti-Depressants Only	14 (6.6)	17 (8.3)
o Opioids and anticonvulsant	5 (2.4)	0 (0)
o Opioids and Anti-Depressants	15 (7.1)	9 (4.4)
o All 3	7 (3.3)	5 (2.5)
Taking "other" concomitant pain medication	64 (30.2)	68 (3.3)
Taking any treatment (concomitant pain medication and/or Other)	151 (71.2)	150 (73.5)

SOURCE: C117 study report body p67/584

Concomitant neuropathic pain medication includes use of antidepressants (non-SSRI), anticonvulsants, or opioids on Day – 1 and for at least 7 consecutive days.

"Other" pain medication includes NSAIDS, salicylates, and acetaminophen that were used on Day – 1 and were taken for a total duration of at least 7 consecutive days.

The patients who were randomized to C117 all had clinically meaningful disease, in that they:

- Experienced moderate pain with baseline scores of 3 to 9 on an 11 point NPRS system
- Had long standing zoster disease – six months post vesicular crusting (by inclusion), with a mean and median duration of disease three and two years respectively (baseline characteristics of treatment population)
- One-half of patient population was taking concomitant pain medication at baseline

There are important implications when one considers the natural history post herpetic neuralgia.

Longitudinal PHN studies demonstrate that pain associated with shingles usually resolve when the skin lesions heal, which is usually within three months. [Thyregood et al ; Pain 128(2007)148-156.]
The group of study participants tested in the development of NGX-4010 undoubtedly had severe longstanding PHN disease, which is a rare disease outcome. Most patients, (more than 90% of post shingles subjects,) tend not to follow this chronic course, with persistent pain that persists for years after the rash heals. The rarity of such long standing PHN should be kept in mind when generalizing the results of the pivotal trials (Studies C116 and C117) to the general treatment PHN population.

PRIMARY EFFICACY RESULTS

PERCENT CHANGE IN "AVERAGE PAIN FOR THE PAST 24 HOURS" NPRS SCORES FROM BASELINE TO WEEKS 2-8

A summary of the change and percent change in the "average pain for the past 24 hours" NPRS scores from Baseline to Weeks 2-8 is presented in Table 5.3.19.
The mean Baseline NPRS scores for the NGX-4010 and Control groups were 5.7 and 5.8, respectively. The mean percent change in NPRS scores from Baseline to Weeks 2-8 was greater in the NGX-4010 group (−32.0%) compared to the Control group (−24.4%), a difference that was statistically significant ($p = 0.0108$).

The absolute mean change in NPRS scores from Baseline to Week 2–8 was also statistically significantly greater in the NGX-4010 group (-1.7 points) compared to the Control group (-1.3 points; $p=0.0344$).

The sponsor analyzed the endpoint by averaging the pain scores over Weeks 2 through Week 8, and determining the percent change from baseline difference. This analysis conceptually approximates an "area under the curve" analysis.

The appropriate efficacy endpoint for this indication is a landmark analysis, whereby the pain intensity at baseline and at end-of-study is compared. For the indication of PHN, the accepted post-therapy point is 8 weeks. Ms. Meaker conducted that analysis and found significant differences favoring NGX-4010. Please see Section 6 of this review for details

TABLE: 5.3.19: SHOWING MEAN CHANGE AND MEAN PERCENTAGE CHANGE IN NPRS SCORES FROM BASELINE IN STUDY C117, WEEK 2 -8 (ITT POPULATION)

NPRS Scores	NGX-4010 (n = 212)	Control (n = 204)
Baseline		
Mean (SE)	5.7 (0.11)	5.8 (0.11)
95% CI	5.46, 5.89	5.54, 5.99
Actual (Weeks 2-8),		
LS Mean (SE)	4.0 (0.12)	4.4 (0.12)
Change from Baseline		
LS Mean (SE)	−1.7 (0.12)	−1.3 (0.12)
95% CI	−1.93, −1.47	−1.58, −1.11
p-value[a]	0.0344	
Percent Change from Baseline		
LS Mean (SE)	−32.0% (2.07)	−24.4% (2.11)
95% CI	−36.06, −27.92	−28.57, −20.27
p-value[a]	0.0108	

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day −14 to Day −1. The Baseline score was imputed for any missing scores on Days 0-8 and any consecutive missing scores that continued from Day 8. If the NPRS score was missing for any day past Day 8, then the last available score was imputed for the missing value.

a. P-value was computed using gender-stratified ANCOVA to test for a difference between the NGX-4010 and Control groups, with Baseline pain level as a covariate.

Source: Table 14.2.1

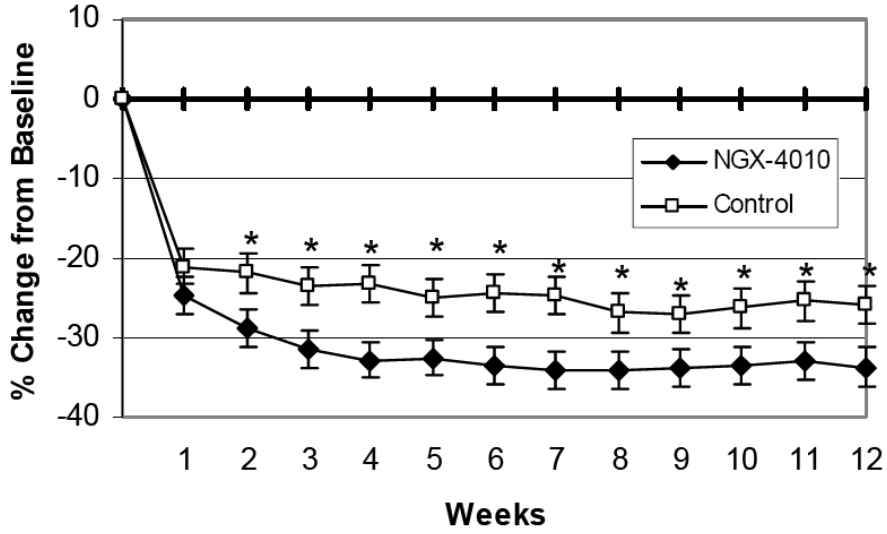
Source p 69 (Clinical Study Report –C117)

SECONDARY EFFICACY RESULTS

1) Cumulative Distribution of Mean Percent Change in "Average Pain for the Past 24 Hours" NPRS Scores from Baseline to Weeks 2–12

Evaluation of the cumulative distribution of mean percent change from Baseline demonstrated that more NGX-4010 subjects than Control subjects reported decreases in pain during Weeks 2-8 at every level of response (i.e., > 0%, ≥ 10%, ≥ 20%, etc.), except the ≥ 80% and ≥ 90% levels where responses were similar between the two groups.
A summary of the cumulative distribution of the percent change in NPRS scores from Baseline to Weeks 2–12 is presented in Table 5.3.20 and a graphical display is provided in Figure 5.3.20.

FIGURE 5.3.20 SHOWING PER CENT CHANGE FROM BASELINE OF NPRS SCORES BY WEEK REPEATED MEASURES ANCOVA (ITT POPULATION), STUDYC117



Note: Baseline pain level was defined as the mean of all available NPRS scores from Day –14 to Day –1. No imputation was performed for missing scores.
P-value was computed using a gender-stratified mixed effect repeated measures ANCOVA to test for difference between NGX-4010 and Control groups. This model includes treatment, treatment*sex, treatment*week effect with Baseline pain as a covariate.
* = $p<0.05$
Source: Table 14.2.6C

SOURCE: C117-study-report-body p76/584

Over 40% of NGX-4010 treated subjects met the protocol-specified definition of "responder" (that is achieved ≥ 30% decrease in mean pain score from Baseline). The proportion of responders was statistically greater for the NGX-4010 group during Weeks 2-8 (46%; p = 0.0196) and Weeks 2-12 (47%; p = 0.0212) compared to the Control group (34% and 35%, respectively). The proportion of subjects who achieved ≥ 50% decrease in pain scores from Baseline was also statistically greater for the NGX-4010 group during Weeks 2−8 (29%; p = 0.0422) and Weeks 2−12 (30%; p=0.0349) compared to the Control group (21% and 20%, respectively).

In a week-by-week comparison, NGX-4010 subjects achieved statistically significant mean percent reductions in NPRS scores compared to the Control group as early as Week 2 (p = 0.0391).

Pain reduction remained greater in the NGX-4010 group compared to the Control group throughout the 12-week study, with statistically greater reductions in pain observed from Week 2 through Week 12 ($p < 0.05$ at each week). In a daily comparison of NPRS scores, the NGX-4010 group demonstrated an approximately 22% reduction in pain on Day 1, which continued to increase during subsequent study days.

The onset of efficacy, defined as the first of 2 consecutive days with statistically significantly greater percent reductions in NPRS score after Day 5, was observed beginning at Day 19. Larger pain reductions continued to be observed in the NGX-4010 group throughout the remainder of the study (Day 84). These data provide further evidence that the treatment effect was observed early and remained stable through the 12-week study period.

- SAFETY RESULTS (C117)

A complete discussion of the integrated safety for NGX-4010 is in Section 7 of this review. Briefly, in Study C117, the most common adverse events were related to the application site and included edema and pain. There was one death, ten SAE's and six adverse discontinuations in this study.

CONCLUSION:

In conclusion, treatment with NGX-4010, a high-concentration capsaicin (640 mcg/cm^2) patch, for 60 minutes was generally safe and well tolerated. A single NGX-4010 treatment was shown to be efficacious and provided a stable reduction in pain over a 12-week period in subjects suffering from PHN.

One death occurred during this study. The subject died from an SAE of diverticulitis, which was judged unrelated to study medication.

6. Integrated Review of Efficacy

Efficacy Summary and Conclusions

The Applicant provided substantial evidence of efficacy for the indication of pain due to postherpetic neuralgia primarily from two Phase 3 studies, Studies C116 and C117. These studies showed that NGX-4010 was superior to a low-dose capsaicin control in treating the pain of postherpetic neuralgia (PHN). The study participants who enrolled in the pivotal trials consisted of a subset of adults with clinically meaningful PHN that is subjects who were more than six months post vesicular PHN crusting rash and a baseline pain score of 3-9 on an 11-point Numerical Pain Rating Scale (NPRS). I note that these patients had a mean duration of PHN of 4 years and that over 50% of the study participants were using prescription medication to help to control the pain of PHN.

NGX-4010 (640 mcg/cm^2) or a low-dose capsaicin control patch (3.2 mcg/cm^2) were applied as a single 60-minute application. A combined total of 818 subjects were evaluated for efficacy in Studies C116 and C117, with 418 subjects receiving a 60-minute NGX-4010 treatment and 400 subjects receiving the lower concentration capsaicin control treatment. Ninety-one (91%) of subjects in both the 60-minute NGX-4010 group and the Control group completed the 12-week portion of these studies.

Overall, the demographic and baseline pain characteristics were similar between the NGX-4010 and Control groups for each of the individual studies. The mean and median duration of PHN was 4 years and 2 years respectively. The average age was 69 to 72 years and the majority of subjects were Caucasian. Gender distribution was fairly equal, with slightly more female than male subjects enrolled. The baseline mean pain scores across the pivotal studies C116 and C117 ranged from 5.7 to 6.0. More than 91% of study participants in both treatment arms completed the 12 week study. The reasons for study discontinuation were balanced in both treatment arms.

Patients who entered the study on stable doses of pain-control medications were required to keep dosing stable throughout the duration of the study. Approximately half of the patients were taking neuropathic pain medications (defined as anticonvulsants, non-SSRI antidepressants, or opioids) for their PHN at study entry.

Prior to study patch application an unapproved, marketed topical anesthetic (LMX4, 4% lidocaine cream) was applied to the treatment area for 60 minutes. Patients were permitted to use local cooling and additional analgesic medications (primarily an oral narcotic) for treatment-related discomfort as needed through Day 5.

The protocol-specified primary efficacy endpoint was the average percent change from baseline in “average pain for the past 24 hours” numerical pain rating scale (NPRS) during Weeks 2 to 8. Patients recorded their pain daily in a diary. In Study C116, following a single 60-minute application of NGX-4010, NGX-4010 demonstrated a statistically superior reduction in pain compared to the control group, during the primary assessment period Week 2 to 8. The percent change in the average pain for the past 24 hours as measured by the NPRS scores from Baseline to Week 8 was -30.0 in the active arm, and -19.4 in the control arm, which yielded a significant

p-value of 0.0013. Similarly, in Study C117, the percent change in the pain index in the active arm was -33.6 and -26.5 in the control arm, which yielded a significant p-value of 0.036.

This effect was independent of the imputation algorithm and was consistent during both the Weeks 2 to 8 and Weeks 2 to 12 analysis periods following treatment. These results support the notion that NGX-4010 treatment is more effective than control in reducing the pain associated with PHN for a period of up to 12 weeks after treatment.

That being said, the protocol-specified primary efficacy endpoint, was, in essence, an "area under curve" (AUC) approach. An AUC approach may overestimate the significance of differences in pain intensity that occur early in a long-term study, a "landmark" analysis whereby the difference in pain intensity at baseline and end-of-study (generally averaged over one week) are compared. FDA's statistician Ms. Meaker re-analyzed the data for Studies C116 and C117. Ms. Meaker's landmark analysis is summarized in Tables 6.1 and 6.2, following.

TABLE 6.1: COMPARISON OF PROTOCOL-SPECIFIED AND LANDMARK ANALYSIS, PRIMARY EFFICACY ENDPOINT, STUDY C116

Change in Average Pain from Baseline		Low concentration 3.2 mcg/cm^2 [CONTROL] (n=196)	High concentration 640 mcg/cm^2 NGX-4010 (n=206)
Applicant's Primary Analysis:* Percent Change from Baseline to Average of Weeks 2 through 8	LSMeans (SE) Diff. p-value vs. control	-19.9 (2.0)	-29.6 (2.0) 9.7 0.001
Applicant's Secondary Analysis:* Actual Change from Baseline to Average of Weeks 2 through 8	LSMeans (SE) Diff. p-value vs. control	-1.2 (0.1)	-1.7 (0.1) 0.5 0.002
DAARP Preferred Analysis:** Percent Change from Baseline to Week 8	LSMeans (SE) Diff. p-value vs. control	-19.2 (2.3)	-29.9 (2.3) 10.7 0.001
DAARP Alternative Analysis:** Actual Change from Baseline to Week 8	LSMeans (SE) Diff. p-value vs. control	-1.1 (0.1)	-1.7 (0.1) 0.6 0.002

* P-value from ANCOVA model with terms for treatment + gender + baseline pain score + pre-LMX4 pain score + percent change in pain score after LMX4
** P-value from ANCOVA model with terms for treatment + gender + baseline pain score (as planned in protocol)
SOURCE: K Meaker's (FDA statistician) review

Ms. Meaker writes of the landmark analysis, "In Study 116, the results for the applicant's analyses, which averaged pain scores over weeks 2 through 8, were nearly the same as the results usning the DAARP landmark timepoint of Week 8. This suggests that the pain scores were consistent across weeks 2 through 8. The applicant presented results (Section 11.4.1.3.3; Figure 2) which support this conclusion."

TABLE 6.2: COMPARISON OF PROTOCOL-SPECIFIED AND LANDMARK ANALYSIS, PRIMARY EFFICACY ENDPOINT, STUDY C117

Change in Average Pain from Baseline		Low concentration 3.2 mcg/cm^2 [CONTROL] n=196	High concentration 640 mcg/cm^2 n=206
Applicant's Primary Analysis:* Percent Change from Baseline to Average of Weeks 2 through 8	LSMeans (SE) Diff. p-value vs. control	-24.4 (2.1)	-32.0 (2.1) 7.6 0.011
Applicant's Secondary Analysis:* Actual Change from Baseline to Average of Weeks 2 through 8	LSMeans (SE) Diff. p-value vs. control	-1.3 (0.1)	-1.7 (0.1) 0.4 0.034
DAARP Preferred Analysis:* Percent Change from Baseline to Week 8	LSMeans (SE) Diff. p-value vs. control	-26.3 (2.4)	-32.9 (2.3) 6.6 0.046
DAARP Alternative Analysis:* Actual Change from Baseline to Week 8	LSMeans (SE) Diff. p-value vs. control	-1.4 (0.1)	-1.7 (0.1) 0.3 0.125

* P-value from ANCOVA model with terms for treatment + gender + baseline pain score (as planned in protocol)
SOURCE: K. Meaker's (FDA statistician) review

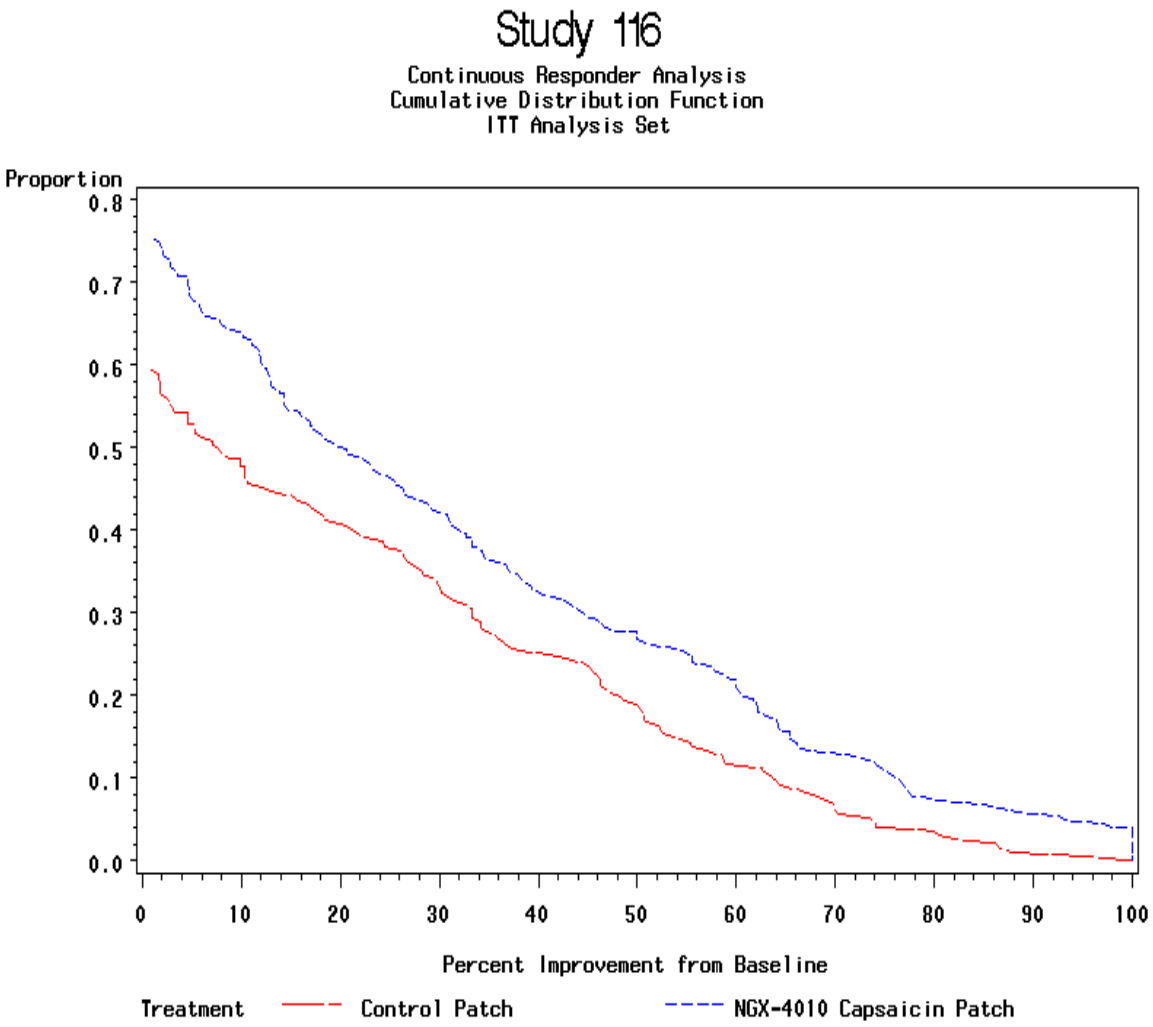
Ms. Meaker writes of the landmark analysis, "In Study 117, the results for the applicant's analyses, which averaged pain scores over weeks 2 through 8, indicated a significant difference between the low concentration (control group) and the high concentration patch. Using the Week 8 landmark analysis preferred by DAARP, the high concentration was statistically significantly superior to the control group for the percent change from baseline to week 8, but was not statistically significantly different for the actual change from baseline. This result suggests that the difference between the groups at Week 8 was not as large as the average

difference over the period from week 2 through 8. The applicant provided the result by week in Section 11.4.1.3.1 and Figure 2 of the study report which supports this. The non-significant test result for the actual change from baseline to week 8 does not contradict the other results.

The group means and differences between the groups were in a consistent direction in both studies. Study 117 provides supportive evidence to the results seen in study 116. There is sufficient evidence in these two studies to support the high concentration patch for this indication."

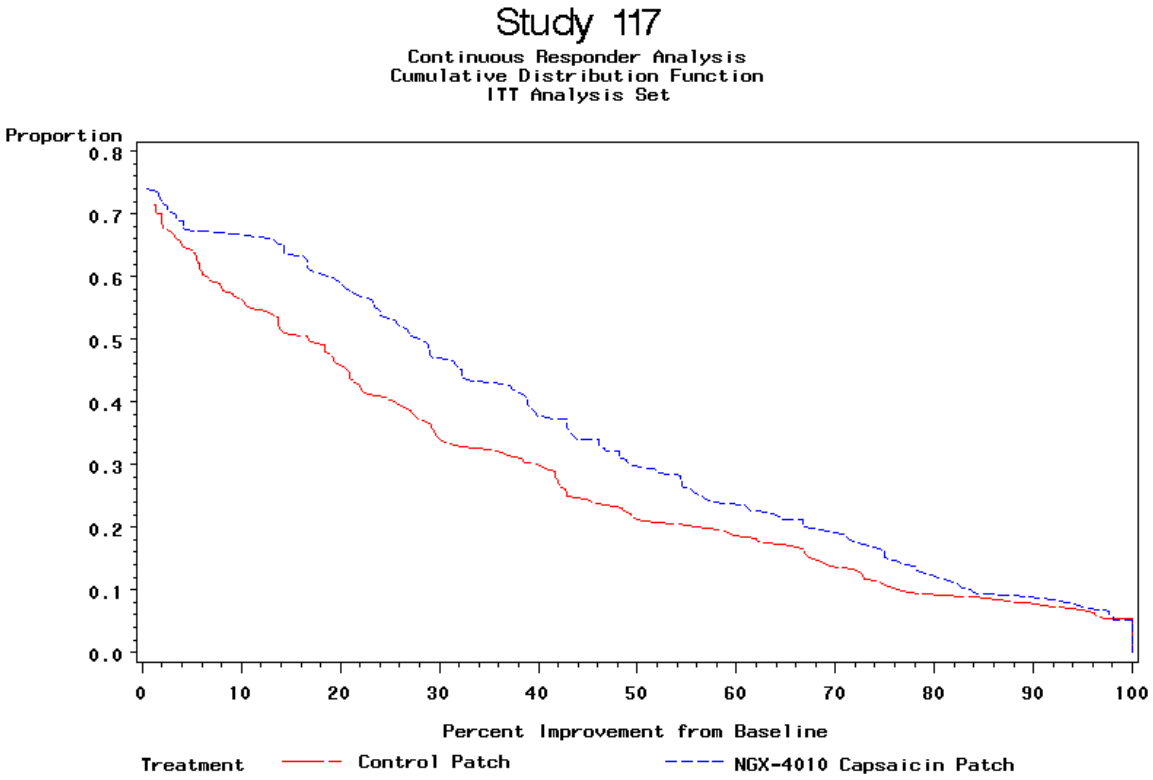
Ms. Meaker also reanalyzed the cumulative responder analysis using the landmark approach and found that the results were similar to that specified by the protocol. This is shown in Figures 6.3 and 6.4, following.

FIGURE 6.3: CUMULATIVE RESPONDER ANALYSIS, LANDMARK, STUDY C116



Source: Katherine Meaker's (FDA statistician) review

FIGURE 6.3: Cumulative responder analysis, landmark, Study C117



Source: Katherine Meaker's (FDA statistician) review

With regard to secondary endpoints, they generally supported the primary.

Subjects who received NGX-4010 in the two pivotal studies experienced a mean percent reduction in pain from Baseline during Weeks 2 to 8 that was at least 30% greater relative to the reduction in pain experienced by the Control group during the same time period.

In Study C116, the proportion of patients with at least a 30% average reduction in pain score from baseline during weeks 2-12 was 44% for NGX-4010 and 35% for Control ($p < 0.05$). Pain reduction occurred as early as Week 1 and persisted throughout the study.

In Study C117, the proportion of patients with at least a 30%, a 50% and a 2-point average reduction in pain score from baseline during weeks 2-12 was 47%, 30% and 43% for NGX-4010 and 35%, 21% and 29% for Control, respectively (all $p < 0.05$).

Analyses of several of other endpoints support the conclusion from the primary analysis that NGX-4010 is effective in the management of PHN in adults:

- The proportion of responders who achieved ≥ 30% mean reduction in NPRS scores from Baseline was approximately 30% greater in the NGX-4010 groups relative to the Control groups. The proportion of responders who achieved ≥ 2 unit mean reduction in NPRS scores from Baseline was over 50% greater in the NGX-4010 groups relative to

the Control groups. The effect of treatment was independent of the imputation algorithm and was consistent during both Weeks 2 to 8 and Weeks 2 to 12.

- The *cumulative distribution of the mean percent change in NPRS scores* from Baseline during Weeks 2 to 8 and Weeks 2 to 12 in the pivotal studies showed a consistently larger proportion of NGX-4010 subjects experienced greater pain relief than the corresponding Control subjects.

- Weekly comparisons of mean percent change in NPRS scores from Baseline demonstrated a rapid and sustained response to NGX-4010 treatment. The pattern of pain relief was similar between NGX-4010 and Control groups, with a reduction after Week 1 and a continued level of pain reduction for 12 weeks thereafter, the superiority of NGX-4010 is observed as early as the first week following treatment and is maintained at each subsequent week through Week 12.

- Daily comparisons of NPRS scores with regard to mean percent change and ≥30% or a ≥ 2 unit decrease during the first week of study was characterized by a rapid response to control treatment and a slightly delayed (1 to 2 days) response to NGX-4010 treatment. Following the first 3 days of the study, the effect of NGX-4010 surpassed that observed in the Control groups and was consistently greater for the remainder of the 12-week observation period.

- The response to treatment was evaluated by assessing the mean percent change in NPRS score from Baseline from Week 2 through Week 8 and from Week 2 through Week 12, using a gender-stratified, mixed-effect repeated measures ANCOVA with no imputation for missing pain scores. Results showed that pain was reduced during the first week following treatment and that pain relief was maintained for 12 weeks.

The results from *open-label* extension/*repeat treatment studies* (Studies C118, C106, and the open-label extension of C108), demonstrated that the long-term efficacy associated with NGX-4010 treatment was maintained for up to 4 treatments over a 1-year period, without the development of tolerance. (See Section 6.1.9)

In conclusion, the results of two controlled clinical trials (C116 and C117) indicate that NGX-4010 is superior to control for reducing the pain associated with PHN. The analgesic effect of NGX-4010 is observed within 1 week of administration and persists for at least 12 weeks. This effect is consistent for men and women, all ages, and duration of PHN.

DISCUSSION OF THE ISSUES ASSOCIATED WITH STUDY DESIGN AND ENDPOINTS
A number of issues relevant to the NGX-4010 development program were addressed in the design of the eight studies conducted in PHN subjects.

The features intrinsic to the study design are discussed under the following headings:

1) Inclusion-Exclusion criteria

- Studies *excluded subjects with significant ongoing pain from other cause*(s) that could interfere with the neuropathic pain evaluation as well as subjects with cognitive impairment that could interfere with his/her ability to accurately assess pain or complete subject diaries.

- The safety and effectiveness of NGX-4010 was assessed in a broad population with *moderate to severe baseline levels of pain*, on an 11-point NPRS.

- Inclusion criteria for Study C118 stipulated that subjects have moderate to severe neuropathic pain secondary to PHN. Subjects with Baseline pain scores less than 3 were excluded from all studies due to the greater potential for higher placebo response rates in these subjects compared with subjects with higher Baseline scores.

- The required *minimum duration* of PHN for subjects enrolled in most studies was *6 months post-vesicle crusting* (Studies C117, C116, C108, C102, and C106). Studies C110 and C111 were unique in that they permitted enrollment of subjects who were only 3 months post-vesicle crusting. However, as spontaneous improvement in PHN is known to occur in the first 6 months after crusting of shingles vesicles and may have impacted efficacy results from study C110, all studies conducted subsequent to C110 and C111 utilized the 6 month criterion.

- The inclusion of subjects taking other concomitant neuropathic pain treatments and the enrollment of subjects with a broad range of Baseline pain scores (i.e., Baseline scores of 3 to 9), resulted in a clinical development program that maximized clinical relevance with regards to the intended patient population

- Subjects with evidence of cognitive impairment including dementia were excluded the study, as cognitive impairment may have interfered with subject's ability to complete daily pain diaries requiring subject's recall of average PHN pain level in the past 24 hours.

2) Choice of a comparator for developmental program
A low-concentration capsaicin patch (3.2 mcg/cm^2; 0.04% w/w) that caused erythema and a perceptible local sensation was chosen as the control/comparator drug for the studies. The use of an inert placebo patch would not have allowed for maintaining the integrity of the double-blind design due to the expected capsaicin-related effects NGX-4010 produces at the

local application site. Therefore, in order to maintain the integrity of the blind, a low concentration comparator was used.

However, although the control patch delivered significantly less capsaicin than the active drug patch, the use of a low-concentration capsaicin control (comparator) may have led to an *underestimation* of the treatment effect of NGX-4010, as the local capsaicin-related effects produced by the low-concentration control would be expected to result in a more robust placebo response than would have been seen with an inert placebo, resulting in an underestimation of the magnitude of the treatment effect and thereby reducing the ability to statistically separate active drug from control..

3) Duration of patch application
The recommended duration (dose) of NGX-4010 application was selected as 60-minutes. This was based on the results from the double-blind, controlled studies (Studies C117, C116, C108, and C110) that evaluated the ***duration of effect*** of a single 60-minute treatment with NGX-4010 for up to 12 weeks following treatment.

4) Use of prohibited medications during pivotal trials
The use of *topical* NSAIDs, local anesthetics, steroids, and capsaicin-containing preparations was prohibited within 21 days of starting all studies, and their use was prohibited throughout the studies.

Studies C106 and C102 excluded subjects taking peripherally acting analgesics. Opioid analgesics were allowed only if subjects had been on a fixed regimen for at least 21 days before the start of Study C102 and, for entry into Study C106, had no change in dosage during Study C102.

Subjects in Studies C117, C116, C111, C110, and C108 were permitted to use pain-control medications if they were on a stable regimen for at least 21 days prior to treatment, and maintained the stable dose throughout the study.

However, to increase the probability that subjects were not tolerant to high doses of opiates and would respond to oral opioid rescue medications if required, *transdermal* or *oral opioid* use was not to exceed 60 mg/day of morphine equivalents, and *parenteral opioid* use was *prohibited.*

5) Changes in concomitant pain medication use were not permitted during the studies.
In order to examine whether changes in concomitant neuropathic pain medication use that may have occurred during the course of a study impacted the study results, subjects in Studies C118, C117, and C116 were categorized as having “no change”, an “increase”, a “decrease”, or “both increase and decrease” in concomitant neuropathic pain medication use.

Concomitant medication use was limited to anticonvulsants, non-selective serotonin reuptake inhibitor [SSRI] antidepressants, and opioids) compared with Baseline during Weeks 2 to 8 (Studies C117 and C116) and Weeks 2 to 12 (Studies C118, C117, and C116), according to a pre-specified algorithm.

To offset the potential pain associated with capsaicin administration, all subjects in all studies had their painful areas pre-treated with a topical local anesthetic cream (4% w/w lidocaine) for 60 minutes prior to study patch application.

6) Use of Rescue Medication
All subjects were *permitted to use rescue medications during and after treatment for treatment-related discomfort*.

In pivotal studies C117 and C116, rescue medications were allowed during treatment and for up to 5 days following the treatment procedure. A rapid-onset, opioid-based oral pain medication such as oxycodone hydrochloride (HCl) oral solution (1 mg/mL; e.g., Roxicodone®) was administered as needed (PRN) while the subject was in the clinic.

Additional opioid-based oral pain medication such as hydrocodone bitartrate/acetaminophen (5/500 mg; PRN, e.g., Vicodin®) was permitted post-treatment through Day 5. Up to 2 tablets of Vicodin® (hydrocodone bitartrate/acetaminophen, 5/500 mg) every 8 hours PRN were permitted post-treatment through Day 5. Study C108 allowed the same rescue medication use, except that Vicodin® was only permitted through Day 3.

EFFICACY CONCLUSIONS

Study C116 showed a significant difference in pain intensity when the baseline score was compared to the mean of the scores in Week 8. The analysis survived multiple different analysis techniques including both landmark and "AUC" strategies and percent change from baseline and absolute change from baseline. Study C117, while not showing statistical significance when a landmark/actual change from baseline was conducted was significantly different in the landmark/percent change from baseline. The secondary endpoints, including a continuous responder analysis, all supported the primary efficacy endpoint analysis. Collectively, these data support a finding of efficacy for the product.

6.1 Proposed Indication
Neuroges X, Inc is seeking approval to market NGX-4010 for "the prolonged reduction of neuropathic pain associated with postherpetic neuralgia."

6.1.2 Methods/Study Design

Studies C117 and C116 were the two pivotal, Phase 3 randomized, double-blind and controlled multi-center evaluations of the efficacy, safety, and tolerability of NGX-4010 for the treatment of PHN. Subjects in both studies were randomized in a 1:1 ratio to receive NGX-4010 or control treatment for 60 minutes.

OTHER CONTROLLED STUDIES performed by the applicant to support the efficacy claim include:

- Study C110 was as a Phase 3 randomized, double-blind, and controlled, multi-center evaluation of the efficacy, safety, and tolerability of NGX-4010 for the treatment of PHN. Subjects were randomized in a 2:1 ratio to receive NGX-4010 or control for 60 minutes.

- Study C108 was a Phase 2/3 randomized, double-blind, controlled, dose-ranging, multi-center evaluation of the efficacy, safety, and tolerability of NGX-4010 for the management of PHN. The study included a 12-week double-blind period during which subjects were randomized in a 3:3:3:1:1:1 ratio to receive NGX-4010 for 90-, 60-, or 30-minutes or control treatment for 90-, 60-, or 30-minutes. The double-blind phase was followed by a 40-week open-label extension during which subjects could be eligible for up to 3 open-label repeat-treatments with NGX-4010 for 60 minutes, each a minimum of 12 weeks apart.

- Study C102 was a Phase 2, multicenter, double-blind controlled pilot study in 2 parts: an initial open-label phase followed by a double-blind, controlled phase to evaluate efficacy, safety, and tolerability over 28 days of a single 60-minute application of NGX-4010 (640 mcg/cm^2) compared with Control (3.2 mcg/cm^2) in subjects with PHN. The initial 6 subjects, who were treated with open-label NGX-4010, are included in the integrated data for the Open-Label Studies.

LONG-TERM EFFICACY AND TOLERANCE IN OPEN-LABEL AND REPEAT-TREATMENT STUDIES
Three long-term studies (C118, C106 and C108) conducted as part of the NGX-4010 clinical development program to provide supportive evidence of the persistence of efficacy following multiple NGX-4010 patch applications for up to a 52-week period in a total of 284 subjects.

- Study C118 was an open-label, Phase 2, single-arm, multicenter evaluation of the safety and efficacy of NGX-4010 for the treatment of PHN and HIV-AN enrolling subjects from C108, C110 and C116. This study offered subjects an initial NGX-4010 treatment at study entry and up to 3 additional NGX-4010 study patch applications at intervals of no less than 12 weeks.
- Study C 106 was an open-label extension of Study C102
- Study C 108 was a Phase 2/3 dose-finding study in PHN subjects.

These repeat-treatment studies are discussed in greater detail in elsewhere in this report:

- Disposition - Section 6.1.3.2
- Persistence of Efficacy and lack of development of tolerance with repeated applications of NGX-4010 - Section 6.1.9
- The Safety of repeated exposures to NGX-4010 and the absence of increased incidences of AE's and SAE's with repeated applications- Section 7.2.2

6.1.2 Demographics

As noted in other parts of this review, patients enrolled in the PHN studies were predominantly elderly (mean age 71 years), Caucasian (92%), had a substantial duration of pain due to their PHN (2.5-3 years post healing), and fifty percent were taking prescription medications for the pain of PHN.

6.1.3 Patient Disposition

The disposition of subjects who were randomized to Pivotal trials C116 and C117 are discussed in Individual Study Report (Section 5.3) of this template in Tables 5.3.2 and Table 5.3.15 respectively.

Controlled Studies in PHN Subjects

The disposition of PHN subjects participating in Controlled Studies is presented overall and by treatment duration in Table 6.1.3.1. One subject in Study C116 was randomized to receive NGX-4010, but received Control treatment. (This subject is included in the NGX-4010 group for enrolled subjects and for all efficacy analyses, but in the Control group for treated subjects and for all safety analyses). In Study C117, two subjects randomized to the NGX-4010 group never received treatment. One subject had an allergic reaction to the topical anesthetic (LMX4®) application and one subject was found not to have met the study entry criteria; these subjects are included in the "terminated prematurely" category.

In the Controlled PHN Studies, a total of 767 subjects received NGX-4010 treatment and 543 subjects received Control treatment. A similar proportion of subjects in the NGX-4010 group (90.9%) and Control group (90.6%) completed the studies. The proportions of NGX-4010 or Control subjects who prematurely discontinued were similar both overall as well as for a specific reason. The most common reasons for premature termination were "unsatisfactory therapeutic response" for 18 subjects (2.3%) in the NGX-4010 group and 21 subjects (3.9%) in the Control group, "other" for 19 subjects (2.5%) in the NGX-4010 group and 9 subjects (1.7%) in the Control group, and "lost to follow-up" for 19 subjects (2.5%) in the NGX-4010 group and 8 subjects (1.5%) in the Control group. An AE was responsible for premature termination in only 8 (1.0%) NGX-4010 subjects and 3 (0.6%) Control subjects.

Subject disposition was also summarized by the 3 treatment durations evaluated (30, 60, and 90 minutes). The majority of treated subjects in Controlled PHN Studies had treatment duration of 60 minutes (622 of 767 subjects in the NGX-4010 group and 495 of 543 subjects in the Control

group). Completion rates and reasons for premature termination were generally similar across the 3 treatment durations. A higher proportion of 90- minute NGX-4010 subjects (15.1%) terminated early compared to the 30- and 60-minute NGX-4010 subjects (8.3% and 9.0%, respectively); the difference was mostly due to a higher proportion of 90-minute subjects being lost to follow-up.

TABLE 6.1.3.1: SHOWING DISPOSITION BY TREATMENT DURATION IN CONTROLLED PHN

	NGX-4010				Control			
Subjects	90 minutes	60 minutes	30 minutes	Total	90 minutes	60 minutes	30 minutes	Total
Number of subjects								
Enrolled	73	625	72	770	25	494	23	542
Receiving Treatment	73	622	72	767	25	495	23	543
Completed Study [a], n (%)[b]	62 (84.9)	569 (91.5)	66 (91.7)	697 (90.9)	24 (96.0)	446 (90.1)	22 (95.7)	492 (90.6)
Terminated Prematurely, n (%)	11 (15.1)	56 (9.0)	6 (8.3)	73 (9.5)	1 (4.0)	48 (9.7)	1 (4.3)	50 (9.2)
Adverse Event [c], n (%)	2 (2.7)	6 (1.0)	0	8 (1.0)	0	3 (0.6)	0	3 (0.6)
Unsatisfactory Therapeutic Response, n (%)	1 (1.4)	16 (2.6)	1 (1.4)	18 (2.3)	0	21 (4.2)	0	21 (3.9)
Non-compliance, n (%)	2 (2.7)	5 (0.8)	1 (1.4)	8 (1.0)	0	8 (1.6)	0	8 (1.5)
Lost to Follow-up, n (%)	4 (5.5)	13 (2.1)	2 (2.8)	19 (2.5)	0	8 (1.6)	0	8 (1.5)
Death, n (%)	0	1 (0.2)	0	1 (0.1)	1 (4.0)	0	0	1 (0.2)
Other, n (%)	2 (2.7)	15 (2.4)	2 (2.8)	19 (2.5)	0	8 (1.6)	1 (4.3)	9 (1.7)

DB=double-blind.
NOTES:
1. If a subject enrolled into a study and did not receive treatment, the subject was included in the "terminating prematurely" category.
2. Data were derived from Studies C102 (DB portion), C108 (DB portion), C110, C116, and C117. Subjects are summarized under received treatment.
3. Time of termination is computed as date of latest study procedure, defined as the latest date from physical exam, neurosensory assessment, patch adhesion assessment, dermal assessment, study visit, and pain diary.
a. For Study C108, completion means completion of the first 12 weeks
b. Percent completed is based on the number of subjects receiving treatment
c. For Study C108, events leading to termination occurring within 12 weeks from initial DB treatment and for Study C102 events within 4 weeks from initial treatment
Source: Source Table 1.2.7 (Section 22).

Repeat-treatment studies

The disposition of all subjects participating in Repeat-Treatment Studies is summarized overall and by indication in Table 6.1.3.2.

A total of 672 subjects were treated in the Repeat-Treatment Studies, and 349 subjects (51.9%) completed the studies. The most frequent reasons for premature termination were "other" (163 [24.3%] of subjects), "unsatisfactory therapeutic response" (80 [11.9%] of subjects), and "lost to follow-up" (40 [6.0%] of subjects). An AE was responsible for premature termination in 19 (2.8%) subjects.

A higher proportion of PHN subjects terminated prematurely from the Repeat-Treatment Studies compared with HIV-AN subjects (64.1% and 30.9%, respectively). This difference was largely due to the fact that Study C108 was prematurely terminated by the Sponsor during the open-label phase. Study C108 enrolled only PHN subjects, which is reflected in the higher proportion of PHN subjects with a reason for premature termination of "other" (37.6% of PHN subjects, 9.6% of HIV-AN subjects). A higher proportion of PHN subjects than HIV-AN subjects terminated prematurely due to "unsatisfactory therapeutic response" (17.5% and 5.9%, respectively); other reasons for termination were similar.

TABLE 6.1.3.2.: SHOWING SUBJECT DISPOSITION (REPEAT-TREATMENT, OPEN-LABEL PHASE)

Subjects	PHN	HIV-AN	Total
Number of subjects			
Enrolled	351	324	675
Receiving Treatment	348	324	672
Completed Study, n (%) [a]	125 (35.9)	224 (69.1)	349 (51.9)
Terminated Prematurely, n (%)	223 (64.1)	100 (30.9)	323 (48.1)
Adverse Event, n (%)	10 (2.9)	9 (2.8)	19 (2.8)
Unsatisfactory Therapeutic Response, n (%)	61 (17.5)	19 (5.9)	80 (11.9)
Non-compliance, n (%)	9 (2.6)	9 (2.8)	18 (2.7)
Lost to Follow-up, n (%)	12 (3.4)	28 (8.6)	40 (6.0)
Death, n (%)	0	3 (0.9)	3 (0.4)
Other, n (%)	131 (37.6)	32 (9.9)	163 (24.3)

OL=open-label.
NOTES:
1. Data were derived from Studies C106 (PHN), C107 (OL portion; HIV-AN), C108 (OL portion; PHN), and C118 (PHN and HIV-AN).
2. For Study C106, subjects received up to a maximum of 3 treatments with a minimum of 6 weeks between each treatment. Following the initial treatment in C102, treatments in C106 could start at Week 12 through Week 24. The total follow-up period was 48 weeks (± 2 weeks) after the first treatment in C102.
3. For Studies C107 and C108, subjects received up to a maximum of 3 re-treatments. The minimum interval between OL re-treatment was 12 weeks (± 7 days). The total follow-up period was 40 weeks after the start of the OL phase.
4. For Study C118, subjects received up to a maximum of 4 treatments. The minimum interval between OL re-treatment was 12 weeks (± 7 days). The total follow-up period was 48 weeks after the first treatment.
5. Time of termination is computed as the date of the latest study procedure, defined as the latest date from physical exam, neurosensory assessment, patch adhesion assessment, dermal assessment, study visit, pain diary, and termination form (if not lost to follow-up).
6. If a subject enrolled into a study and did not receive treatment, the subject was included in the "terminating prematurely" category.

a. Percent completed is based on the number of subjects receiving treatment.
Source: Source Table 1.4.6 (Section 22).

The primary efficacy variable for the studies in the NGX-4010 clinical program was the percent change in "average pain for the past 24 hours" in NPRS scores from Baseline to Week 8 except for the pivotal Studies C116/C117 and the supportive efficacy studies C110 and C108.
The primary efficacy endpoint for the 12-week controlled studies (Studies C117, C116, C110, and C108) was the mean percent change in "average pain for the past 24 hours" NPRS score

from Baseline during Weeks 2 to 8. The Week 1 NPRS scores were not analyzed for the primary endpoint to avoid the potential for bias due to the permissible use of rescue medications during the first 3 or 5 days after treatment.
Subjects recorded their pain scores on a daily basis throughout the studies, and the mean percent change from Baseline in NPRS scores was compared between the NGX-4010 and Control groups over the primary analysis period (i.e., during Weeks 2 to 8). The mean percent change from Baseline in NPRS scores was also evaluated during Weeks 2 to 12 as a secondary endpoint.

For Study C102, a 4-week controlled study, the primary efficacy endpoint was a change in mean NPRS scores (average of morning and evening scores) during Days 8 to 28.

6.1.4 Primary Efficacy Endpoints

The primary efficacy endpoints for the repeat-treatment studies C118, the open-label portion of C108, and C106) varied slightly across each study. For Study C118, the primary efficacy endpoint was the mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline during Week 12. The mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline during Week 48 was also evaluated. For Study C108 (open-label, repeat-treatment phase), no primary efficacy endpoint was defined; however, mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline during Weeks 2 to 8, after the last treatment, by number of NGX-4010 treatments administered was evaluated during the open-label phase of this study. For Study C106, the primary efficacy endpoints included the change in mean NPRS scores (morning and evening average) compared with Study C102 Baseline as follows: (1) from Study C102 treatment to Week 12 (Study C106), (2) from Study C102 treatment to Study C106 Termination, and (3) for each treatment cycle in Study C106.

For open-label Study C111, the primary efficacy endpoint was the mean percent change in "average pain for the past 24 hours" NPRS scores from Baseline during Weeks 2 to 12.

6.1.5 Analysis of Secondary Endpoints(s)

Section 5.3 provides a list of the secondary efficacy endpoints and their results.

Generally, analyses of the secondary efficacy endpoints supported the primary efficacy endpoint analysis.

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

<u>Evaluation of Mean Percent Change from Baseline by Gender</u>

NGX-4010 subjects reported greater reductions in mean percent changes in NPRS score from Baseline during Weeks 2 to 8 compared with Control subjects in both male and female subjects ($p = 0.0002$ for male subjects and $p = 0.0023$ for female subjects.

Female NGX-4010 subjects reported a greater reduction in mean percent change from Baseline (−35.3%) compared with male NGX-4010 subjects (−26.7%), a similar trend was observed in the Control groups (−27.0% for female Control subjects vs. −17.2% for male Control subjects) resulting in comparable treatment differences (−9.5% for male subjects and −8.4% for female subjects). Results during Weeks 2 to 8 were comparable using BOCF imputation where treatment with NGX-4010 compared with control also resulted in greater reductions in mean percent change in NPRS score from Baseline ($p < 0.0001$ for male subjects and $p = 0.0035$ for female subjects;

Evaluation of Achieving a ≥ 30% Response by Gender

A greater proportion of NGX-4010 subjects achieved a ≥ 30% response compared with Control subjects regardless of gender ($p = 0.0081$ for male subjects and $p = 0.0161$ for female subjects; during Weeks 2 to 8. For male subjects, the odds of achieving a ≥ 30% response was 1.665-times more likely in the NGX-4010 group compared with the Control group. Similar odds of achieving a ≥ 30% response in the NGX-4010 group compared with the Control group were observed for female subjects (1.501). Results during Weeks 2 to 8 were comparable using BOCF imputation where a greater proportion of NGX-4010 subjects achieved a ≥ 30% response compared with Control subjects regardless of gender ($p = 0.0040$ for male subjects and $p = 0.0143$ for female subjects;

Gender: Overall Conclusion

Data shown in Table 6.1.7.1 demonstrate that women appear to experience a greater reduction in pain, regardless of treatment. However, the differences between NGX-4010 and Control groups were similar for both men and women and the analysis did not suggest any treatment by gender interaction. This implies that NGX-4010 is effective in both men and women.

TABLE 6.1.7.1 SHOWING: SUMMARY OF MEAN PERCENT CHANGE IN NPRS SCORES FROM BASELINE AND PERCENT RESPONDERS BY GENDER (LOCF), WEEKS 2 TO 8

	C117		C116		C110		C108[a]		Total[b]	
	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control
Males, n	93	97	99	91	47	25	112	38	286	251
LS Mean % Change	–29.3	–17.4	–26.5	–15.7	–31.4	–28.6	–21.5	–12.8	–26.7	–17.2
95% CI of LS Mean	*–34.7, –24.0*	*–22.6, –12.2*	*–32.2, –20.7*	*–21.7, –9.7*	*–41.7, –21.1*	*–42.8, –14.5*	*–26.9, –16.1*	*–21.9, –3.7*	*–30.1, –23.3*	*–20.8, –13.6*
p-value[c]									*0.0002*	
Treatment[d] difference (95% CI)	*–11.9 (–19.4, –4.4)*		*–10.7 (–19.0, –2.5)*		*–2.8 (–20.3, 14.7)*		*–8.6 (–19.2, 2.0)*		*–9.5 (–14.4, –4.6)*	
≥30% Response n (%)	40 (43.0)	23 (23.7)	33 (33.3)	24 (26.4)	21 (44.7)	12 (48.0)	34 (30.4)	6 (15.8)	104 (36.4)	65 (25.9)
p-value[e]									*0.0081*	
Odds Ratio[f] (95% CI)	*2.485 (1.306, 4.727)*		*1.409 (0.749, 2.651)*		*0.905 (0.339, 2.413)*		*2.568 (0.969, 6.805)*		*1.665 (1.142, 2.427)*	
≥2 Unit Decrease n (%)	32 (34.4)	17 (17.5)	33 (33.3)	18 (19.8)	15 (31.9)	9 (36.0)	29 (25.9)	4 (10.5)	90 (31.5)	48 (19.1)
p-value[e]									*0.0012*	
Odds Ratio[f] (95% CI)	*2.455 (1.248, 4.831)*		*2.027 (1.043, 3.939)*		*0.790 (0.280, 2.226)*		*2.959 (0.962, 9.100)*		*1.942 (1.300, 2.902)*	
Females, n	119	107	107	105	55	28	110	39	311	279
LS Mean % Change	–34.2	–30.3	–32.4	–23.6	–40.6	–31.2	–32.7	–23.3	–35.3	–27.0
95% CI of LS Mean	*–40.2, –28.2*	*–36.6, –24.0*	*–38.1, –26.8*	*–29.3, –17.9*	*–51.0, –30.3*	*–45.7, –16.7*	*–39.1, –26.2*	*–34.0, –12.5*	*–39.0, –31.6*	*–30.9, –23.0*
p-value[c]									*0.0023*	
Treatment[d] difference (95% CI)	*–3.9 (–12.6, 4.8)*		*–8.8 (–16.8, –0.8)*		*–9.4 (–27.2, 8.4)*		*–9.4 (–21.9, 3.1)*		*–8.4 (–13.8, –3.0)*	
≥30% Response n (%)	57 (47.9)	46 (43.0)	53 (49.5)	39 (37.1)	29 (52.7)	12 (42.9)	49 (44.5)	16 (41.0)	156 (50.2)	113 (40.5)
p-value[e]									*0.0161*	
Odds Ratio[f] (95% CI)	*1.203 (0.707, 2.049)*		*1.672 (0.965, 2.897)*		*1.577 (0.598, 4.156)*		*1.288 (0.602, 2.754)*		*1.501 (1.078, 2.088)*	
≥2 Unit Decrease n (%)	56 (47.1)	37 (34.6)	50 (46.7)	33 (31.4)	26 (47.3)	12 (42.9)	39 (35.5)	11 (28.2)	144 (46.3)	93 (33.3)
p-value[e]									*0.0014*	
Odds Ratio[f] (95% CI)	*1.697 (0.991, 2.908)*		*1.864 (1.059, 3.278)*		*1.203 (0.478, 3.026)*		*1.401 (0.628, 3.128)*		*1.723 (1.233, 2.408)*	

Source: ISE, p106/148

Evaluation of Mean Percent change from baseline by Age

The median age for all studies combined (C117, C116, C110, and C108) was 73 years. This median age was used for the analyses of the individual studies and integrated data.

NGX-4010 subjects reported greater reductions in mean percent change in NPRS score from Baseline during Weeks 2 to 8 compared with Control subjects in both age subgroups ($p = 0.0005$ for subjects whose age was ≥ median [73 years] and $p = 0.0012$ for subjects whose age was < median [73 years];

Overall, the results of the subgroup assessments support the conclusion that NGX-4010 is effective to a similar degree in reducing pain in both younger (<73 years) and older (>73 years) subjects with PHN.

TABLE 6.1.7.1: SHOWING MEAN PERCENT CHANGE IN NPRS SCORES FROM BASELINE AND PERCENT RESPONDERS BY AGE (LOCF), WEEKS 2 TO 8

	C117		C116		C110		C108[a]		Total[b]	
	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control	NGX-4010	Control
Age ≥ median, n	107	107	106	105	45	29	117	36	305	277
LS Mean % Change	–27.1	–16.4	–25.8	–17.8	–27.8	–24.5	–21.3	–11.5	–25.7	–17.2
95% CI of LS Mean	*–32.4, –21.9*	*–21.7, –11.2*	*–31.1, –20.6*	*–23.1, –12.5*	*–38.7, –16.8*	*–38.1, –10.9*	*–26.9, –15.7*	*–21.2, –1.7*	*–29.0, –22.4*	*–20.7, –13.7*
p-value[c]									*0.0005*	
Treatment[d] difference (95% CI)	*–10.7 (–18.2, –3.3)*		*–8.0 (–15.5, –0.5)*		*–3.2 (–20.7, 14.2)*		*–9.9 (–21.1, 1.4)*		*–8.5 (–13.3, –3.7)*	
≥30% Response n (%)	40 (37.4)	25 (23.4)	39 (36.8)	30 (28.6)	18 (40.0)	11 (37.9)	32 (27.4)	6 (16.7)	108 (35.4)	72 (26.0)
p-value[e]									*0.0164*	
Odds Ratio[f] (95% CI)	*1.975 (1.071, 3.640)*		*1.392 (0.773, 2.504)*		*1.164 (0.426, 3.181)*		*2.007 (0.750, 5.372)*		*1.562 (1.085, 2.249)*	
≥2 Unit Decrease n (%)	38 (35.5)	15 (14.0)	38 (35.8)	23 (21.9)	13 (28.9)	9 (31.0)	23 (19.7)	4 (11.1)	97 (31.8)	51 (18.4)
p-value[e]									*0.0002*	
Odds Ratio[f] (95% CI)	*3.385 (1.703, 6.729)*		*1.997 (1.082, 3.684)*		*0.923 (0.327, 2.605)*		*1.884 (0.598, 5.937)*		*2.095 (1.417, 3.099)*	
Age < median, n	105	97	100	91	57	24	105	41	292	253
LS Mean % Change	–36.7	–33.1	–33.3	–22.8	–43.4	–36.1	–33.1	–24.0	–37.0	–27.9
95% CI of LS Mean	*–42.8, –30.6*	*–39.4, –26.8*	*–39.4, –27.3*	*–29.1, –16.4*	*–53.1, –33.7*	*–51.1, –21.2*	*–39.5, –26.8*	*–34.1, –13.9*	*–40.8, –33.3*	*–31.9, –23.9*
p-value[c]									*0.0012*	
Treatment[d] difference (95% CI)	*–3.6 (–12.4, 5.2)*		*–10.6 (–19.4, –1.7)*		*–7.2 (–25.1, 10.6)*		*–9.1 (–21.0, 2.8)*		*–9.1 (–14.6, –3.6)*	
≥30% Response n (%)	57 (54.3)	44 (45.4)	47 (47.0)	33 (36.3)	32 (56.1)	13 (54.2)	51 (48.6)	16 (39.0)	152 (52.1)	106 (41.9)
p-value[e]									*0.0095*	
Odds Ratio[f] (95% CI)	*1.359 (0.769, 2.400)*		*1.668 (0.908, 3.062)*		*1.092 (0.408, 2.919)*		*1.652 (0.770, 3.547)*		*1.584 (1.119, 2.243)*	
≥2 Unit Decrease n (%)	50 (47.6)	39 (40.2)	45 (45.0)	28 (30.8)	28 (49.1)	12 (50.0)	45 (42.9)	11 (26.8)	137 (46.9)	90 (35.6)
p-value[e]									*0.0064*	
Odds Ratio[f] (95% CI)	*1.338 (0.760, 2.354)*		*1.763 (0.944, 3.294)*		*0.965 (0.369, 2.524)*		*2.079 (0.933, 4.634)*		*1.629 (1.147, 2.315)*	

Source: ISE, p108/148

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two studies in the NGX-4010 clinical development program assessed the efficacy of multiple doses (i.e., duration of patch application; 30, 60 or 90 minutes).

Efficacy results from the following two studies, Study C108 and C111 in the NGX-4010 clinical development program provided evidence in support of the choice of 60 minutes as the recommended duration of patch application_Post hoc analysis of study C108 provided preliminary evidence of efficacy for the 60-minute dose.

(1) Study C108, was a Phase 2/3 randomized, double-blind, controlled, dose-ranging, evaluation of the efficacy, safety, and tolerability of NGX-4010 for the management of PHN. The study included a 12-week double-blind period during which subjects were randomized in a 3:3:3:1:1:1 ratio to receive NGX-4010 for 90-, 60-, or 30-minutes or control treatment for 90-, 60-or 30-minutes. The double-blind phase was followed by a 40-week open-label extension during which subjects could be eligible for up to 3 open-label repeat-treatments with NGX-4010 for 60 minutes, each a minimum of 12 weeks apart.

Study C108 assessed the efficacy of multiple durations of patch applications in subjects with PHN. The duration of patch application did not appear to affect the reduction in the NPRS score from baseline.

Each patch application duration, that is the 30, 60 and 90 minute applications was associated with similar reductions in NPRS scores from baseline; the 30 minute application resulted in a 26.2% reduction in NPRS score from baseline, the 60 minute patch application resulted in a 25.6% reduction in NPRS score from baseline, while the 90 minute patch application resulted in a 27.8 % reduction in NPRS score from baseline. (See Table 6.1.8.1 noted below).

TABLE 6.1.8.1: SHOWING THE RESULTS OF STUDY C108 SHOWING THE RESULTS OF VARYING DURATIONS OF PATCH APPLICATIONS

DURATION OF PATCH APPLICATION	% REDUCTION IN NPRS Score from BASELINE
30 minute application	↓ 26.2 %
60 minute application	↓ 25.6 %
90 minute application	↓ 27.9 %

Source: FDA's compilation based on information supplied by the sponsor

The differences between the 30- and 60-minute treatment with NGX-4010 and control did not reach statistical significance. The 60 minute group had a larger percentage of males compared with the other groups. When a post-hoc analysis including a gender-stratified ANCOVA model was applied to the data, the LS mean percent reduction in pain was similar, and the difference between the NGX-4010 60 minute group and the pooled Control group was significant with a p-value of 0.0331.

(2) Study C111, was an open-label mixed neuropathic pain population study conducted to assess the tolerability of NGX-4010 in conjunction with pre-patch topical application of 1 of 3 lidocaine-based local anesthetic products in a mixed disease indication population model. No appreciable difference in efficacy, as assessed by the mean percent change in NPRS score from Baseline was noted between the 60-minute or 90-minute dose groups.
(See Table 6.1.8.2 noted below).

TABLE 6.1.8.2: OPEN LABEL STUDY OF THE TOLERABILITY OF THREE LOCAL ANESTHETIC FORMULATIONS IN CONJUNCTION WITH NGX-4010 FOR THE TREATMENT OF NEUROPATHIC PAIN

STUDY	STUDY DESIGN	TOTAL # STUDIED	DOSAGE	RESULTS
PHASE	STUDY POPULATION		Rx DURATION	
C111	12 week, rand, OL eval of tolerability w 60 min or 90 min applic of NGX 4010 in conjunction with 1of 3 lidocaine 4% pre-patch applic products Efficacy Safety/tolerability	N= 117 - LMX 4% (n=39) - Topicaine (n= 38) - Betacaine (n=40)	60 or 90 minutes	No significant differences were observed between L.M.X.4® and Topicaine® or Betacaine® with regard to tolerability and preliminary efficacy was demonstrated equally well with either 60 or 90 min NGX-4010 treatment.
Phase 2	Mixed neuropathy population (PHN, PDN &HIV)			

Source: FDA compilation based on information supplied by the sponsor

Conclusion on duration of patch application studies (Studies C108 and C111)
The efficacy results of Studies C108 and C111 demonstrated that a longer time of application (i.e., a higher dose) was not associated with increased efficacy of NGX-4010 in reducing the NPRS score from baseline.levels. However the 60 minute duration patch application was more tolerable than the 90 minute application. Based on the above results the Applicant felt that the best compromise between tolerability and potential for treatment effect was 60 minutes.

In the subsequent pivotal PHN efficacy studies, C116 and C117, patch application duration was standardized to 60 minutes.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Three long-term studies (C118, C106 and C108) conducted as part of the NGX-4010 clinical development program to provide supportive evidence of the persistence of efficacy following multiple NGX-4010 patch applications for up to a 52-week period in a total of 284 subjects.

Study C118 was an open-label, Phase 2, single-arm, multicenter evaluation of the safety and efficacy of NGX-4010 for the treatment of PHN and HIV-AN.
This study enrolled subjects who:

- Had successfully completed a previous NGX-4010 study
- Subjects could not have received open-label NGX-4010 or
- Blinded NGX-4010 study patches within 12 weeks of receiving an initial open-label study patch application in this study.

Subjects received an initial open-label treatment with NGX-4010 at study entry and up to 3 additional open-label NGX-4010 study patch applications at intervals of no less than 12 weeks,

RESULTS OF STUDY C118
(The ensuing results were reported by the sponsor, and were not independently confirmed by the Agency).

In Study C118, NPRS scores were collected at Baseline and during Week 12 and Week 48.

The primary efficacy assessment was the percent change in "average pain for the past 24 hours" NPRS scores from Baseline.

(See Table 6.1.9.1 below)

TABLE 6.1.9.1: SHOWING SUMMARY OF CHANGE FROM BASELINE IN "AVERAGE PAIN FOR THE PAST 24 HOURS" NPRS SCORES DURING WEEK 12 IN STUDY C118 (PHN POPULATION)

NPRS Scores	PHN (N = 54)
Baseline, n	54
Mean (SD)	5.2 (2.11)
95% CI	4.58, 5.73
Percent Change from Baseline during Week 12, n	46
Mean (SD)	–19.4 (32.21)
95% CI	–28.98, –9.85
≥ 30% Decrease from Baseline during Week 12	
Yes	11 (24%)
≥ 2 unit reduction from Baseline during Week 12	
Yes	7 (15%)
Percent Change from Baseline during Week 48, n	41
Mean (SD)	–35.6 (40.72)
95% CI	–48.45, –22.75
≥ 30% Decrease from Baseline during Week 12	
Yes	21 (51%)
≥ 2 unit reduction from Baseline during Week 12	
Yes	15 (37%)

SD: Standard Deviation.
Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day –7 to Day –1.
Source: C118 CSR Table 14.2.1 (Module 5).

Source: p 136, Integrated Summary of Efficacy

Twelve weeks following the initial 60-minute NGX-4010 application, 46 PHN subjects reported a reduction in mean percent change in NPRS score from Baseline of -19.4% during Week 12 and 41 subjects reported further reduction by the end of the 48-week treatment period (-35.6%).

Additionally, 24% of PHN subjects at Week 12 and 51% of PHN subjects at Week 48 achieved a ≥30% decrease in mean NPRS score from Baseline.

Similarly, 15% of PHN subjects at Week 12 and 37% of PHN subjects at Week 48 reported a decrease of ≥ 2 units in their NPRS score

A small proportion of PHN subjects (4%) indicated they felt worse (very much, much, or slightly).

The proportion of subjects reporting improvement increased at Week 48 (75% of PHN subjects feeling improved, with 44% feeling much/very much improved). The BPI subject-rated questionnaire demonstrated improvements in all 5 pain index categories at Week 12 and Week 48 termination. The majority of PHN subjects indicated they would undergo this treatment again, and preferred this study treatment compared with previous therapies they had undergone.

Study C106 was a Phase 2, uncontrolled open-label extension of Study C102. (Study C102 was a 4-week Phase 2 study comprised of a small (6 subjects) open-label enrollment phase, followed by enrollment of double-blind treatment groups (NGX-4010 or Control). Study C106 extended the combined study duration to 1 year, starting with the initial treatment in Study C102, and offered up to 3 additional single-dose treatments with open-label NGX-4010 (with at least 12 weeks between the final Study C102 treatment and the first Study C106 re-treatment and 6 weeks between subsequent re-treatments). Twenty-four (24) PHN subjects (9 previously treated with Control) entered this study and 22 completed the 48-week period.

Results of Study C106
In Study C106, subjects treated with NGX-4010 in Study C106 reported an approximately 30% decrease from Baseline (C102) in mean NPRS (morning and evening average) scores during each treatment cycle (Weeks 2 to End), regardless of number of treatments received. A summary of the percent change in the mean of morning and evening average NPRS scores from Study C102 Baseline for Treatment Cycles 1 to 3 (Study C106) by number of treatments received in Study C106 is presented in Table 6.1.9.2 below. These results were similar to the improvements reported by subjects receiving double-blind NGX-4010 treatment in Study C102 (−32.7 %) and provide further evidence that the degree of relief provided from NGX-4010 treatment is maintained with repeated treatments for up to 48 weeks.

TABLE 6.1.9.2: SUMMARY OF MORNING AND EVENING AVERAGE NPRS SCORES BY NUMBER OF C106 TREATMENTS: CYCLES 1 TO 3 (SUBJECTS RECEIVING TREATMENT IN C106)

NPRS Score (Weeks 2–End)	NGX-4010 (n = 21)		
	n	Mean ± SD	95% CI
Subjects Receiving At Least One C106 Treatment			
Baseline	21	5.8 ± 1.08	5.3, 6.3
% Change from Baseline			
Cycle 1		–31.3 ± 27.10	–43.7, –19.0
Subjects Receiving At Least Two C106 Treatments			
Baseline	15	5.9 ± 1.11	5.3, 6.5
% Change from Baseline			
Cycle 1		–28.4 ± 20.58	–39.8, –17.0
Cycle 2		–29.7 ± 23.92	–42.9, –16.4
Subjects Receiving Three C106 Treatments			
Baseline	9	6.1 ± 1.27	5.1, 7.1
% Change from Baseline			
Cycle 1		–32.4 ± 20.93	–48.5, –16.3
Cycle 2		–35.2 ± 23.34	–53.1, –17.2
Cycle 3		–33.3 ± 24.60	–52.2, –14.4

Note: Baseline score was defined as the mean of the Day –10 to Day –1 morning and evening scores from Study C102, as available. Weeks 2–End score was defined as the mean of the Day 8 to end of cycle morning and evening scores, as available for that cycle. Percent change was defined as 100 × [(Mean Rating at Time Point) - (Mean Baseline Rating)] ÷ (Mean Baseline Rating).
Source: C106 CSR, Tables 14.2.3 and 14.2.9 (Module 5).

Source p136 ISE

Study C108 was a Phase 2/3, randomized, double-blind, controlled, dose-finding study to evaluate the efficacy, safety, and tolerability of a single application of the NGX-4010 or Control patch for 30, 60, or 90 minutes. The study duration of 52 weeks consisted of a 12-week double-blind period followed by a 40-week open-label extension in which subjects could be eligible for up to 3 open-label repeated treatments, administered a minimum of 12 weeks apart. The open-label extension portion of Study C108 provides data for the analysis of safety of NGX-4010 following repeated treatment in subjects with PHN. Two-hundred ninety-nine PHN subjects entered the double-blind phase of this study, 206 received one or more treatments in the open-label portion of the study.

This study was prematurely terminated by the sponsor during the open-label extension phase (once analysis of the double-blind phase showed that the primary endpoint had not been met) and only 63 subjects completed the full 52-week period.

RESULTS OF C108

In Study C108, differences in pain intensity continued to be observed for up to 3 additional NGX-4010 treatments over the 40-week open-label treatment period as shown by reductions from Baseline in average pain, worst pain, and pain now scores.

A summary of percent change in "average pain for the past 24 hours", "worst pain in the past 24 hours", and "pain now" NPRS scores from Baseline to Weeks 2 to 8 after the last treatment, by number of NGX-4010 treatments received is provided in Table 6.1.9.3.

The mean percent change from Baseline to Weeks 2 to 8 in "average pain for the past 24 hours" was -36.6%, -21.7%, -23.3%, and -19.8% for subjects receiving 1, 2, 3, and 4 NGX-4010 treatments, respectively. Results were comparable for "worst pain in the past 24 hours" and "pain now" scores. Reductions in pain scores were similar in subjects who received 2 or more treatments but were smaller than in subjects receiving one NGX-4010 treatment.

This may be explained by the fact that some subjects who only received 1 treatment did not get additional treatments because they were doing well and did not qualify for additional treatments according to the criteria specified in the protocol. In addition, the assessment of efficacy during the open-label phase may have been confounded by the early termination of this study. Results for the modified BPI, SFMPQ, PGIC, CGIC, and SAT mirrored those of the other pain assessments.

TABLE 6.1.9.3: SHOWING SUMMARY OF NPRS SCORES FROM BASELINE TO WEEKS 2 TO 8 FOR RE-TREATMENTS (ITT Population) STUDY C108

	Total Number of NGX-4010 Treatments			
	1 (n = 101)	2 (n = 69)	3 (n = 54)	4 (n = 19)
"Average Pain for the past 24 hours" NPRS Score				
Baseline, Mean (SE)	5.1 (0.16)	5.6 (0.18)	6.0 (0.20)	6.1 (0.35)
% Change, Mean (SE)	–36.6 (3.78)	–21.7 (3.86)	–23.3 (4.12)	–19.8 (6.17)
Proportion of Responders				
≥ 30% Decrease from Baseline	49 (49%)	26 (38%)	17 (31%)	4 (21%)
"Worst Pain for the past 24 hours" NPRS Score				
Baseline, Mean (SE)	6.4 (0.16)	6.9 (0.17)	7.3 (0.22)	7.4 (0.32)
% Change, Mean (SE)	–35.6 (3.49)	–23.9 (3.46)	–24.8 (3.81)	–22.4 (5.81)
Proportion of Responders				
≥ 30% Decrease from Baseline	48 (48%)	27 (39%)	18 (33%)	5 (26%)
"Pain Now" NPRS Score				
Baseline, Mean (SE)	5.3 (0.20)	5.7 (0.21)	6.5 (0.24)	6.4 (0.43)
% Change, Mean (SE)	–31.2 (6.91)	–25.1 (3.94)	–25.9 (4.19)	–26.3 (6.34)
Proportion of Responders				
≥ 30% Decrease from Baseline	54 (53%)	28 (41%)	21 (39%)	7 (37%)

SE: Standard Error.
Note: Baseline pain level was defined as the mean of all available non-biased Screening NPRS scores in that category. If the last treatment was during the double-blind phase, then missing scores on Day 8 were estimated using the Baseline score; missing scores during Days 9 to 84 were estimated using the previous non-missing score. If the last treatment was an open-label treatment, then missing scores were not imputed, and subjects with less than 25 pain scores during Weeks 2 to 8 after the last treatment were excluded.
Source: C108 CSR Tables 14.2.1, 14.2.2, and 14.2.3 (Module 5).

SOURCE: p137, ISE

In conclusion, while the studies were not properly controlled, Studies C118, C106, and C108 support the notion that additional patch applications appear beneficial in certain patients. As will be shown in Section 7, additional applications were not associated with unexpected toxicity.

6.1.10 Additional Efficacy Issues/Analyses
This reviewer has not identified any additional efficacy issues for discussion.

7. Integrated Review of Safety

Safety Summary and Safety Conclusions

A total of 2357 subjects were involved in the development program of NGX-4010; studies were performed in participants with three disease indications: post herpetic neuralgia (PHN), HIV neuropathy (HIV-AN) and diabetic neuropathy (PDN).

1696 participants received NGX-4010 and form the basis for the exposure, demographic, and safety information collected for the development program of NGX-4010. Of those subjects receiving NGX-4010, 1267 (74.4% received one treatment), 429 subjects (25.6%) received two or more treatment and 7% of subjects (n = 107) received 4 treatments. Two hundred and seventy one subjects were followed for 48 weeks or more.

The majority of patch application treatments were of 60 minute duration. The size of the treatment area ranged from 9 cm^2 to 1120 cm^2.

Most subjects with PHN (76%) had treatment areas of 500 cm^2 or below, while the majority of HIV-AN and PDN subjects had treatment areas above 1000 cm^2 (60% and 67%, respectively).

A total of eight studies were conducted in study participants with PHN. These studies were of three types: controlled studies, open label studies and repeat treatment studies.

As the applicant is seeking an indication for the use of NGX-4010 in the prolonged reduction of neuropathic pain associated with PHN, the predominant focus of the review will be the data collected in PHN study participants.

In the controlled PHN studies, 1327 received active treatment, and 789 received control treatment.

The safety of NGX-4010 and control was evaluated by the following parameters:

- The duration of patch application - 30, 60 or 90 minutes. (In PHN participants 81% of active subjects and 91% control subjects received treatment for 60 mins).

- By treatment area $\leq$ 250 cm^2; > 250 to $\leq$ 500 cm^2; >500 and $\leq$ 750 cm^2 and > 750 cm^2. (In the PHN participants, 75% of patients received treatment to an area less than 500cm^2).

- By number of exposures- allowing for analysis of the potential relationship between AE profile and the number of exposures

Two deaths occurred in participants in PHN studies. One death occurred in an 81 year old female, secondary to diverticulitis, 31 days after receiving active treatment. This patient had a past history of colonic polyps, diverticulitis, coronary artery disease, chronic obstructive pulmonary disease. The second PHN death occurred in a 91 year old man who was randomized to the control arm, and who died secondary to multi-organ failure, after hospitalization with

ileus, pneumonia, and acute renal failure. Both deaths were considered to be unrelated to study treatment.

The overall incidence of severe adverse events (SAE's) was low during the NGX-4010 clinical development program, and was balanced in the active and the control study arms, 5.9% in the active arm and 4.3% in the control arm. The majority of the SAE events (29 of 37) events were considered unrelated to study treatment. Seven SAE's were considered to be related to application site pain and burning, and exacerbations of pain. One SAE (accelerated hypertension) occurred in a 69 year old man (*Subject # 191018*) who randomized to the active arm. This participant developed a BP of 230/120 on Day 3 after patch removal, requiring three days of hospitalization for control of hypertension.

The proportion of adverse discontinuations was low (< 1%); Within the controlled PHN studies, an early termination due to AE's occurred in 11 NGX-4010 subjects (0.8%) and 5 control subjects (0.6%). In the NGX-4010 treatment group, the adverse reaction most frequently leading to discontinuation was pain exacerbation (0.3%).

In the repeat treatment studies, 19 (2.8%) subjects terminated early due to an AE. In the open label studies, no subjects terminated early due to an AE.

In the controlled PHN studies, treatment-emergent adverse events (TEAE's) occurred in 98% subjects in the NGX-4010 group and 88% of the controls. The majority of these were TEAE's were application site reactions, occurring in 98% of NGX-randomized subjects and 75% of the control subjects. The incidence of application site was consistently greater in the active arm as compared to the control arm. Within the realm of application site reactions, *application site erythema* occurred most frequently, followed by *application site pain*, then *application site papules,* and lastly *application site edem*a. The application site reactions were transient and self-limited and resolved by Day 3 following patch removal.

Of the most frequently reported *non-application site* AEs during this developmental program, nausea, vomiting, and dizziness (may possibly be attributed to the use of opioids as rescue medication for treatment-related discomfort and pain).

Subjects who experienced larger increases in pain (≥2 units), who required pain medication for treatment-associated pain or who had a treatment-associated increase in systolic blood pressure (≥ 30 mmHg) did not appear to experience any significant clinical sequelae or an altered AE profile.

Apart from the application site reactions described above, submission specific safety concerns include the following:

1) Elevations in blood pressure were slightly higher in NGX-4010 subjects compared with control subjects. This reflects the small, transient increases in blood pressure that were seen on the day of treatment and were associated with treatment-related changes in pain, and were probably as a result of increased sympathetic outflow because of pain.

Transient increases in pain were commonly observed on the day of treatment in patients treated with NGX-4010. Pain increases occurring during patch application usually began to resolve after patch removal. On average, pain scores returned to baseline by the end of the treatment day and then remained at or below baseline levels.

2) Cardiac Disorders

The incidences of treatment-emergent AE's and SAEs coded to the SOC of "Cardiac Disorders" in PHN subjects were higher in the NGX-4010 group (4.6%) compared with the control group (2.9%). The overall incidence of cardiac SAEs in the Pooled C116 and C117 studies (PHN) was low, but slightly higher in the NGX-4010, 6 of 417 [1.4%] versus 1/401 [0.25%] in placebo. However, it is important to note that the incidence of treatment-related Cardiac AEs and cardiac AE's that occurred *within the first 7 days after treatment*, a timeframe during which most of the transient treatment-associated effects of NGX-4010 would be expected to occur, was low (< 1%) and similar between the treatment groups. Given the pharmacokinetics of the product, it seems unlikely that the cardiac adverse events observed much beyond the first few days after dosing are related to the study drug.

The incidence of cardiac disorders appeared to be highest in subjects with high cardiovascular risk, defined as a prior medical history of cerebrovascular accident or cardiovascular disease (with or without prior intervention). The overall incidence of SAE's was 18 % in NGX-4010 subjects with a CV risk factor, as compared with 10.2 % in NGX-4010 subjects with no CV risk.

In the controlled PHN Studies, the frequencies of AE's and SAE's in the "Cardiac Disorders" SOC were *not* related to: detectable plasma capsaicin levels, to the pain experienced during treatment (maximum change in NPRS score), to the change in BP during treatment or to the use of rescue medication.

3) Treatment-related incidences of coughing and sneezing related to inadvertent capsaicin contamination.

This specific adverse event occurs when the patch is removed too quickly and some capsaicin is aerosolized. It is minimized by careful patch removal.

The overall adverse reaction profile of NGX-4010 was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

NGX-4010 did not appear to be associated with any systemic AEs. There was an increased incidence of nausea and vomiting in patients treated with active drug that is explained by the relatively high use of rescue analgesics (narcotics). Only transient, low levels of systemic exposure to NGX-4010 have been shown to occur in one-third of patients treated with NGX-4010. These levels returned to below levels of quantification within hours of treatment. No

differences in AE incidences were observed that would suggest that systemic capsaicin exposures impacted the AE profile of NGX-4010.

No clinical drug interaction studies were performed as data from *in vitro* cytochrome P450 inhibition and induction studies showed that capsaicin did not inhibit or induce liver cytochrome P450 enzymes at concentrations which far exceeded those measured in blood samples. Therefore, interactions with systemic medicinal products were considered unlikely.

Neurological testing, both clinical and by QST, did not demonstrate any evidence of detrimental effects of NGX-4010 on sensory function in subjects with PHN, HIV-AN and PDN.

No evidence of a reduction in protective sensory function was observed in subjects who received up to four NGX-4010 treatments over the course of 1 year and there was no evidence of an increased incidence of adverse events, dermal irritation or intolerability with repeated treatment.

OVERALL SAFETY CONCLUSION(S)

NGX-4010 is relatively safe to administer. The incidence of application site reactions was greater in the NGX-4010 arm. Any adverse event such as hypertension around the time of dosing was monitorable and self-limited.

7.1 Methods

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

The NGX-4010 clinical development program, informing to the safety of the drug in subjects with peripheral neuropathic pain consists of 12 controlled and uncontrolled clinical studies.

Studies were conducted in subjects with peripheral neuropathic related to the following diseases:

1. Postherpetic neuralgia (PHN)
2. Human Immunodeficiency Virus-associated neuropathy (HIV-AN), and
3. Painful diabetic neuropathy (PDN).

A total of 2,357 subjects were enrolled in these studies and 1,696 received NGX-4010. Of those subjects receiving NGX-4010, 1,267 subjects (74.4%) received 1 treatment and 429 (25.6%) received 2 or more treatments. Data from these studies form the basis for the exposure, demographic, and safety information for the NGX-4010 program.

Five controlled studies were conducted in subjects with PHN, including the two pivotal Phase 3 studies (Studies C116 and C117), discussed in detail in Sections 5 and 6 of this report. [Table 7.1.1(a)].

Three Phase 2 /3 studies (Studies C102, C108, and C110) supported the pivotal studies. (See Table 7.1.1(b), following).

Table 7.1.1(c) shows the open label repeated treatment studies used in comparing the incidence of AE's occurring with repeated treatment applicationss.

Studies C116 and C117 were two pivotal Phase 3, 12-week, randomized, double-blind, controlled, multicenter evaluation of the efficacy, safety, and tolerability of a single 60-minute application of NGX-4010 compared with a low concentration capsaicin control patch for the treatment of PHN. These studies were discussed in detail in Section 5.3 of this review. [(See Schematic Table 7.1.1(a)]

TABLE 7.1.1(a): SCHEMATIC TABLE SHOWING CONTROLLED TRIALS CONDUCTED IN PATIENTS WITH PHN

STUDY#	PHASE Disease	DESIGN Duration of Study	N Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
PIVOTAL CONTROLLED STUDIES					
C116	3 PHN	Rand 1:1 DB, PC 12 weeks	N=402; (Active- 206 Control- 196) 60 min	Clinical effectiveness & safety/tol	Pivotal
C117	3 PHN	Rand 1:1 DB, PC 12 weeks	N= 416; (Active-212 Control- 204) 60 min	Clinical effectiveness & safety/tol	Pivotal

Supportive controlled studies in PHN -[TABLE 7.1.1(b)]

Study C102 was a Phase 2, multicenter, double-blind controlled pilot study in two parts: an initial open-label phase followed by a double-blind, controlled phase to evaluate efficacy, safety, and tolerability over 28 days of a single 60-minute application of NGX-4010 (640 mcg/cm^2) compared with Control (3.2 mcg/cm^2) in subjects with PHN. The initial 6 subjects, who were treated with open-label NGX-4010, are included in the integrated data for the Open-Label Studies.

Study C108 was a Phase 2/3, multicenter, randomized, double-blind, controlled, dose-finding study to evaluate the efficacy, safety, and tolerability of a single application of NGX-4010 (640 mcg/cm^2) or Control (3.2 mcg/cm^2) for 30, 60, or 90 minutes. The study duration of 52 weeks consisted of a 12-week double-blind period followed by a 40-week open-label extension in which subjects could be eligible for up to 3 open-label repeated treatments, administered a minimum of 12 weeks apart. During the initial 12-week double-blind period, subjects were seen at 3 follow-up visits subsequent to the patch application (Week 4, Week 8, and Week 12). Data from the open-label extension portion of this study are included in the Repeat-Treatment Studies grouping.

Study C110 was a Phase 3, multicenter, 12-week, randomized, double-blind, controlled study to evaluate efficacy, safety, and tolerability of a single 60-minute application of NGX-4010, compared with Control in subjects with PHN.

TABLE 7.1.1(b): SCHEMATIC TABLE SHOWING CONTROLLED TRIALS CONDUCTED IN PATIENTS WITH PHN

STUDY#	PHASE Disease	DESIGN Duration of Study	N Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
SUPPORTIVE CONTROLLED STUDIES					
C108	2/3 PHN	Rand 3:3:3 to 1:1:1 ; PC, DB Foll by OL extension Phase Stdy #118 x 40 wks, w q12 wkly applic	Active N= 72 (30 mins) N= 77 (60 mins N= 73 (90 mins) Control N= 23 (30 mins) N= 29 (60 mins) N= 25 (90 mins) 90- 60- 30 mins	Clinical effectiveness & safety/tol	Assessed efficacy in multiple durations of patch application
C102 2 parts: 1) Initial OL 2) DB Phase (over 28 days)	2 PHN	Rand 2:1, PC, DB Eligible to continue Stdy # 106	N= 6 subjects only	Feasibility, Tol, safety & efficacy	Supportive of pivotal trials, BUT trial Only 4 weeks duration
C110	3 PHN		N=155; (102- active 53- control) 60 min	Clinical effectiveness & safety/tol	Only study enrolling subjects - 3 months post vesicular crusting

TABLE: 7.1.1(c): SCHEMATIC TABLE SHOWING REPEAT TREATMENT, OPEN LABEL STUDIES

STUDY#	PHASE Disease	DESIGN Duration of Study	N Duration of application	PURPOSE	RELEVANCE TO EFFICACY & SAFETY
REPEAT TREATMENT /OPEN LABEL STUDIES					
C106	Phase 2 PHN	OL extension of Study 102 48 to 52 weeks	N = 24 60 mins	Safety/ tolerability of repeated dosing	Provided an OL extension to Study 102. Offered 6 week between subsequent re-treatment
C118 (enrolled subjects who completed Studies C116/C110, & C108)	2	OL extension study, single arm, safety & efficacy	N= 106 PHN(n= 54) HIV (n= 52)	Safety/ tolerability of repeated dosing	OL extension provides data for analysis following repeated treatment & development of tolerance
	PHN & HIV	Up to one year	60 mins		
C108 12 week DB, Foll by 40 week OL portion	2/3	40 week OL portion	N=222 (DB) N=77 (OL) 30-60-90 mins	Safety/ tolerability of repeated dosing	OL extension provides data for analysis following repeated Rx, & development of tolerance Systemic lidocaine blood levels performed

Source: FDA Compilation (based on information supplied by sponsor)

The applicant is seeking an indication of *the prolonged reduction of neuropathic pain associated with post herpetic neuralgia*; therefore the predominant focus of this safety analysis will be on the safety data collected in the controlled PHN studies.

However the relative proportions of the application site reactions between active and control groups were *confounded* by the differential reporting of the application site AE's in the early (supportive trials) versus the later (pivotal) trials.

In the early trials, the patch was applied for 30, 60 and 90 minutes, and the application site AE's of pain and erythema occurring on the day of treatment were recorded as a part of NPRS assessments (i.e., pain) or dermal assessments, unless they constituted an SAE; in the later *pivotal studies*, the patch was uniformly applied for 60 minutes on all participants, and all application site reactions were collected as AE's. Consequently, in evaluating the more commonly occurring adverse events, I will comparatively evaluate the relative proportions of AE's occurring in the active and control arms of the later pivotal trials C116 and C117.

7.1.2 Adequacy of Data

Verbatim AE's were mapped to a preferred term and SOC using MedRA (version 9.0). The number and proportion of subjects reporting one or more AE's were tabulated and summarized by AE preferred term and AE SOC. Similar summaries were created for AE's that led to study withdrawal and SAE's.

Overall, the applicant's categorization of adverse events was appropriate.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The most common adverse events were related to the application site. Therefore, as described previously, it should be noted that in Study C116, C117 and later studies, all application site reactions that occurred on the day of treatment were recorded as AE's. However, in earlier controlled PHN Studies, application site erythema and pain that occurred on the day of treatment were recorded as a part of NPRS assessments (i.e., pain) or dermal assessments, unless they constituted an SAE.

As a result, the integrated 60-minute duration groups (for both the NGX-4010 and control groups) generally have higher incidences of application site AE's compared with the 30- and 90-minute duration groups. Therefore, an integrated analysis of the relationship between the

incidences of application site erythema and pain and duration of exposure to NGX-4010 is confounded by the *differential reporting of application site AEs* between early and later studies. Consequently, the potential relationships between the incidences of the aforementioned application site AE's (application site erythema and pain) and duration of exposure cannot be fully assessed for the combined/pooled controlled PHN Studies. Therefore in assessing the common adverse events by treatment arm, the primary source was the pooled adverse event data of the later pivotal trials, C116 and C117, where all application site reactions were collected as AE's.

A high proportion of study participants (99% of subjects on NGX-4010 arm and 88% participants randomized to the control arm) reported at least one AE. Most of the TEAE's were administration site conditions (97% in the active arm, and 76% in the control arm).

Of the non application site AE's, nausea and vomiting occurred in a greater proportion of NGX-4010 randomized subjects 5% and 3% respectively, versus 2% and 1% respectively in the control randomized subjects. This finding is attributed to the use greater use of opioid narcotics in the subjects randomized to the active group.

TABLE 7.1.3: SUMMARY OF TEAE FOR C116 AND C117, PHN INDICATION INCLUDING EVENTS WITH >/=1% INCIDENCE IN POOLED TREATED GROUP AND WHERE POOLED TREATED GROUP IS MORE FREQUENT BY AT LEAST 1%

System Organ Class / Preferred Term	NGX-4010 60 Mins (N=417)	Control 60 Mins (N=401)
Number of subjects with at least one adverse event reported	411 (98.6%)	351 (87.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	406 (97.4%)	303 (75.6%)
APPLICATION SITE ERYTHEMA	387 (92.8%)	269 (67.1%)
APPLICATION SITE PAIN	248 (59.5%)	100 (24.9%)
APPLICATION SITE PAPULES	35 (8.4%)	11 (2.7%)
APPLICATION SITE OEDEMA	25 (6.0%)	2 (0.5%)
APPLICATION SITE PRURITUS	16 (3.8%)	9 (2.2%)
INFECTIONS AND INFESTATIONS	72 (17.3%)	69 (17.2%)
NASOPHARYNGITIS	12 (2.9%)	7 (1.7%)
SINUSITIS	12 (2.9%)	3 (0.7%)
BRONCHITIS	9 (2.2%)	5 (1.2%)
GASTROINTESTINAL DISORDERS	42 (10.1%)	36 (9.0%)
NAUSEA	19 (4.6%)	7 (1.7%)
VOMITING	12 (2.9%)	3 (0.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	46 (11.0%)	28 (7.0%)
PRURITUS	9 (2.2%)	2 (0.5%)
ECCHYMOSIS	4 (1.0%)	0 (0.0%)
INVESTIGATIONS	19 (4.6%)	17 (4.2%)
BLOOD PRESSURE INCREASED	7 (1.7%)	3 (0.7%)

Note: Control = Capsaicin 3.2 mcg/cm2 ; NGX-4010 = Capsaicin 640 mcg/cm2 . Patients are summarized under received treatment.
Note: At each level of summation (overall, system organ class, preferred term), patients reporting more than one adverse event are counted only once.
Note: NGX-4010 60 minutes: From studies C116 and C117.
Control 60 minutes: From studies C116 and C117.
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SOURCE: FDA 1.3 SUPPLIED BY SPONSOR AT FDA'S REQUEST

7.2 Adequacy of Safety Assessments

An adequate number of study participants were exposed to study drug as part of the developmental program of NGX-4010.

A total of 2,357 subjects were involved in the overall development program of NGX-4010. While adequate numbers of patients were exposed to drug, the predominant demographic group exposed was Caucasian (90%), and these proportions are not representative of racial make-up of the external "real world" population in which the drug will be dispensed.

Of the 1,395 subjects participated in the PHN clinical studies, nine hundred and twenty were exposed to NGX-4010, while 475 were exposed to the control patch. The sponsor is seeking an indication for treatment of PHN, therefore the focus of the safety analysis will be the pooled PHN controlled trials.

The safety and tolerability of NGX-4010 were evaluated during the NGX-4010 clinical development program by the following safety assessments:

• Adverse event (AE) monitoring

• Clinical laboratory tests – hematology and serum chemistry parameters

• Vital signs and physical examinations – (oral temperature, blood pressure [BP], heart rate [HR], and respiratory rate [RR]) were collected at the Screening, Treatment, Interim and Termination Visits.

On the day of treatment, vital signs were recorded immediately prior to application of the topical anesthetic, during anesthetic application, during patch application, and at several time points after patch removal. On the day of treatment, oral temperature was only recorded prior to application of local anesthetic.

• Electrocardiograms (ECGs) (Studies C102, C116 and C117)

For *Study C102*, continuous ECG monitoring was conducted at screening and during patch application, for the purpose of safety monitoring.

For *Study C116*, ECG's were conducted at the Screening, Study Patch Application (Day 0), Week 4, and Week 8 Visits. During the Study Patch Application Visit, an ECG was conducted immediately after patch removal.

For *Study C117*, ECG's were conducted at the Screening and Week 12/Termination Visit.

Additionally, ECG's were done at Screening for the following studies: C107, C108, C109, C110, C111, C112 and C119.

• Evaluation of duration of patch application

• Pain assessment (Numeric Pain Rating Scale [NPRS]) and change in NPRS scores during and after treatment.

• Change in NPRS scores on the evening of the day of treatment (Studies C107, C108, C110, C116, C117, and C119 only)

• Number of subjects requiring rescue pain medication during the first 5 or 7 days after patch application

• Dermal assessments using the following scoring system:
0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible/ minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site.

The treated areas were inspected for dermal changes at the Screening, Treatment, Interim, and Termination Visits. At the Treatment Visits, dermal assessments were performed prior to anesthetic application, immediately after anesthetic removal, immediately after patch removal, and 2 hours post-patch removal.

The doses and durations of exposure were appropriate. All appropriate clinical tests were performed on the patients who were exposed to the drug.

All necessary and appropriate animal tests were performed. The drug assessment of the drug's metabolism was adequate.

Blood draws to test for systemic levels of capsaicin and capsaicin metabolites were performed in subsets of patients in specific studies. Capsaicin or capsaicin metabolite levels were rarely detected in the plasma, and therefore drug-drug interaction studies were not considered to be vital.

Overall, the quality and completeness of the safety data was appropriate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The *extent of exposure* is presented for all indications overall, and by treatment duration, treatment area, and indication for All Controlled Studies in Table 7.2.1.

Adequate numbers of participants were exposed to NGX-4010 were enrolled. A total of 1327 subjects received NGX-4010 treatment in the controlled Studies, while 789 subjects received control treatment. Overall, the majority of subjects (65% and 78% of NGX-4010 and control subjects, respectively) received a 60-minute patch application.

Within the PHN population, 81% and 91% of NGX-4010 and control subjects, respectively, received treatments for 60 minutes.

TABLE 7.2.1: SHOWING EXPOSURE BY TREATMENT DURATION, TREATMENT AREA, AND INDICATION FOR ALL CONTROLLED STUDIES

	NGX-4010			Control		
Subjects, n (%)	**PHN**	**HIV-AN**	**Total**	**PHN**	**HIV-AN**	**Total**
Duration (of the first active treatment)						
N	767	560	1327	543	246	789
90 minutes	73 (9.5)	75 (13.4)	148 (11.2)	25 (4.6)	29 (11.8)	54 (6.8)
60 minutes	622 (81.1)	246 (43.9)	868 (65.4)	495 (91.2)	118 (48.0)	613 (77.7)
30 minutes	72 (9.4)	239 (42.7)	311 (23.4)	23 (4.2)	99 (40.2)	122 (15.5)
Area (cm^2)						
N	766	560	1326	543	246	789
≤ 250	315 (41.1)	5 (0.9%)	320 (24.1%)	238 (43.8)	3 (1.2%)	241 (30.5%)
> 250 and ≤ 500	270 (35.2)	35 (6.3%)	305 (23.0%)	190 (35.0)	18 (7.3%)	208 (26.4%)
> 500 and ≤ 750	127 (16.6)	85 (15.2%)	212 (16.0%)	86 (15.8)	33 (13.4%)	119 (15.1%)
> 750	54 (7.0)	435 (77.7%)	489 (36.9%)	29 (5.3)	192 (78.0%)	221 (28.0%)

DB=double-blind.
NOTES:
1. PHN data were derived from Studies C102 (DB portion), C108 (DB portion), C110, C116, and C117.
2. HIV-AN data were derived from Studies C107 (DB portion), C112, and C119.
Source: Source Table 1.2.1 (Section 22).

Source: ISS p96/330

With regard to the *area of skin treated,* in PHN subjects over three-quarters of PHN subjects received treatment to an area of ≤500 cm^2 in size, for both NGX-4010 and control groups, whereas in HIV-AN subjects, over three-quarters of study participants received treatment on both limbs for a combined treatment area of ≥750 cm^2.

TABLE 7.2.2: EXPOSURE BY INDICATION AND SIZE OF TREATMENT AREA (ALL STUDIES)

Subjects, n (%) [a]	PHN	HIV-AN	PDN	Total
NGX-4010				
Area ≤ 250 cm^2	382 (41.6)	7 (1.0)	0	389 (22.9)
Area > 250 cm^2 and ≤ 500 cm^2	319 (34.7)	42 (6.1)	1 (1.1)	362 (21.4)
Area > 500 cm^2 and ≤ 750 cm^2	151 (16.4)	102 (14.9)	11 (12.1)	264 (15.6)
Area > 750 cm^2	67 (7.3)	534 (78.0)	79 (86.8)	680 (40.1)
Total Number of Subjects [b]	919	685	91	1695
Control				
Area ≤ 250 cm^2	207 (43.6)	3 (1.6)	0	210 (31.8)
Area > 250 cm^2 and ≤ 500 cm^2	167 (35.2)	17 (9.1)	0	184 (27.8)
Area > 500 cm^2 and ≤ 750 cm^2	74 (15.6)	30 (16.1)	0	104 (15.7)
Area > 750 cm^2	27 (5.7)	136 (73.1)	0	163 (24.7)
Total Number of Subjects	475	186	0	661

DB=double-blind; OL=open-label.
NOTES:
1. Subjects in extension studies (C106, C107, C108) who first received Control and subsequently received active are counted under NGX-4010. The Control group only contains subjects that never received NGX-4010.
2. PHN data were derived from Studies C102, C106, C108 (DB and OL portions), C110, C111 (PHN patients), C116, C117, and C118 (PHN patients). For Study C106, the number of exposures in previous trials is included.
3. HIV-AN data were derived from Studies C107 (DB and OL portions), C109, C111 (HIV-AN patients), C112, C118 (HIV-AN patients), and C119.
4. PDN data were derived from Study C111 (PDN patients).
a. Treatment areas of the first active treatment.
b. One PHN subject had missing data for treatment area.
Source: Source Table 1.1.1 (Section 22).

SOURCE: ISS p97/330

7.2.2 Explorations for Dose Response

The extent of exposure to NGX-4010 for subjects in All Studies is summarized overall, by indication, and by the size of treatment area as shown in Table 7.2.1. The size of the treatment area tended to vary by indication. About three-quarters of subjects with PHN received NGX-4010 or control treatment over an area of ≤500 cm^2 in size, whereas the majority of HIV-AN and PDN subjects received treatment to both feet for a combined treatment area of ≥750 cm^2. In an effort to examine the safety of repeated exposures the incidence of AE's occurring in two repeated treatment studies (C118 and C106) were analyzed.

Study C118 was an open-label, Phase 2, single-arm, multicenter evaluation of the safety and efficacy of NGX-4010 for the treatment of PHN and HIV-AN.

The study design of C118 allowed for the analysis of safety following repeated applications.

Subjects who received multiple treatments were more likely to be in the study longer than subjects receiving 0 or 1 treatment and, thus, had more opportunity to experience AEs. Therefore, an analysis of treatment-emergent AEs with an onset date within 12 weeks of treatment was performed and summarized for each NGX-4010 treatment received (i.e., first, second, third, or fourth)

The results of this analysis showed a similar proportion of PHN subjects reporting any AEs within 12 weeks following the first (98%), second (95%), third (100%), or fourth (95%) to NGX-4010 treatment. Likewise, an analysis of HIV-AN subjects reporting any AEs within 12 weeks showed similar proportions following the first (88%), second (90%), third (83%), or fourth (84%) to NGX-4010 treatment.

Among PHN subjects, the incidence of general disorders and administration site conditions was similar with multiple treatments

- First exposure = 98%;
- Second exposure = 93%;
- Third exposure = 97%;
- Fourth exposure = 95%

Similar results were observed for HIV-AN subjects.

No relationship between number of exposures and the occurrence of AEs was noted for any AE category. The results of this analysis also suggest that there was no cumulative toxicity that occurred for any increased treatment-emergent AEs..

A similar analysis was performed for severe AE's within 12 weeks following the first treatment cycle (9%):

- Second treatment cycle (10%),
- Third treatment cycle (9%), or
- Fourth treatment cycle (10%) NGX-4010 treatment.

No relationship between number of exposures and occurrence of severe AEs was noted for any AE category, including general disorders and administration site conditions.

The results of this analysis suggest that no cumulative toxicity occurred for any severe treatment-emergent AEs.

Study C106 was a Phase 2, uncontrolled open-label extension of Study C102. The design of this study offered another opportunity to evaluate the safety of exposure to repeated cycles of NGX-4010. Study C106 was an extension study to Study C102, extended the combined study duration to 1 year, and offered up to 3 additional single-dose treatments with open-label NGX-4010.

This study demonstrated that long-term (up to 1 year) treatment with NGX-4010 was feasible and with a good overall tolerability in subjects with painful PHN, with all subjects completing at least 90% of the 60 minute treatment with NGX-4010 during each cycle.

No evidence of increased reporting of AEs in subjects receiving 1 or more re-treatments was observed.

Dermal irritation was not severe and generally resolved within a few days.

Clinically significant changes in laboratory values, vital signs, and physical findings were not observed during the course of the study. Within-subject changes in vital signs measurements on the day of treatment were consistent with random fluctuations typically seen with repeated measurements.

While a small number of patients were enrolled in Study 106, sensory examinations of the treated areas and determination of percentage of allodynia in painful areas were highly variable with no evidence of a trend over the course of the study that would indicate permanent sensory nerve damage.

Evidence for safety and tolerability was found in dermal assessments, duration of patch application, and pain assessments during treatment, as well as use of rescue medication during and after treatment.

All subjects completed at least 90% of the 60 minute treatment with NGX-4010 during each cycle. Tolerability of treatment was consistent with each subsequent treatment. No safety issues were identified by AEs or significant changes in blood chemistry or vital signs.

Preliminary efficacy as evidenced by NPRS scores suggested that a 60 minute treatment with NGX-4010 provided pain relief in subjects with PHN which lasted at least 12 weeks. A mean decrease in pain scores of approximately 30% was maintained during each treatment cycle regardless of the number of treatments received. Responses on the BPI indicated that subjects' pain relief, pain scores, and how the subject's pain interfered with daily activities were maintained from Study Entry to Termination.

The results of these extension studies suggest that NGX-4010 treatment is associated with a reduction in PHN pain over a 12 week period and appears to be safe and well-tolerated when administered up to 4 times over the course of a year.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical data revealed no particular safety concerns for humans based on conventional studies of safety pharmacology, single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive toxicity, or carcinogenic potential. The results of these studies are summarized in the Pharmacology/Toxicology Review performed by Dr Lawrence Leschin.

No special in vitro testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical laboratory tests and ECG's and serum pregnancy tests (in females) were performed at screening, at termination and at early termination study visits.

Adverse events and vital signs were collected at the Study Patch application visits and at regular intervals up to 2 hours after study patch removal. Adverse event data was also collected at the Week 4 and Week 8 interval visits and at the Week 12 termination or early termination visit.

The frequency of collection of routine clinical and adverse event data was considered adequate for this single dosing product.

7.2.5 Metabolic, Clearance, and Interaction Workup

No clinical drug interaction studies were performed as only transient, low levels of systemic exposure to NGX-4010 have been shown to occur in one-third of patients treated with NGX-4010. Data from *in vitro* cytochrome P450 inhibition and induction studies showed that capsaicin did not inhibit or induce liver cytochrome P450 enzymes at concentrations which far exceeded those measured in blood samples. Therefore, interactions with systemic medicinal products were considered unlikely.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Targeted neurological/sensory assessments were performed in Studies C115, C101 and C107 in order to evaluate whether the nerve function was permanently impaired as a result of application of the 8% capsaicin patch. At Baseline, neurological/sensory assessments were performed and assessments were similar in the two treatment groups,

There were few differences during the study between the two treatment groups in the results of the neurological/sensory assessments. At some time points, better mean scores were observed in the NGX-4010 group compared to the Control group. These results indicate that the capsaicin in

NGX-4010 did not adversely affect sensory nerve function, supporting the neurological safety of the product.

7.3 Major Safety Results and Discussions

Case report forms (CRFs) and the narrative summaries of all deaths, severe adverse events (SAE's), and adverse dropouts in all the disease indications studied in the developmental program of NGX-4010 were reviewed in detail.

7.3.1 Deaths

Throughout the overall NGX-4010 development program, nine study participants died while on study.

Seven deaths occurred on the HIV neuropathy trials, while two deaths occurred in subjects in the PHN trials. Of the two deaths occurring in the PHN trials, one death occurred in a study participant from Study C117 who was randomized to the active arm, while the other death occurred in a subject assigned to the control arm of Study C108. None of these deaths were considered to be related to study treatment.

More detailed narratives of the deaths occurring on the PHN studies are noted below:

Subject 1934597, assigned to the *active* arm of Study C117, was an 81-year-old white female with a medical history of PHN, herpes zoster, medullary sponge kidneys, colon polyps, diverticulitis, gastric polyps, coronary artery disease, myocardial infarction, congestive heart failure, hypertension, and chronic obstructive pulmonary disease (COPD), who was hospitalized for diverticulitis and subsequently died.

On Day 31, after treatment with *active drug* for 60 minutes, the subject was admitted to the ER with complaints of feeling ill and weak. Diverticulitis was reported as the primary cause of death, with COPD exacerbation contributing to the death. The death was not reasonably associated with the study drug.

Subject 1905, a 91-year-old white male who received 90-minute *control* treatment in Study C108, died of multi-organ failure. On Day 92 of study, the subject complained of abdominal pain and presented to the ER. The subject was felt to have an ileus, right lower lobe pneumonia, anemia, and cholecystitis. No surgical intervention was performed. The family requested that the patient not be resuscitated. The subject continued to be in respiratory distress and died on Day 108 of multi-organ failure primarily aspirate pneumonia and acute renal failure. No autopsy was performed. The event was considered by the Investigator to be of remote or no relationship to study treatment and was attributed to intercurrent illnesses. The death was not reasonably associated with the study drug.

The deaths that occurred in the PHN study population appeared to be deaths that would not be

unexpected in an elderly patient population, and were felt to be unrelated to study drug.

The patients who died while on the HIV neuropathy trials included the following:

Six HIV-AN subjects from Study C107 (a 12-week Phase 3, randomized, double-blind, controlled evaluation of the efficacy, safety, and tolerability of a single application of NGX-4010 compared with control for the treatment of painful HIV-AN. The 12-week double-blind phase was followed by a 40-week open-label phase.)

Of the six HIV-AN subjects who died in Study C107, four subjects died while on *active* drug, while two subjects died while on *control* arm.

The four subjects who died on the active drug arm included:

- S*ubject # 1208* died due to sepsis during the 12-week double-blind phase
- The remaining three HIV-AN subjects died during the 40-week open-label extension phase. *Subject #1824 and Subject # 3109* died due to pneumonia, and *Subject # 4501* died due to a suspected drug and alcohol overdose.

The two control subjects died during the 12-week double-blind phase included *Subject # 1519* who died due to unknown causes and *Subject # 4617* died at home due to a presumed drug overdose.

The reader is reminded that in Study 107, participants were randomized 3:1 to receive NGX-4010 or control. This 3:1 allocation ratio may explain the disparity between proportions of deaths on the active arm relative to the deaths occurring in the control study arm.

The seventh death occurring on the HIV neuropathy trials occurred in Study C119. (*Subject # 212-1560* died from pre-existing arteriosclerosis).

None of the deaths in the HIV neuropathy trials appeared to be associated with NGX-4010.

7.3.2 Nonfatal Serious Adverse Events (SAE's)

In Study C116,
Sixteen subjects (11 in the NGX-4010 group and 5 in the Control group) experienced 20 SAE's.

All SAE's were considered to be of remote or no relationship to study medication, with the exception of one event of accelerated hypertension which is related to NGX-4010.

A summary of this treatment-related event is presented below:

Subject 191018 experienced an SAE of increased blood pressure that occurred on the day of treatment with NGX-4010 and was considered to be possibly related to study medication. The subject, a 69-year-old male, had a history of hypertension and was receiving treatment with multiple antihypertensive medications. Prior to patch application the subject's blood pressure

ranged from 150–170/90–100 mmHg. The subject experienced a further increase in blood pressure during and after patch application (210/110 mmHg 85 minutes after patch removal) that returned to near pre-patch application levels (150–180/80–108 mmHg) the next day (Day 1). The subject had a plasma capsaicin level of 1.19 ng/mL 1 hour after patch removal; there were no detectable plasma capsaicin levels at any other time points on Day 0 or at 24 hours after patch removal.

On Day 3, the subject presented to the emergency room with a blood pressure of 230/120 mmHg. The subject did not respond to treatment in the emergency room and was admitted for the treatment of accelerated hypertension.

On Day 6 the event resolved, his blood pressure was 144/85 mmHg and heart rate was 59 bpm. He was discharged with clonidine patch, amlodipine, labetalol, hydrochlorothiazide, lisinopril, and lovastatin.

This episode of accelerated hypertension was likely associated with the pain of NGX-4010 application. The issue of application site pain and cardiovascular effects is explored in detail in Section 7.3.4 of this review. Given the small number of individual SAE's reported, comparisons of individual SAE incidences should be interpreted with caution.

Three subjects in the NGX-4010 treatment arm experienced severe cardiac SAE's and 1 subject in the Control group experienced a cardiac SAE of moderate severity.

Summaries of these SAE's are presented below:

Subject 1420234, a 71-year-old female with a history of hypertension, diabetes mellitus, and severe bilateral internal carotid artery stenosis, experienced severe acute coronary syndrome and severe cardiac tamponade. She had a markedly abnormal ECG at Screening (severe bradycardia [heart rate of 38 bpm] and inverted T-waves). Due to severe bradycardia, her baseline dose of metoprolol was decreased. She subsequently underwent treatment with NGX-4010 without difficulty. A transient increase in pain and blood pressure during treatment was observed. Both of these parameters returned to baseline 85 minutes after patch removal. Following patch removal, her ECG showed a heart rate of 51 bpm and flat T-waves.

On Days 4 and 9, the subject complained of chest pain and noted she had had similar sensations since her metoprolol dose was decreased due to the bradycardia. She was told by her physician to increase her metoprolol dosage.

On Days 28 and 63, ECG's demonstrated sinus bradycardia and inverted T-waves. On Day 80, the subject was admitted for evaluation of severe chest pain, was found to have severe coronary artery disease, was diagnosed with acute coronary syndrome, and a coronary artery bypass graft was performed on Day 81. She was underwent a re-operation on Day 82 for a cardiac tamponade due to a leak of the right coronary artery graft. The subject was discharged from the hospital on Day 91. The acute coronary syndrome resolved on Day 90 and the cardiac tamponade resolved

on Day 82. Given the history of heart disease, the limited systemic absorption of NGX-4010, abd the short half-life of capsaicin, this SAE does not appear to be related to study drug.,

Subject 181330, a 78-year-old male with a history of severe ischemic cardiomyopathy, hypertension, diabetes mellitus, and status post aortic valve replacement, experienced severe congestive cardiac failure. Prior to treatment, the subject developed severe contact dermatitis due to poison ivy and was treated with dexamethasone on Days -14 to -1. He tolerated treatment with NGX-4010 well; despite a transient increase in pain, the subject's blood pressure remained relatively stable during and after treatment. Blood samples for capsaicin and capsaicin metabolites were obtained over 3 hours after patch removal and again at 24 hours. There was no detectable plasma capsaicin levels observed in any of these blood samples. The subject had been experiencing fluid retention and worsened control of diabetes mellitus, likely due to the dexamethasone treatment. He did not respond to outpatient diuresis, and was admitted to the hospital on Day 6 for management of congestive cardiac failure (diuresis) and diabetes mellitus. The subject was discharged on Day 15 on increased doses of furosemide and insulin. The event resolved on Day 60. It is most likely that the fluid retention and worsening of cardiac function was related to dexamethasone treatment, and was unrelated to NGX-4010 treatment, given the history of heart disease, the limited systemic absorption of NGX-4010, and the short half-life of capsaicin.

Subject 91021, a 73-year-old male with a history of hypertension and increased cholesterol, experienced severe coronary artery disease. The subject received NGX-4010 treatment without event. After patch removal, the subject's ECG was noted to have changed (inverted T-waves) compared to the Screening ECG performed on Day -16. Upon further questioning, the subject admitted to experiencing chest pain, usually associated with meals, since Day -4 (4 days prior to the day of treatment). He did not report chest pain on Day 0 or after. He was referred to the ER and was subsequently admitted with a diagnosis of chest pain. Myocardial infarction was ruled out. A work-up was positive for coronary artery disease.
On Day 1, he was discharged on aspirin and nitrates and scheduled for cardiac catheterization.
On Day 4, the subject was re-admitted for the catheterization and was found to have multi-vessel coronary artery disease, including significant left main coronary artery disease.
On Day 5, a coronary artery bypass graft was performed.
On Day 10, the event resolved and the subject was discharged from the hospital on aspirin, clopidogrel, lopressor, triamterene/hydrochlorothiazide, and amlodipine/atorvastatin.

One subject in the Control group experienced a moderate SAE of coronary artery disease.

Subject 701203 was a 77-year-old male with a history of coronary artery disease, status post percutaneous transluminal coronary angioplasty, status post coronary artery bypass graft, hypertension, and hypercholesterolemia. On Day 3, a scheduled stress test was performed; however, no information from that test was available.

On Day 17, a cardiac catheterization revealed coronary artery "calcification".

On Day 25, the subject was admitted for angioplasty of a 90% first diagonal artery lesion.

On Day 26, the event resolved and he was discharged to home.

Given the underlying age and comorbidities of the subjects experiencing these cardiac SAEs, the limited systemic absorption of NGX-4010 and the short half-life of capsaicin, with the exception of Subject 191018, it seems unlikely that NGX-4010 contributed to the event reported.

In Study C117, nineteen subjects (10 in the NGX-4010 group and 9 in the Control group) experienced SAE's. The SAE's were all events that might be observed in a population of older PHN patients followed for several months. These 19 subjects experienced 21 SAE's, all of which were considered remotely or unrelated to study medication.

Five subjects (2 in the NGX-4010 group and 3 in the control group) withdrew due to non-fatal AE's, all of which were serious, severe, and considered remotely or not related to study medication.

In the Repeat-Treatment PHN Studies the overall incidence of SAE's was low and was not associated with the number of NGX-4010 treatments received:

- First application [4.1%]
- Second application [2.6%]
- Third application [3.1%]

and

- Fourth application [2.3%].

All CRF's in participants with reports of SAE's were evaluated individually. The SAE's reported in the Repeat-Treatment PHN Studies were considered to be of remote or unrelated to study treatment.

A total of 4 events were reported in more than 1 subject: myocardial infarction (3 subjects following the first exposure), colon cancer (1 subject each following the second and fourth exposures), cardiac failure congestive (1 subject each following the second and third exposures), and chest pain (1 subject each following the second and third exposures).

Overall, there is no relationship between the number of exposures and the occurrence severe AE's for any AE category, including general disorders and administration site conditions. The results of this analysis suggest that no cumulative toxicity occurred in response to repeated applications of the patch.

7.3.3 Dropouts and/or Discontinuations

Overall, there were 35 patients who discontinued due to adverse events occurring in the 12 integrated studies, resulting in an overall rate of 35/2357 or 1.5%. Within the controlled studies, early terminations due to AE's occurred in 11 NGX-4010 subjects (0.5%) and 5 control subjects (0.6%)

Narrative summaries and CRF's of patients experiencing adverse withdrawals were reviewed. The withdrawals were largely unrelated to the study medication.

Table 7.3.3.1 shown below provides a summary of the adverse events experienced by study participants that led to study participant's withdrawal from the pivotal trials C116 and C117. Only one study participant in the pivotal trials (*Subject # 1523420)* experienced a dermal skin response to the pre-patch lidocaine.

The other subjects listed in the table below did not experience an AE that could be reasonably attributed to the patch.

TABLE 7.3.3.1: SHOWING ADVERSE EVENTS EXPERIENCED BY STUDY SUBJECTS IN PIVOTAL STUDIES C116 and C117 THAT LED TO WITHDRAWAL FROM STUDY

Study No	Subject #	Sex/ Age	Verbatim Term	Most recent Rx	Day of onset
C116	680023	F/68	Increased chronic back pain	Active 60 mins	13
C117	183368	M/82	Prostate Ca	Active 60 mins	79
C117	282380	F/62	Worsening of Aortic Aneurysm	Active 60 mins	36
C117	1292332	F/80	Pathological Fx (sacral insuffic fx)	Control 60 mins	54
C117	1523420	M/60	Dermal response to lidocaine (Skin reaction)	Active 60 mins	-
C117	1772428	F/68	Cervical vertebral fx	Control 60 mins	78
C117	2342700	F/82	Back pain	Control 60 mins	21

SOURCE: Adapted from ISS, Table 50,p 167/330;Non-Fatal Adverse Events Leading to Study Withdrawal

None of the study participants in either the *open label studies*, or the *healthy volunteer studies* withdrew because of adverse events.

7.3.4 Significant Adverse Events

Not applicable

7.3.4 Submission Specific Primary Safety Concerns

Not applicable

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

The most common adverse events occurring in Studies C116 and C117 are summarized in Table 7.4.1.1 , following:
The five types of application site AE's were the most common AE's, particularly application site erythema and application site pain. The median time to resolution of the four most common application site reactions (application site pain, erythema, pruritus and papules) was one to three days.

Of the 7 non-application site AE's, 4 (dizziness, headache, postherpetic neuralgia, and erythema) occurred at an equal or higher incidence in the Control group compared with the NGX-4010 group.

The remaining three AE's (nausea, vomiting, and nasopharyngitis) occurred at a slightly higher incidence in the NGX-4010 group compared with the Control group; however, the majority of these AEs were not considered to be related to study treatment.

The AE's of nausea and vomiting may be associated with the opioid rescue medications used for the treatment of procedure-associated pain.

The AE profile of the most common treatment-related AEs in the Controlled PHN Studies was similar to the treatment-emergent AE profile.

TABLE SHOWING 7.4.1.1: SUMMARY OF TEAE'S, IN C116 AND C117,(includes events with >=1% incidence in pooled treated group and where pooled treated group is more frequent by at least 1%)

System Organ Class / Preferred Term	NGX-4010 60 Mins (N=417)	Control 60 Mins (N=401)
Number of subjects with at least one adverse event reported	411 (98.6%)	351 (87.5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	406 (97.4%)	303 (75.6%)
APPLICATION SITE ERYTHEMA	387 (92.8%)	269 (67.1%)
APPLICATION SITE PAIN	248 (59.5%)	100 (24.9%)
APPLICATION SITE PAPULES	35 (8.4%)	11 (2.7%)
APPLICATION SITE OEDEMA	25 (6.0%)	2 (0.5%)
APPLICATION SITE PRURITUS	16 (3.8%)	9 (2.2%)
INFECTIONS AND INFESTATIONS	72 (17.3%)	69 (17.2%)
NASOPHARYNGITIS	12 (2.9%)	7 (1.7%)
SINUSITIS	12 (2.9%)	3 (0.7%)
BRONCHITIS	9 (2.2%)	5 (1.2%)
GASTROINTESTINAL DISORDERS	42 (10.1%)	36 (9.0%)
NAUSEA	19 (4.6%)	7 (1.7%)
VOMITING	12 (2.9%)	3 (0.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	46 (11.0%)	28 (7.0%)
PRURITUS	9 (2.2%)	2 (0.5%)
ECCHYMOSIS	4 (1.0%)	0 (0.0%)
INVESTIGATIONS	19 (4.6%)	17 (4.2%)
BLOOD PRESSURE INCREASED	7 (1.7%)	3 (0.7%)

SOURCE: TABLE FDA1.3

The incidence of nausea and vomiting are higher in the active as compared with the control group. This increased opioid rescue medication use is attributed to the opioid use. Patients treated with active used rescue (an oral opioid such as single-ingredient oxycodone or oxycodone/acetaminophen) at a rate of approximately 50% versus 16-21% in the patients treated with control.

Further discussions of the safety issues identified in this review include the following topics:

1. Application site reactions

2. Treatment-Emergent blood pressure-associated adverse events reported by 2 or more subjects in either treatment group by Hypertension around the time of patch application.
3. Treatment-emergent cardiac events.
4. Treatment-related incidences of coughing and sneezing related to inadvertent capsaicin contamination.

1) APPLICATION SITE REACTIONS

As evidenced in the preceeding table, the majority of AE's reported were application site reactions. The incidence of treatment-emergent AE's and treatment-related AE's was higher in the NGX-4010 group (97%) compared to the control group (76%). Most of the application site-related AE's in both treatment groups were mild or moderate in severity.

The most frequently reported treatment-emergent AE's across all study groupings were application site erythema and pain. Application site erythema occurred at similar incidences between treatment groups, while application site pain occurred at a higher incidence in the active group compared with the control group. These application site reactions were transient and on average resolved within 1-3 days.

In order to assess NGX-4010 tolerability, dermal assessment scores, pain evaluations following treatment, and rescue medication use were recorded.

A higher proportion of subjects in the NGX-4010 group, compared to the Control group, reported maximum dermal assessment scores ≥ 2 on the day of treatment. The dermal assessment scores diminished over time; by Week 4, the majority of subjects in both groups had no evidence of dermal irritation (score = 0). Subjects receiving NGX-4010 treatment reported increased mean NPRS scores during patch application.

In the pivotal trials C117 and C116, the proportion of patients using rescue medication was higher in subjects receiving NGX-4010 (~50%) compared to the Control group (16-21%). Similarly in the control arms of the pivotal trials a greater proportion of subjects 79% in C117 and 84% in C116 did not use rescue medication. (See Table 7.4.1.2)

TABLE: 7.4.1.2: SHOWING RESCUE MEDICATION USE IN C117 and C116

	C117			C116	
	Rescue med use	No rescue med		Rescue med use	No rescue med
NGX-4010 N= 212	113 (53%)	99 (47%)	NGX-4010 N= 206	96 (46%)	110 (54%)
CONTROL N= 204	43 (21%)	161 (79%)	CONTROL N= 196	32 (16%)	164 (84%)

SOURCE: Compilation from ISE p132/143

The reason for this is unclear, although this phenomenon may be a reflection of pain resulting from the application of the NGX-4010. Of the subjects who used Roxicodone® or Vicodin® for pain, the mean dose used was similar in the 2 treatment groups. By Days 4 or 5, there were no differences between the 2 treatment groups in the proportion of subjects using Vicodin®, indicating decreased pain and need for rescue medication.
When pain increase following treatment was assessed, a higher proportion of subjects receiving NGX-4010 reported an increase from Baseline in NPRS pain score compared to the Control group.

To assess whether the pain intensity of the application site reaction was associated with the area treated, the Applicant was asked to group patients into various anatomical sites and provide summary statistics for pain and certain vital signs. This analysis is shown in Table 7.4.1.3, below. :

TABLE 7.4.1.3: PAIN AND VITAL SIGN CHANGES BY ANATOMIC AREA TREATED, STUDIES C116 AND 117

Summary of Vital Signs and Pain in Studies C116 and C117 by Treatment Area

	Mean Maximum Increase in Pain Intensity* (NPRS Score)		Mean Maximum Increase in Systolic Blood Pressure* (mmHG)		Mean Maximum Increase in Heart Rate* (beats/min)	
Treated Site	N	Mean	N	Mean	N	Mean
Leg	33	1.9	33	14.1	33	3.0
Arm	28	2.6	28	16.3	28	4.7
Anterior Trunk^	226	2.7	226	20.2	226	4.7
Posterior Trunk^	262	2.9	263	19.0	263	5.3
Lateral Trunk^	191	3.0	191	20.9	191	5.4
Upper Trunk^^	151	2.6	151	20.3	151	5.5
Mid Trunk^^	193	2.8	194	20.2	194	4.6
Lower Trunk^^	72	2.9	72	18.1	72	5.8
Body Surface Area Treated < 250 cm^2	181	2.7	181	17.8	181	4.4
Body Surface Area Treated >= 250 cm^2	234	2.8	234	19.8	234	5.4

Source: Applicant's Submission of 13 April 2009

These data show that, except for patients treated on the leg (where the pain and vital signs changes were less), all sites were similar.

In summary, NGX-4010 is associated with application site complaints, most notably pain and erythema. These complaints peak just after patch removal and require rescue analgesia in approximately half of the patients. The adverse events resolve within a few days of treatment.

2) TREATMENT-EMERGENT BLOOD PRESSURE-ASSOCIATED ADVERSE EVENTS

Treatment-emergent blood pressure (BP) changes will be discussed under two headings:

i) Changes occurring over the course of the controlled studies with NGX-4010
ii) Changes occurring on the day of treatment

i) CHANGES OCCURRING OVER THE COURSE OF THE CONTROLLED STUDIES

The proportion of subjects experiencing BP changes during the pivotal trials (C116 and C117) were 1.7 % in the active group versus 0.7 % in the control group. There were no clinically meaningful differences or trends observed between the two treatment groups in the changes in BP (systolic and diastolic), HR, and RR from Day 1 to Week 4, Week 8, or Week 12 overall or by treatment duration. (See Table 7.4.1.4 below)

TABLE 7.4.1.4: SHOWING MEAN CHANGE IN VITAL SIGNS OVER TIME (CONTROLLED PHN STUDIES)

Change from Baseline	NGX-4010		Control		*p-value* [a]
	N	Mean (SD)	N	Mean (SD)	
Systolic BP (mmHg)					
Screening	765	134.8 (17.6)	543	134.4 (17.7)	*0.7309*
Change at Week 4	735	–5.0 (16.4)	516	–5.1 (15.7)	*0.8811*
Change at Week 8	669	–5.0 (17.2)	489	–4.5 (15.8)	*0.5964*
Change at Week 12	365	–5.7 (19.1)	261	–3.9 (17.3)	*0.2256*
Diastolic BP (mmHg)					
Screening	765	76.8 (9.6)	543	76.9 (10.2)	*0.8532*
Change at Week 4	735	–2.3 (9.3)	516	–3.0 (10.2)	*0.1866*
Change at Week 8	668	–2.3 (10.0)	489	–3.0 (10.1)	*0.2611*
Change at Week 12	365	–2.5 (10.8)	261	–2.4 (10.6)	*0.8833*
Heart Rate (bpm)					
Screening	764	70.6 (11.0)	543	71.3 (11.0)	*0.2708*
Change at Week 4	734	2.2 (10.5)	516	1.4 (10.3)	*0.1709*
Change at Week 8	668	1.5 (10.5)	489	1.2 (11.0)	*0.6208*
Change at Week 12	364	1.1 (11.2)	260	1.6 (10.2)	*0.5632*
Respiratory Rate (breaths/min)					
Screening	762	16.6 (2.5)	543	16.5 (2.6)	*0.6655*
Change at Week 4	730	–0.1 (2.4)	516	0.0 (2.3)	*0.3587*
Change at Week 8	665	–0.2 (2.4)	487	0.0 (2.3)	*0.1991*
Change at Week 12	361	–0.3 (2.6)	258	–0.1 (2.8)	*0.3837*

BP=blood pressure; bpm=beats per minute; DB=double-blind; mmHg=millimeters of mercury; SD=standard deviation.
NOTE: Pooled data (30, 60, and 90 minutes) were derived from Studies C102 (DB portion), C108 (DB portion), C110, C116 and C117.
a. The p-value was computed from a t-test comparing the means between the pooled NGX-4010 and Control groups.
Source: Source Table 4.2.1.2 (Section 22).

Source: p 237/330 ISS

ii) CHANGES OCCURRING ON THE DAY OF TREATMENT

Blood pressure was measured at reasonably close intervals (~Q30 minutes) during and shortly following the treatment procedure. Changes in BP on the day of treatment were highly variable. However, it is clear that the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased slightly after application of the topical anesthetic in both treatment groups, and increased after patch application in both the NGX-4010 and control groups. (See Figure 7.4.1.5)

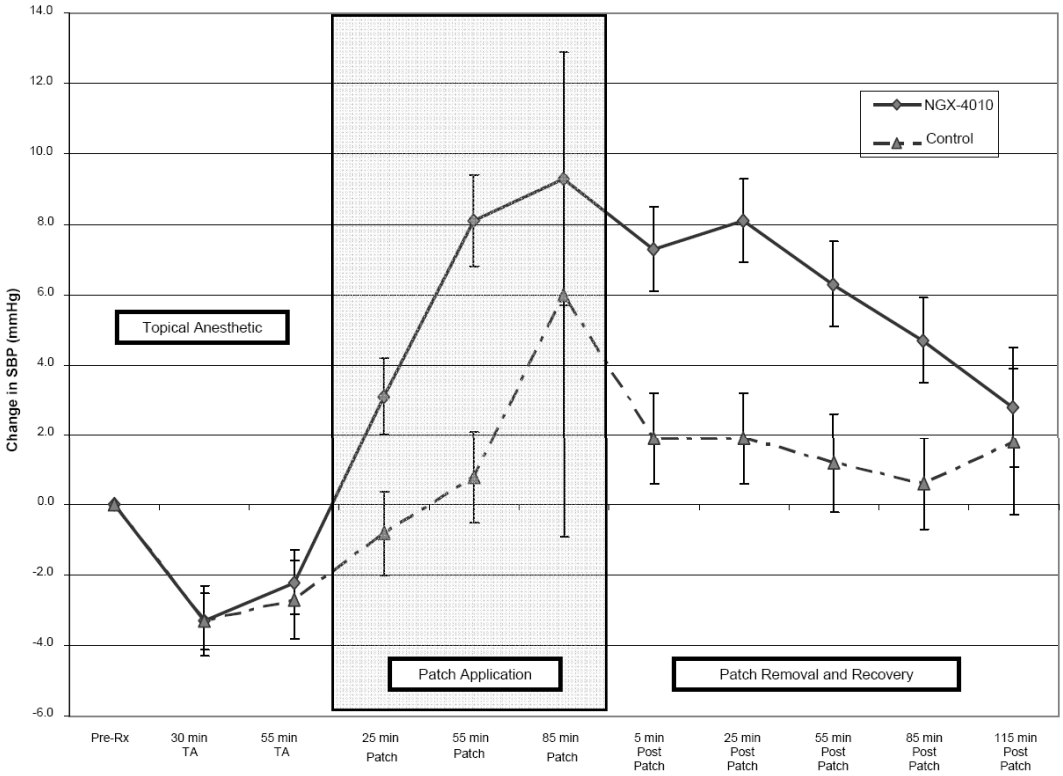
Increases in SBP and DBP were greater in the NGX-4010 group compared with the control group. The mean maximum increase in BP on the day of treatment was greater in NGX-4010 than Control subjects for SBP (17.7 vs. 11.7 mmHg, $p < 0.0001$) and DBP (10.4 vs. 7.6 mmHg, $p < 0.0001$).

Blood pressures began returning toward baseline values within 60 minutes after patch removal.

Systolic and diastolic BP returned to near Baseline levels and was similar between treatment groups by 1 hour and 55 minutes after removal of the patch.

The increases in systolic and diastolic blood pressure seen during and after patch application were small and transient. In the NGX-4010 group, the increases in mean and median systolic and diastolic blood pressure seen during and after patch application were greater than those observed in the Control group. Mean increases in blood pressure for the NGX-4010 group at all time points were < 9.9 mmHg for systolic and < 4.0 mmHg for diastolic blood pressures. Mean increases in blood pressure for the Control group at all time points were < 3.5 mmHg for systolic and < 1.6 mmHg for diastolic blood pressures within 60 minutes after patch removal. (Figure 7.4.1.5 noted below illustrates the BP changes occurring on the day of treatment).

FIGURE 7.4.1.5: SHOWING MEAN CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE ON THE DAY OF TREATMENT IN CONTROLLED PHN STUDIES (C110, C116 and C117)



SP=patch with study medication (NGX-4010 or Control); TA=topical anesthetic.
NOTE: Data derived from Studies C102, C108 (double-blind portion), C110, C116 and C117.
Source: Source Table 4.2.2.2 (Section 22).

Source: ISS, p243/330

On the day of treatment, the increases in mean systolic and diastolic BP and mean heart rate were greatest in the 90 minute dose group, as compared to the 60 minute or the 30 minute dose group. This trend was suggestive of a dose-response effect. (See Table 7.4.1.6)

TABLE 7.4.1.6: MAXIMUM CHANGE IN VITAL SIGNS ON THE *day of treatment* BY TREATMENT DURATION (CONTROLLED PHN STUDIES)

Maximum Change from Baseline	NGX-4010		Control		*p-value*[a]
	N	Mean (SD)	N	Mean (SD)	
Systolic BP (mmHg)					
Total	766	17.7 (16.7)	543	11.7 (14.4)	*<0.0001*
90 minutes	73	19.1 (16.1)	25	13.0 (16.8)	*<0.0001*
60 minutes	621	18.4 (16.8)	495	11.8 (14.3)	*<0.0001*
30 minutes	72	10.8 (14.9)	23	8.2 (14.4)	*0.5988*
Diastolic BP (mmHg)					
Total	766	10.4 (9.8)	543	7.6 (8.9)	*<0.0001*
90 minutes	73	11.8 (9.1)	25	7.4 (8.6)	*0.0002*
60 minutes	621	10.4 (9.9)	495	7.7 (8.9)	*<0.0001*
30 minutes	72	9.1 (9.4)	23	7.2 (9.5)	*0.1824*
Heart Rate (bpm)					
Total	767	4.8 (8.3)	543	3.7 (7.9)	*0.0169*
90 minutes	73	5.5 (8.1)	25	2.7 (5.7)	*0.0659*
60 minutes	622	4.9 (8.6)	495	3.8 (8.0)	*0.0131*
30 minutes	72	3.1 (5.8)	23	3.2 (8.2)	*0.5217*
Respiratory Rate (breaths/min)					
Total	767	1.5 (2.3)	543	0.9 (2.0)	*<0.0001*
90 minutes	73	1.2 (2.0)	25	1.0 (1.4)	*0.2156*
60 minutes	622	1.6 (2.4)	495	0.9 (2.0)	*<0.0001*
30 minutes	72	0.9 (1.4)	23	0.4 (1.3)	*0.9801*

BP=blood pressure; bpm=beats per minute; DB=double blind; LMX4®=topical anesthetic; mmHg=millimeters of mercury; SD=standard deviation.
NOTES:
1. Treatment duration data (30, 60, and 90 minutes) were derived from Studies C102 (60 min; DB portion), C108 (30, 60, and 90 min; DB portion), C110 (60 min), C116 (60 min), and C117 (60 min).
2. Maximum change during and after patch application from preLMX4 timepoint.
a. The p-value was computed from a t-test comparing means between each NGX-4010 group and the pooled control group.
Source: Source Table 4.2.3.2 (Section 22).

The range of values for vital sign parameters at Screening and Weeks 4, 8, and 12/Termination was broad.
Eleven subjects experienced AE's related to abnormal blood pressure or heart rate.

Nine of these subjects (7 in the NGX-4010 group and two in the Control group) experienced AE's related to blood pressure or heart rate *on the day of treatment*.

All of the events were considered mild or moderate in severity, with the exception of 1 subject in the NGX-4010 group (#191018) who experienced severe hypotension. All events were considered to be possibly or probably related to study medication, except for 1 AE in a NGX-

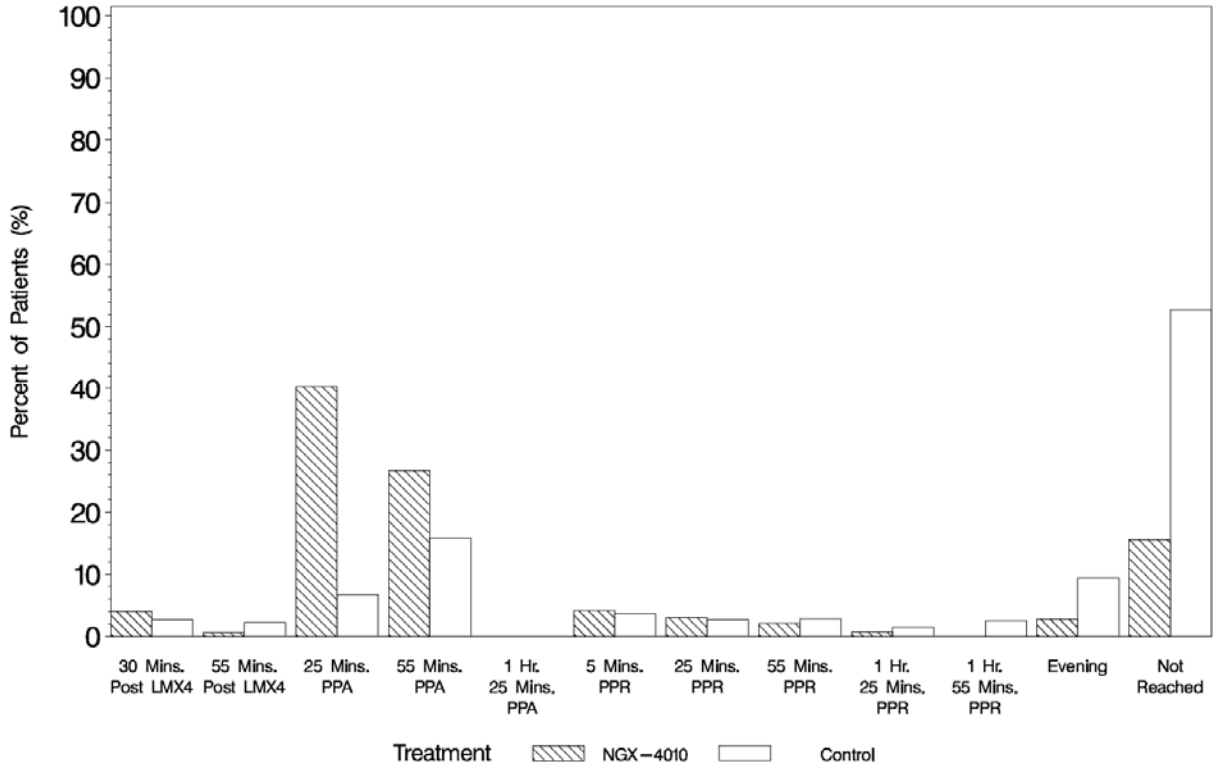
4010 subject with low blood pressure, judged to be of remote or no relationship to study medication.

The Applicant believes that the blood pressure changes are due to the pain experienced by patients with and shortly following treatment. That conclusion is supported by the blood pressure-time plot, shown previously. However, to further characterize the changes to vital signs around the time of dosing, the Agency requested that the Applicant conduct further analyses to assess whether there is a temporal relationship between vital signs and either pain or application site reactions including:

- Constructing histograms for:
  - Time to when a skin reaction initially appeared, peaked, and resolved (for correlation to vital sign data)
  - Time to rescue medication use
- Plots similar to that shown in Table 7.4.1.6 (above) for other vital signs, severity of application site reaction and pain intensity.

Unfortunately, for some of the analyses requested, the data collected were too coarse or not the correct modality to add to our understanding of the pain/blood pressure issue. For instance to address the question of the time to when the painful response to patch application peaked, the Applicant defined the painful response as an increase of >1 unit in the pain score from baseline. That allowed them to make the following histogram (Figure 7.4.1.7).

FIGURE 7.4.1.7: HISTOGRAM OF TIME TO AN INCREASE >1 POINT FROM BASELINE PAIN SCORE, STUDIES C116 AND 117



Source: Applicant's Submission of 13 April 2009

While limited due to the quantity and quality of data collected, the additional analysis to assess the association of pain due to NGX-4010 application and vital sign changes is consistent with a conclusion that the changes are directly due to the pain during and following patch application, not due to another mechanism.

3) TREATMENT EMERGENT CARDIAC ADVERSE EVENTS

In controlled PHN Studies, there was a slightly higher incidence of treatment-emergent AE's coded to the "Cardiac Disorders" SOC in the total NGX-4010 group (4.6%; 35 subjects) compared with the total control group (2.9%; 16 subjects). The sponsor purports that this difference was primarily due to an imbalance in Cardiac Disorder AE's observed in the earlier controlled PHN, (Studies C108 and C110).

The incidence of treatment-related AE's coded to the "Cardiac Disorders" SOC was low and similar between the total NGX-4010 and control groups (0.9% and 0.6%, respectively).

In the later pooled pivotal studies, C116 and C117, where randomization was stratified by CV risk, the overall incidence of "Cardiac Disorders" AE's in the active and control arm was similar and was 17/417 or (4.1%) and 15/401 or (3.8%) respectively.

Subjects with a high risk of cardiovascular disease were defined as subjects with a prior medical history of: cerebrovascular accident, transient ischemic attack, myocardial infarction, stable or unstable angina, current arrhythmia, coronary artery disease, any heart surgery including coronary artery bypass graft surgery, percutaneous coronary angioplasty/stent placement or valvular heart disease.

Subjects with a high risk for cardiovascular (CV risk) events at Baseline tended to have a higher incidence of severe and serious cardiac AE's compared with NGX-4010-treated subjects without a high baseline CV risk.

The overall incidence of SAE's was higher in NGX-4010 subjects with a CV risk factor was (18.0%) compared with subjects with no CV risk (10.2%).

In the controlled PHN Studies, the frequencies of AE's and SAE's in the "Cardiac Disorders" SOC were *not* related to: detectable plasma capsaicin levels, to the pain experienced during treatment (maximum change in NPRS score), to the change in BP during treatment or to the use of rescue medication.

The overall incidence of cardiac SAE's in the Pooled C116 and C117 studies was low, but slightly higher in the NGX-4010, six of 417 [1.4%] versus 1/401 [0.25%]

In general, no consistent differences in the overall incidences or the incidences of the most common treatment-emergent AE's, treatment-related AE's, and SAE's were observed that would suggest that CV risk impacts the AE profile of NGX-4010.
There were no ECG changes related to treatment with NGX-4010. The majority of subjects in both treatment groups had normal ECG's during the study. At Week 12/Termination, there were

no clinically important mean changes, compared to Screening, in either treatment group. Changes from normal ECG at Screening to abnormal at Week 12/Termination were uncommon in both treatment groups. Five subjects had AEs related to ECG observations (3 in the NGX-4010 group and 2 in the Control group).
A thorough QT Study was not performed as part of the clinical development program of NGX-4010, as this is a topical product with a highly localized distribution, a short half-life and very low bioavailability.

4) TREATMENT-RELATED INCIDENCES OF COUGHING AND SNEEZING RELATED TO INADVERTENT CAPSAICIN CONTAMINATION

Aerosolization of capsaicin can occur when the removal of the patch occurs too quickly and can cause irritation primarily to the nose and throat. Due to the high concentration of capsaicin, coughing and sneezing were reported in clinical trials of NGX-4010.

Contamination may also have been caused by manual transfer of capsaicin from the patch or treated areas to bodily sites other than the treatment area, resulting in skin irritation.

The contamination AE's were infrequent; a total of 25 AEs were reported in 19 (0.8%) of 2357 subjects.

Twelve subjects, including 2 subjects receiving the low-concentration capsaicin patch, experienced a cough or throat irritation reported as an AE.
Five subjects experienced nasal irritation reported as an AE.
Five subjects, including 1 subject who received the low-concentration capsaicin patch, experienced AEs resulting from inadvertent manual transfer of capsaicin from the treatment area to other areas of the body (eye, abdomen, and scrotum).

- Additionally, two study coordinators indicated that they experiencing cough when removing the patch

In all cases, the events were considered to be of mild or moderate intensity and resolved within 8 days or less. None of these events were serious.

This is a preventable AE; that may be prevented by careful application and removal of the patch; by use of a mask at time of application and removal, by slow and careful removal of the patch, use of cleansing gel and by avoiding manual transfer of capsaicin to mucous membrane and other sensitive areas of the body.

7.4.2 Laboratory Findings

Laboratory findings will be discussed from the perspective of:
i) Routine hematology and biochemistry laboratory tests

and
ii) Plasma capsaicin level testing.

Routine laboratory tests
The number of PHN subjects in Controlled Studies with TEAEs, SAEs, and severe AEs associated with laboratory abnormalities are summarized by SOC and preferred term for the NGX-4010 and Control treatment groups in Table 7.4.2.1

The incidences of treatment-emergent AE's, TEAEs, and severe AE's associated with laboratory abnormalities were small and similar for NGX-4010 and control subjects.

The most common AE associated with a laboratory abnormality was blood urea increase which was reported in 5 (0.7%) NGX-4010 subjects and 6 (1.1%) Control subjects. No SAE's were associated with laboratory abnormalities in either treatment group and only one severe AE (anemia) was reported in the NGX-4010 group.

Overall, there was no significant change in the laboratory findings collected over the course of the study.

The pattern of laboratory-related AEs did not suggest any effect of exposure to study medication on hematology or clinical chemistry laboratory values.

TABLE 7.4.2.1: SHOWING THE NUMBER OF SUBJECTS WITH AE's RELATED TO LABORATORY ABNORMALITIES (CONTROLLED PHN STUDIES)

System Organ Class Preferred Term, n	AEs, Possibly Related AEs [a]		SAEs, Severe AEs	
	NGX-4010 (N = 767)	Control (N = 543)	NGX-4010 (N = 767)	Control (N = 543)
Investigations				
Ammonia Increased	1, 0	0, 0	0, 0	0, 0
Aspartate Aminotransferase Increased	0, 0	1, 0	0, 0	0, 0
Blood Cholesterol Increased	1, 0	0, 0	0, 0	0, 0
Blood Creatinine Increased	4, 0	1, 0	0, 0	0, 0
Blood Potassium Increased	2, 0	1, 0	0, 0	0, 0
Blood Testosterone Decreased	0, 0	1, 0	0, 0	0, 0
Blood Urea Increased	5, 1	6, 2	0, 0	0, 0
Hematocrit Decreased	1, 0	0, 0	0, 0	0, 0
Laboratory Test Abnormal	0, 0	1, 0	0, 0	0, 0
Platelet Count Decreased	1, 0	0, 0	0, 0	0, 0
Transaminases Increased	0, 0	1, 1	0, 0	0, 0
Metabolism and Nutrition Disorders				
Hypercholesterolemia	4, 0	1, 0	0, 0	0, 0
Hyperlipidemia	2, 0	1, 0	0, 0	0, 0
Hypoalbuminemia	1, 0	0, 0	0, 0	0, 0
Hypokalemia	1, 0	2, 0	0, 0	0, 0
Vitamin D Deficiency	1, 0	0, 0	0, 0	0, 0
Blood and Lymphatic System Disorders				
Anemia	4, 1	1, 0	0, 1	0, 0
Leukocytosis	0, 0	1, 1	0, 0	0, 0
Leukopenia	1, 0	0, 0	0, 0	0, 0
Thrombocytopenia	1, 0	0, 0	0, 0	0, 0

AE= adverse event; DB=double-blind; SAE=serious adverse event.
NOTES:
1. Pooled data (30, 60, and 90 minutes) were derived from Studies C102 (DB portion), C108 (DB portion), C110, C116, and C117.
2. At each level of summation (overall, system organ class, preferred term), subjects reporting more than one AE are counted only once.
3. Adverse events with an onset date on or after the first day of treatment are included.
a. Relationship to study medication was determined by the Investigator.
Source: Source Tables 2.2.1.2, 2.2.2.2, 2.2.3.2, and 2.2.4.2 (Section 22).

Source: p229/330, ISS

Plasma Capsaicin levels

The plasma capsaicin level was performed on specific subsets of patients in Studies C107, C108, C111, and C116.

The number (percent) of subjects with any quantifiable systemic exposure to capsaicin (> LLQ, = LLQ) is summarized by treatment area for PHN subjects, HIV-AN subjects, PDN subjects and All Subjects in All Indications (Table 7.4.2.2). Systemic capsaicin was detected in 31.3% of PHN subjects, 6.8% of HIV-AN subjects, and 3.0% of PDN subjects. Though the proportions of PHN subjects with systemic exposure to capsaicin increased with larger treatment areas, a population PK analysis demonstrated that larger treatment areas were not associated with higher mean exposures to capsaicin.

Data comparing systemic exposure to capsaicin (> LLQ, ≤ LLQ) by treatment duration for PHN subjects, HIV-AN subjects, PDN subjects and All Subjects in All Indications are summarized in Table 7.4.2.2

The number of HIV-AN or PDN subjects who had quantifiable systemic exposure to capsaicin was too low to make any meaningful conclusions, however, the few subjects with levels > LLQ received treatment over larger areas. The lower proportion of HIV-AN and PDN subjects with detectable systemic capsaicin exposure may be related to the differences in skin anatomy between the treatment areas, i.e., thicker stratum corneum on the feet in HIV-AN and PDN compared with the thinner stratum corneum of the trunk and more proximal limbs in PHN.

TABLE 7.4.2.2: SHOWING SYSTEMIC CAPSAICIN EXPOSURE BY TREATMENT AREA AND INDICATION

Indication	Treatment Area				
	≤ 250 cm²	> 250 and ≤ 500 cm²	> 500 and ≤ 750 cm²	> 750 cm²	Total NGX-4010
PHN [a]					
N	40	36	15	8	96
Capsaicin > LLQ, n (%)	7 (17.5)	13 (36.1)	5 (33.3)	6 (75.0)	30 (31.3)
Capsaicin ≤ LLQ, n (%)	33 (82.5)	23 (63.9)	10 (66.7)	2 (25.0)	66 (68.8)
HIV-AN [b]					
N	0	4	5	35	44
Capsaicin > LLQ, n (%)	NA	0	1 (20.0)	2 (5.7)	3 (6.8)
Capsaicin ≤ LLQ, n (%)	NA	4 (100.0)	4 (80.0)	33 (94.3)	41 (93.2)
PDN [c]					
N	0	1	4	28	33
Capsaicin > LLQ, n (%)	NA	0	0	1 (3.6)	1 (3.0)
Capsaicin ≤ LLQ, n (%)	NA	1 (100.0)	4 (100.0)	27 (96.4)	32 (97.0)
All Indications [d]					
N	40	41	24	71	173
Capsaicin > LLQ, n (%)	7 (17.5)	13 (31.7)	6 (25.0)	9 (12.7)	34 (19.7)
Capsaicin ≤ LLQ, n (%)	33 (82.5)	28 (68.3)	18 (75.0)	62 (87.3)	139 (80.3)

DB=double-blind; LLQ=lower limit of quantification; NA=not applicable; OL=open-label.
NOTES:
1. The LLQ for this study was 0.5 ng/mL.
2. Subjects in Repeat-Treatment Studies (C107 and C108) may be counted more than once.
a. PHN data were derived from Studies C108 (DB and OL portions), C111 (PHN subjects), and C116.
b. HIV-AN data were derived from Studies C107 (DB and OL portions) and C111 (HIV-AN subjects).
c. PDN data were derived from Study C111.
d. Data for All Indications were derived from Studies C107 (DB and OL portions), C108 (DB and OL portions), C111, and C116.
Source: Source Table 3.1.3.1 (Section 22)

Source; p 233/330, ISS

In PHN subjects, the proportion of subjects with systemic capsaicin exposure was higher following a 90-minute treatment (46.7%) compared with a 60-minute NGX-4010 treatment (28.9%); see Table 7.4.2.3. Only a small number (n=4) of HIV-AN or PDN subjects had quantifiable systemic exposure to capsaicin. The lower proportion of subjects with quantifiable systemic capsaicin in this population is likely related to thicker skin in the feet, corresponding to the painful area(s) of patch application in HIV and diabetes mellitus study population.

(A population PK analysis in PHN subjects showed that based on post-hoc estimates, 90-minute applications of NGX-4010 resulted in capsaicin geometric mean exposure and peak exposure approximately 2-fold higher than those observed in patients treated with 60-minute applications of NGX-4010).This is demonstrated in Table 7.4.2.3 noted below.

TABLE 7.4.2.3: SHOWING SYSTEMIC CAPSAICIN EXPOSURE BY TREATMENT DURATION AND INDICATION

Indication	Treatment Duration		
	90 minutes	60 minutes	Total NGX-4010
PHN [a]			
N	30	76	96
Capsaicin > LLQ, n (%)	14 (46.7)	22 (28.9)	30 (31.3)
Capsaicin ≤ LLQ, n (%)	16 (53.3)	54 (71.1)	66 (68.8)
HIV-AN [b]			
N	37	16	44
Capsaicin > LLQ, n (%)	3 (8.1)	0	3 (6.8)
Capsaicin ≤ LLQ, n (%)	34 (91.9)	16 (100.0)	41 (93.2)
PDN [c]			
N	22	11	33
Capsaicin > LLQ, n (%)	0	1 (9.1)	1 (3.0)
Capsaicin ≤ LLQ, n (%)	22 (100.0)	10 (90.9)	32 (97.0)
All Indications [b]			
N	89	103	173
Capsaicin > LLQ, n (%)	17 (19.1)	23 (22.3)	34 (19.7)
Capsaicin ≤ LLQ, n (%)	72 (80.9)	80 (77.7)	139 (80.3)

DB=double-blind; LLQ=lower limit of quantification; OL=open-label.
NOTES:
1. The LLQ for this study was 0.5 ng/mL.
2. Subjects in Repeat-Treatment Studies (C107 and C108) may be counted more than once.
a. PHN data were derived from Studies C108 (DB and OL portions), C111 (PHN subjects), and C116.
b. HIV-AN data were derived from Studies C107 (DB and OL portions) and C111 (HIV-AN subjects).
c. PDN data were derived from Study C111.
d. Data for All Indications were derived from Studies C107 (DB and OL portions), C108 (DB and OL portions), C111, and C116.
Source: Source Table 3.1.3.2 (Section 22).

Source: p234/330

AE's in Subjects with Plasma Capsaicin Levels > LLQ

Treatment-emergent AEs, SAEs, TEAEs, and severe AEs in subjects from Studies C107, C108, C111, and C116 are presented by the presence or absence of quantifiable plasma capsaicin

The overall incidence of treatment-emergent AE's was higher in subjects with a plasma capsaicin level ≤ LLQ (84.2%, 117 subjects) compared with those subjects with a plasma capsaicin level > LLQ (61.8%, 21 subjects). In the 21 subjects with plasma capsaicin levels > LLQ, seven AE's were reported in more than two subjects, including application site pain and application site erythema (11 subjects each, 32.4%) and application site pruritus, arthralgia, dizziness, nausea, and vomiting (3 subjects each, 8.8%). Of these seven AEs, 3 were considered treatment related (application site pain, erythema, and pruritus), and four were considered severe

(application site pain, application site pruritus, arthralgia, and nausea). None of these 7 AEs were considered serious.

The incidence of treatment-emergent cardiac AEs was similar in subjects with a plasma capsaicin level ≤ LLQ (5.8%, 8 subjects) compared with those subjects with a plasma capsaicin level > LLQ (5.9%, 2 subjects).

In studies that evaluated systemic exposure to capsaicin after treatment with NGX-4010, the majority of subjects had no quantifiable plasma levels of capsaicin. Low, transient systemic exposure to capsaicin that were below the limits of quantification within hours of treatment occurred in a minority of subjects treated with NGX-4010.

No differences in AE incidences (overall or individual AEs) were observed that would suggest that systemic capsaicin exposures impacted the AE profile of NGX-4010.

Overall, the incidences of treatment-emergent AEs, treatment-related AEs, SAEs, or severe AEs associated with laboratory abnormalities were small (< 1% by preferred term) and similar between the NGX-4010 and Control groups.

The overall incidence of treatment-emergent AEs was higher in subjects with a plasma capsaicin level ≤ LLQ (approximately 84%) compared with those subjects with a plasma capsaicin level > LLQ (approximately 62%).

The AE profile in subjects with a plasma capsaicin level > LLQ was no different from those subjects without quantifiable systemic exposure.

Given the minimal systemic capsaicin exposure associated with NGX-4010 treatment as well as the infrequent dosing (no more often than once every 12 weeks), it is not surprising that no discernable systemic effects on clinical laboratory values were observed. No evidence of increased risk or alteration of the overall AE profile was seen in those subjects with systemic capsaicin exposure.

7.4.3 Vital Signs

Treatment-emergent blood pressure changes are discussed in detail in Section 7.3.4
On the day of treatment, NPRS scores were captured at the following time points:

- 30 and 55 minutes *post local anesthetic application*
- 25 minutes and 55 minutes *after NGX-4010 patch application*
- 5, 25, 55 and 85 minutes *after NGX-4010 patch removal*
- The evening of patch removal

Heart rate (HR) and Respiratory Rate (RR)
Mean changes from Baseline in HR and RR were small and similar for the NGX-4010 and Control groups.

Small increases in mean maximum change from Baseline for HR and RR were also observed in both groups, with significant differences between the NGX-4010 and Control groups for HR (4.8 vs. 3.7 bpm, $p = 0.0169$) and RR (1.5 vs 0.9 breaths/minute, $p < 0.0001$). Significant differences between NGX-4010 and Control were observed for the 60-minute treatment duration for SBP, DBP, HR, and RR.

It should be pointed out that for studies C102, C108, and C110, "pain now" scores were collected in the evening , while in studies C116 and C117 "average pain scores for the past 24 hours" were collected and were used as the pain scores on the evening of the day of treatment. These subtle differences in end points measure differences between the earlier as compared to the later studies may have confounded.

The transient elevation in BP, RR and HR occurring at time of patch application are likely related to increased sympathetic outflow related to pain.

7.4.4 Electrocardiograms (ECGs)

In the pivotal PHN Studies, electrocardiograms (12-lead) were obtained at Screening (Studies C116 and C117), Study Patch Application (Day 0; Study C116), Week 4 (Study C116), and Week 8 (Study C116) or Week 12/Termination (Study C117).

During the Study Patch Application Visit, an ECG was conducted immediately after patch removal.

In Study C102, (a Phase 2 controlled pilot study) ECG's were performed during screening and continuously during the treatment period, no changes related to treatment with NGX-4010 were observed.

ECG's performed as parts of the development of NGX-4010 were interpreted prior to unblinding, by a study-specified central ECG laboratory. The overall results for ECG's performed on NGX-4010 and Control subjects during Screening and Week 8 or Week 12/Termination were similar between both treatment arms.

The number of abnormal or clinically significantly abnormal ECG's, or the number of ECGs that shifted to normal or abnormal between Screening and Weeks 8 and 12 or Termination were similar between treatment groups. Approximately 32% of the ECG's performed on all subjects at Screening were interpreted as being abnormal and 3% of these were considered to be clinically significantly abnormal. Change values were similar between treatment groups for all of the following mean ECG intervals: RR, PR, QRS, QT, QTcB, and QTcF. Mean QTc intervals at Week 8 or Week 12/Termination were less than Baseline in both the NGX-4010 and Control groups.

There were no ECG changes related to treatment with NGX-4010. The majority of subjects in both treatment groups had normal ECG's during the study. All mean and median changes in ECG parameters following treatment on Day 0, and at Weeks 4 and 8 were small and were similar between the 2 treatment groups.

Changes from normal ECG at Screening to abnormal at Weeks 4 or 8 were uncommon in both treatment groups. Fourteen subjects had AE's related to ECG observations (4 in the NGX-4010 group and 10 in the Control group).

7.4.5 Special Safety Studies
No special clinical dermal safety studies (cumulative irritancy, photosensitization and photoallergenicity, and sensitization) were performed prior to the NDA submission of this product.
As noted in the Regulatory History section of this review, during this review cycle, the Applicant was notified that such studies were necessary although the Applicant was advised that it could submit a rationale why such studies were not necessary. The Applicant made the argument that due to the manner of use (mostly single-use), such studies were not appropriate.

We consulted this argument to the Division of Dermatology and Dental Products (DDDP). The final consult is pending at this time. However, informally, Dr. Joanna Ku has notified us that it would be possible to waive the phototoxicity, allergicity and cumulative irritancy studies and had the following comments.

Cumulative irritancy studies are usually performed to determine whether irritancy potential exists for the product. This product has been shown to be significantly irritating and this potential needs to be stated in the label. DDDP is likely to recommend that the product label clearly communicate the substantial pain/burning invoking potential of the product without minimizing the severity/extent of such potential. For example, the adverse reaction section of the label should clearly state that the incidence of pain reflects the incidence of pain *after* pre-treatment with topical lidocaine anesthetic, and that the incidence of pain would have been much greater without pre-treatment with topical local anesthetic.

Photosafety and phototoxicity studies were performed in rats and demonstrated no dermal responses indicative of phototoxicity due to NGX-4010 applications. Phototoxicity and photoallergenicty (photo contact allergy) studies which may be waived if there is no drug absorbance in the 280-700 nm spectrum or in instances where the patch under study is opaque or the only indications for use are in areas where there is a minimal chance of exposure to UV light. In the PHN patients, most of the painful treatment areas were on the trunk and therefore were not exposed to light.

In the NGX-4010 development program, of the 1615 patients receiving a total of 2471 treatments, only one isolated photosensitivity AE was identified. This reaction occurred in a 40 y/o Caucasian male, with HIV neuropathy who displayed this rash bilaterally on his feet and ankles, 51 days after patch was applied to the area. This patient was also taking sulfamethoxazole-trimethoprim, a known cause of a photosensitivity reaction. Consequently this

isolated case of possible photosensitivity reaction may or may not have been related to NGX-4010.

- A delayed contact hypersensitivity study in guinea pigs was conducted, in which Qutenza was found to be a weak sensitizer, based on a relatively low incidence and mild severity of challenge reactions to the NGX-4010 patch in the test group that exceed the highest respective naïve control reaction. In the clinical setting, application site adverse events and dermal irritation have been studied in 429 patients in Phase 2 and 3 studies treated more than once with Qutenza, applied at least 12 weeks apart. Application site reactions were present in about 67% of PHN patients, and dermal irritation (i.e., dermal assessment score > 0) were present in >95% of PHN patients There was no increase in the incidence and severity of dermal irritation or application site events, demonstrated with repeated treatment there was no evidence of dermal sensitization. This is demonstrated in Table 7.4.5.1 noted below, where there is no appreciable trend in the proportion of subjects with an increase in dermal scores immediately or 1 to 2 hours after patch removal, during the second, third or fourth treatment cycle.

TABLE 7.4.5.1: SHOWING A SUMMARY OF DERMAL ASSESSMENT SCORES ON TREATMENT DAY, BY TREATMENT CYCLE, IN REPEAT TREATMENT STUDIES IN PHN

Table 5: Summary of Dermal Assessment Scores On Treatment Day By Treatment Cycle (Repeat-Treatment Studies in PHN Patients)

	NGX-4010 Treatment Cycle		
	2	3	4
Number of Patients	229	129	44
Immediately After Patch Removal	229	128	44
N (%) of patients with an increase in dermal score compared to treatment cycle 1	34 (14.8)	14 (10.9)	8 (18.2)
N (%) of patients with no change in dermal score compared to treatment cycle 1	158 (69.0)	90 (70.3)	25 (56.8)
N (%) of patients with a decrease in dermal score compared to treatment cycle 1	37 (16.2)	24 (18.8)	11 (25.0)
1-2 Hours After Patch Removal	215	117	37
N (%) of patients with an increase in dermal score compared to treatment cycle 1	29 (13.5)	15 (12.8)	4 (10.8)
N (%) of patients with no change in dermal score compared to treatment cycle 1	139 (64.7)	76 (65.0)	26 (70.3)
N (%) of patients with a decrease in dermal score compared to treatment cycle 1	47 (21.9)	26 (22.2)	7 (18.9)
Maximum Score On Day 0[1]	229	129	44
N (%) of patients with an increase in maximum dermal score compared to treatment cycle 1	27 (11.8)	11 (8.5)	8 (18.2)
N (%) of patients with no change in maximum dermal score compared to treatment cycle 1	169 (73.8)	93 (72.1)	26 (59.1)
N (%) of patients with a decrease in maximum dermal score compared to treatment cycle 1	33 (14.4)	25 (19.4)	10 (22.7)

Source: Source Table 4.4.3.4.2.

Additionally, safety studies were conducted (Studies C101 and C115)d to assess the effects of NGX 4010 on intraepidermal nerve fiber density and quantitative sensory testing.

Study C101 was a randomized, open label study performed to determine the exposure time(s) that would induce a significant loss of immunoreactivity of capsaicin-sensitive cutaneous nociceptors at 7 days after exposure to NGX-4010

The study was conducted in healthy volunteers, and utilized four patches of differing duration

- Placebo x 120 mins
- Low conc NGX-4010 (3.2mcg/cm^2) x 120 mins duration
- NGX-4010 x 30 mins duration
- NGX-4010 x 60 mins duration
- NGX-4010 x 120 mins duration

Consistent with the known pharmacodynamic effects of capsaicin on TRPV1-expressing nociceptive nerve endings, reduced ENF density and minor changes in cutaneous nociceptive

function (heat detection and sharp sensation) were noted one week after exposure to Qutenza. ENF density reduction and sensory changes were fully reversible.

Study C115 was a randomized, open-label study designed to assess the difference between NGX-4010 treated-skin areas in ENFD as quantified by PGP 9.5 immunohistochemical staining of skin biopsy samples obtained at 1, 12 and 24 weeks following a 60 minute application.

Results of ENFD reduction studies (C101 and C115) are summarized in Table 4.4.2.1. (The sponsor purports that the apparent differences among the two studies in number of neurites/mm can be explained by the use of a highly sensitive confocal microscopy method in Study C115).

In Study C101, one of the study endpoints was effect on epidermal nerve fiber density, based on the results of biopsy of treated sites at Day 7. Exposure to NGX-4010 for 60 and 120 minutes resulted in similar mean nerve fiber densities (4.8 and 4.4 neurites/mm, respectively). Both 60- and 120-minute NGX-4010 treated sites had a significantly lower mean nerve fiber density than sites treated with placebo (11.8 neurites/mm; $p < 0.001$) or low-concentration capsaicin for 120 minutes (10.9 neurites/mm; $p < 0.01$). NGX-4010 for 30 minutes also showed a lower mean nerve fiber density (7.6 neurites/mm) compared to placebo, but failed to meet statistical significance.

A second study endpoint in C101 was comparison of the changes in epidermal nerve fiber function from Day 0 to Day 7. Results of QST for warm sensation threshold indicated that both 60 minutes and 120 minutes of high-concentration capsaicin on Day 0 resulted in a small reduction in warmth sensitivity (i.e., higher threshold temperature) on Day 7 (+1.9 °C and +1.1 °C, respectively). However, only the sites exposed for 60 minutes showed a statistically significant difference from placebo-treated sites in change from baseline. There were no statistically significant within-treatment or between-treatment effects for cooling sensitivity as measured by QST.

TABLE 7.4.2.2: SHOWS A SUMMARY OF C101 AND C115 - NERVE FIBER DENSITY STUDY RESULTS

Study Number	Total Number of Subjects/ Males (%)	Mean Age/ Range (yr)	Treatments		Mean Nerve Fibre Density (neurites/ mm) ± SD	ENFD Ratio (Treated/ Placebo or Untreated Control) ± SD[a]
			Patch Type	Application Time (min)		
C101	20/14 (70%)	45.3/18 to 68	Placebo	120	Wk 1: 11.8 ± 8.99	NA
			Low-concentration	120	Wk 1: 10.9 ± 6.56	0.92[b]
			NGX-4010	30	Wk 1: 7.6 ± 7.70	0.64[b]
			NGX-4010	60	Wk 1: 4.8 ± 4.93	0.41[b]
			NGX-4010	120	Wk 1: 4.4 ± 5.86	0.37[b]
C115	36/18 (50%)	26.1/20 to 40	Untreated	NA	Wk 1: 48.7 ± 15.92 Wk 12: 47.8 ± 13.65 Wk 24: 44.5 ± 15.19	NA
			NGX-4010	60	Wk 1: 10.4 ± 8.87 Wk 12: 37.7 ± 14.49 Wk 24: 41.3 ± 11.78	0.2 ± 0.13 0.8 ± 0.23 1.0 ± 0.18

[a] For C115 study only
[b] Values calculated from mean nerve fibre density results
SD = Standard deviation
NA = Not applicable

SOURCE: Summary of Clinical Pharmacology p 40/46

In Study C115, exposure to NGX-4010 for 60 minutes resulted in:

- An 80% reduction in ENFD compared to untreated sites at Week 1 post-exposure.
- A return of ENFD was noted at Week 12 with only a 20% reduction in ENFD in the NGX-4010 treated areas.
- Full recovery of ENFD was achieved by Week 24.
- The reduction in ENFD was associated with small, transient alterations in nerve fiber function.
- At Week 1 after patch application, subjects reported: slightly reduced detection of sharp pain at treated sites relative to untreated sites; mean percent sharp pain detection dropped by 15.1 percent at the treated sites and remained essentially unchanged at untreated sites.
- The effect on sharp pain perception normalized by Week 12. Heat perception (0.5 and 5.0 threshold JNDs) was largely unchanged from Day 0 to Weeks 1, 12, or 24. There were no differences in mean cooling thermal threshold JNDs during the study
- In female subjects, the treated sites had a higher cooling thermal threshold JND on Day 0 (Baseline), compared to untreated sites; at Weeks 1, 12, and 24, the mean cooling thermal threshold JNDs at the treated sites were no different than the values reported for the untreated sites.
- Male subjects reported no difference in cooling perception at any point during the study. Tactile threshold was unaffected by NGX-4010 patch application.
- There was no appreciable difference between treated and untreated sites or between pre-treatment and post-treatment assessments in the smallest bending force perceived at least 50% of the time at any assessment time (Day 0: treated sites = 4.07 mN ± 2.586; untreated sites = 4.03 mN ± 2.306). With the exception of the cold perception results at baseline, treatment-emergent changes were not different between male and female subjects.

These results suggest that ENFD and sharp pain perception are transiently decreased by a 60-minute application of NGX-4010. Sensory function recovered by Week 12, and by Week 24, all treatment-emergent changes in ENFD had recovered.

Taken together, these Phase 1 clinical studies suggest that a single 60- to 90- minute application of NGX-4010 has the potential to reduce ENFD without significant adverse effect on protective sensory function such as the ability to detect heat, cold, sharp and tactile sensations. ENFD and sensory changes are reversible and return to baseline levels after a few months.

Neurological function testing in PHN patients treated with NGX-4010 did not demonstrate any consistent changes in light brush, pinprick, vibration and warmth sensation.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Age
In general, in PHN subjects, there were no consistent differences in the overall incidences or the incidences of the most common treatment emergent AE's that would suggest that NGX-4010 impacted the AE profile of NGX-4010.

7.5.1 Dose Dependency for Adverse Events
Table 7.5.1 shown below shows a summary of TEAE's for the pooled controlled PHN population, with the three durations of patch in the two treatment arms. The only consistent trends that can be gleaned are that application site reaction (particularly pain, edema and papules) and hypertension occurred more frequently in the NGX-4010 treatment arm than in the control arm.
As noted previously, differential collection application site pain and erythema data early trials versus the later trials may have confounded the analysis.

TABLE 7.5.1: SHOWING A SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS, CONTROLLED STUDIES, PHN INDICATION ONLY INCLUDES EVENTS WITH >/=1% INCIDENCE IN POOLED TREATED GROUP AND WHERE POOLED TREATED GROUP IS MORE FREQUENT BY AT LEAST 1%

System Organ Class/ Preferred Term	**NGX-4010**				**Control**			
	Total (N=767)	90 min (N=73)	60 min (N=622)	30 min (N=72)	Total (N=543)	90 min (N=25)	60 min (N=495)	30 min (N=23)
# Subjects at least 1 AE reported	**637 (83%)**	**42 (58%)**	**548 (88%)**	**47 (66%)**	**429 (79%)**	**18 (72%)**	**399 (81%)**	**12 (52%)**
Gen disorders & Admin Site Condit	**493 (64%)**	**15 (21%)**	**463 (75%)**	**15 (21%)**	**333 (61%)**	**7 (28%)**	**323 (65%)**	**3 (13%)**
Applic site Erythema	392 (51)	1 (1)	391 (63)	0 (0)	270 (50)	0 (0)	269 (54)	1 (4)
Applic site Pain	265 (35)	4 (6)	260 (42)	1 (1)	104 (19)	0 (0)	103 (21)	1 (4)
Applic site Pruritus	52 (7)	6 (8)	38 (6)	8 (11)	25 (5)	3 (12)	21 (4)	1 (4)
Applic site Papules	42 (6	0 (0)	40 (7)	2 (3)	15 (3)	1 (4)	4 (3)	0 (0)
Applic site Edema	26 (3)	0 (0)	26 (4)	0 (0)	3 (1)	0 (0)	3 (1)	0 (0)
Applic site Dryness	13 (2)	0 (0)	11 (2)	2 (3)	3 (1)	0 (0)	3 (1)	0 (0)
Infections & Infestations	**145 (19%)**	**13 (18%)**	**116 (19%)**	**16 (17%)**	**95 (17.5%)**	**6 (24%)**	**85 (17%)**	**4 (17%)**
o Nasopharyngitis	32 (4)	3 (4)	23 (4)	6 (8)	11 (2)	0 (0)	10 (2)	1 (4)
o Bronchitis	16 (2)	0 (0)	15 (2)	1 (1)	6 (1)	1 (4)	5 (1)	0 (0)
o Sinusitis	18 (2)	2 (3)	16 (3)	0 (0)	4 (1)	0 (0)	4 (1)	0 (0)
GI Disorders	**94 (12%)**	**11 (15%)**	**71 (11%)**	**12 (17%)**	**52 (10%)**	**6 (24%)**	**44 (9%)**	**2 (9%)**
o Nausea	41 (5)	6 (8)	31(5)	4 (6)	15 (3)	4 (16)	11 (2)	0 (0)
o Vomiting	24 (3)	4 (6)	18 (3)	2 (3)	4 (1)	1 (4)	3 (1)	0 (0)
Skin & Subcut Disorders	**62 (8%)**	**2 (3%)**	**55 (9%)**	**5 (7%)**	**32 (6 %)**	**1(4 %)**	**31 (6 %)**	**0 (0%)**
o Pruritus	12 (2)	0 (0)	12 (2)	0 (0)	2 (0.5)	0 (0)	2 (0.5)	0 (0)
Vascular Disorders	32 (4)	3 (4)	24 (4)	5 (7)	13 (2)	1 (4)	12 (2)	0 (0)
o HTN	21 (3)	2 (3)	15(2)	4 (6)	5 (1)	0 (0)	5 (1)	0 (0)

7.5.2 Time Dependency for Adverse Events

This has been covered elsewhere in this report. Almost all adverse events occur at the time of patch application or immediately after removal and resolve within a few days.

7.5.3 Drug-Demographic Interactions

In the controlled PHN studies 75% of study subjects were 65 years or older, while 43% of subjects were 75 years or older. Safety and effectiveness were similar in geriatric and in younger patients. In general there was no consistent difference in the overall incidences and the incidences of the most common treatment-emergent AE's, and SAE's that would suggest that age or gender impacts the AE profile of NGX-4010.
The overall incidences of treatment-emergent AE's, and SAE's coded to the "Cardiac Disorders" SOC were higher among older subjects compared with younger subjects in both treatment groups. Male PHN subjects tended to experience fewer overall AE's compared with female subjects but had a higher incidence of cardiac AE's in both the NGX-4010 and Control groups.

In the controlled PHN, any comparisons by race should be interpreted with caution due to the small sample sizes of Blacks, Asians and Others relative to Caucasians.

7.5.4 Drug-Disease Interactions

Results for the controlled PHN Studies suggest that demographic and disease characteristics have no appreciable affect on the incidences of AE's on vital sign changes during and after NGX-4010 treatment.

7.5.5 Drug-Drug Interactions

No formal drug interaction studies have been performed as part of the drug development program of NGX-4010. Only transient, low levels of systemic exposure have been shown to occur in a minority of subjects treated with NGX-4010.

Capsaicin has been shown not to inhibit or induce liver cytochrome P450 enzymes at concentrations which far exceed those measured in clinical blood samples from subjects treated with NGX-4010 for 60 minutes. Given these findings, interactions with other systemic medicinal products are highly unlikely.

7.6 Additional Safety Explorations

Not applicable.

7.6.1 Human Carcinogenicity

The human carcinogenicity studies submitted by the sponsor are said to be virtually uninterpretable and fraught with methodological irregularities, reporting inaccuracies and other quality assurance issues; because of the inadequacies, the ECAC is unable to interpret the results of the report.

However, carcinogenic studies are not a requirement for such an application, as there is three month duration between treatment exposures.

7.6.2 Human Reproduction and Pregnancy Data

The study was designed such that female subjects with child-bearing potential must have had a negative serum beta human chorionic gonadotropin (hCG) pregnancy test, performed within 7 days of the Study Patch Application Visit (Day 0).

There is very little clinical information on exposed pregnancies available; one 32-year-old HIV-AN subject became pregnant during Study C107, 60 days after the study patch application. This subject terminated the study early when she was 6 weeks pregnant. She planned to carry the pregnancy to full term, but was subsequently lost to follow-up.

No other clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or post-natal development.

7.6.3 Pediatrics and Effect on Growth
The safety and effectiveness of NGX- 4010 in patients younger than 18 years of age have not been studied. The sponsor has requested a waiver of pediatric studies for the whole pediatric population, extending from birth to age 16 years. The reason for waiving pediatric assessment requirements is that the incidence of PHN in this age group is extremely low and NGX-4010 is therefore not likely to be used in a substantial number of patients.
PHN is associated with older individuals (94% of cases are > 60 years). The likelihood of developing PHN after shingles increases with age; the risk of PHN is low (2%) in patients younger than 50 years of age, ~20% in those older than 50 years and approximately 35% in those over the age of 80 years [Opstelten et al. 2001].

Though reports of Herpes Zoster can be found in children [Watson 2001], none have been associated with postherpetic neuralgia [Rogers and Tindall 1972, Hope-Simpson RE 1975, Guess et al. 1985, Petursson G et al. 1998, Lee et al. 2006].

The Applicant's proposed waiver was reviewed by the Pediatric Research Committee on April 1st 2009. The Committee agreed with the waiver as proposed by the Division.

NeurogesX was assigned Orphan Drug designation for NGX-4010 for the management of neuropathic pain in patients with PHN.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

NGX-4010 is not a controlled substance. There is limited clinical experience with NGX-4010 overdose in humans. In the pre-marketing clinical trials in patients with neuropathic pain, 239 patients received NGX-4010 for up to 90 minutes, with one subject being treated for 100 minutes without notable clinical consequences. The types of adverse reaction experienced by patients exposed to longer treatment durations (> 60 minutes) with NGX-4010 were not clinically different from those of patients administered 60-minute treatments. The highest reported treated area in pre-marketing clinical trials was 1120 cm^2.

Due to the limited systemic absorption of capsaicin, overdosing is unlikely to occur. Capsaicin overdose is prevented by not exceeding the maximum number of patches, and, by removing the patch from the treated skin no later than the prescribed duration.

Incidence of capsaicin overdose also is minimized because the NGX-4010 is a treatment provided by healthcare professionals; it is not a self-administered medicinal product.

There is no specific antidote for overdose with capsaicin. In case of suspected overdose, the sponsor recommends gentle removal of the patch, followed by application of Cleansing Gel for one minute, wiping off with dry gauze and gently washing the area with soap and water. Patients enrolled in the pivotal studies were permitted to local cooling and additional analgesic medications for treatment related discomfort.

The potential for dependence on the use of NGX-4010 is highly unlikely. NGX-4010 produces minimal to no systemic exposure to capsaicin. Capsaicin has no recognized abuse potential. Neither topical formulations of capsaicin nor foods containing capsaicin have been associated with dependence.

Withdrawal and rebound from treatment with NGX-4010 was not specifically addressed in the clinical studies. However, no notable withdrawal effects and no evidence of rebound pain, either acute (7 days) or for up to 12 weeks, were observed following treatment with NGX-4010. Additionally, based on the results from the repeat treatment studies, there was no evidence of withdrawal or of rebound pain observed after up to 4-treatments over a 48- to 52-week treatment period.

7.7 Additional Submissions

On February 4th 2009, in accordance with 21 CFR 314.50(d)(5)(vi)(b), the sponsor, NeurogesX submitted the 120 day safety update and reported that there have been no new safety data generated subsequent to the NDA submission.

On 19th March 2009, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending to grant a marketing authorization for the medicinal product Qutenza 179 mg cutaneous patch intended for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

The approved indication is: “the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain”. It is proposed that Qutenza is administered by a physician or by a health care professional under the supervision of a physician.

A pharmacovigilance plan for Qutenza, as for all medicinal products, will be implemented as part of the European marketing authorization.

8.0 Post marketing Experience

There is no post marketing information available for this novel high concentration capsaicin product intended for the prolonged reduction of neuropathic pain associated with PHN.

9. Appendices

9.1 Literature Review/References

The sponsor provided a thorough literature search for information on the safety of topical capsaicin in human subjects with pain conducted in the following databases with a cut-off date of 11 June 2008:

(1) MEDLINE® 1950-2008
(2) EMBASE 1974-2008;
(3) Biosis Previews® 1926-2008;
(4) Derwent Drug File 1983-2008.

From the 80 articles identified by the electronic search, abstracts were reviewed and 39 articles evaluating the safety of topical capsaicin for pain in humans were selected for inclusion in this literature review based on the relevance to the proposed indication for NGX-4010.

Of the 39 articles selected to evaluate safety of topical capsaicin in subjects with neuropathic or related pain, 20 were randomized, double-blind, vehicle-controlled or parallel studies, one was a randomized, single-blind study, 14 were open-label studies, and 4 were collections of case histories.

Throughout these studies, the most frequently reported AE was mild to moderate burning at the application site. Coughing was reported in 6 of the studies.

Discontinuations due to AEs in capsaicin-treated subjects were reported to have occurred in 22 of the 39 clinical studies and case history collections. Across these studies, the percentage of capsaicin-treated subjects that discontinued due to AEs in these studies ranged from 3% to 33%.

No treatment-related SAEs were reported in the 39 studies reviewed.

Overall, no new safety concerns were detected in the literature compared with safety information known for NGX-4010. Thus, the safety of topical capsaicin to treat pain observed in the literature is consistent with the safety profile of NGX-4010.

9.2 Labeling Recommendations

In addition to the special warnings and precautions are listed by the applicant and written in Section 2.4 of this report required for the safe use of NGX-4010:

The following major changes are to be recommended in the applicant's proposed labeling:

1. Transient increases in blood pressure, thought to be as a result of treatment-related increases in pain may occur during and shortly after the NGX-4010 treatment. Blood pressure should be monitored at regular intervals pretreatment, during treatment, and for several hours after the treatment procedure. Patients experiencing increased pain should be provided with supportive treatment such as local cooling or oral analgesics such as short acting opioids. Patients with unstable or poorly controlled hypertension, a recent history of cardiovascular or cerebrovascular events, such as transient ischemic events, or persons who have had be at an increased risk of adverse cardiovascular effects due to the potential stress of the procedure. These factors should be considered prior to initiating NGX-4010 treatment.

2. Care should be taken to avoid prescribing this treatment in persons who do not tolerate opioids. In such patients, an alternative pain reduction strategy should be in place prior to initiating NGX-4010 treatment.

3. Procedural pain is associated with the administration of NGX-4010; consequently co-administration of opioids is frequently required at the time of patch application. Opioids may impair one's ability to drive and/or use heavy machines. This may require that patients receiving NGX-4010 be required to abstain from driving or operating heavy machinery for the first few days of NGX-4010 treatment and for the duration of time that they are receiving opioids. It would be preferable if arrangements were made for patients to be transported from the treatment facility prior to the treatment and at the end of the treatment observation period.

4. The product label should clearly communicate the substantial pain associated with use of the product without minimizing the severity/extent of such potential. For example, the Adverse Reactions section of labeling should clearly state that the incidence of pain reflects the incidence of pain *after* pre-treatment with topical lidocaine anesthetics. Without pre-treatment incidence of pain would have been expected to have been higher.

5. Additionally, product labeling should include information on possible contact allergy and sensitization data in the label, including the pre-clinical studies conducted in the guinea pig.

6. When product is being applied to skin that is normally exposed to light, such as the arms or legs, patients should avoid exposure of the affected skin to sunlight for 7 days post application.

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting held for this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Neville Gibbs
6/30/2009 01:57:40 PM
MEDICAL OFFICER

Robert Shibuya
7/1/2009 08:55:00 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR NDA 22395

CLINICAL:

(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?
Yes.

(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?
Yes

(3) On its face, is the clinical section of the NDA legible so that substantive review can being?
Yes

If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?

Yes

(4) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?
Yes

(5) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?
Yes

(6) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?
Yes

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?
Yes

(8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?
Yes

(10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the US population?
Not relevant to this product.

(11) Has the application submitted all additional required case records forms (beyond deaths and drop-outs) previously requested by the Division?
Yes

Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division.
Yes

CLINICAL:

(12) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?
Yes

(13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?
Yes

(14) Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor ?
Yes

(15)From a clinical perspective, is this NDA fileable? If "no", please state below why it is not?
Yes

_ NAG _____
Reviewing Medical Officer - Neville A Gibbs
Date: December 18, 2008

_____
Supervisory Medical Officer

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/s/

Neville Gibbs
12/22/2008 01:20:21 PM
MEDICAL OFFICER

Robert Shibuya
12/22/2008 03:20:21 PM
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