

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-395

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum to Cross-Discipline Team Leader Review

Date	30 October 2009
From	Robert B. Shibuya, M.D.
Subject	Addendum to Cross-Discipline Team Leader Review
NDA/BLA #	22-395 (000)
Name	Qutenza (capsaicin 8% patch)
Applicant	Neurogesx
Date of initial Submission	13 October 2008
Date of major amendment	30 July 2009
PDUFA date	16 November 2009

This NDA was not presented at Advisory Committee. The reasons for not taking this New Molecular Entity to Advisory Committee follow:

- Capsaicin is a component of chile peppers and is ingested by millions of people on a daily basis.
- There is essentially no systemic absorption of capsaicin.
- Capsaicin, as a drug product, is used daily by millions of patients as an over-the-counter, monograph product.
- No unexpected safety issues were identified during clinical development and the efficacy of the product was clear.
- The product does not appear to have any properties that require risk mitigation.

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

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/s/

ROBERT B SHIBUYA
10/30/2009

Cross-Discipline Team Leader Review

Date	9 July 2009
From	Robert B. Shibuya, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-395
Supplement#	
Applicant	NeurogesX
Date of Submission	13 October 2008
PDUFA Goal Date	13 August 2009
Proprietary Name / Established (USAN) names	Qutenza (capsaicin patch 8%)
Dosage forms / Strength	8% (179 mg/patch = 640 mcg/cm ²)
Proposed Indication(s)	“...the prolonged reduction of neuropathic pain associated with postherpetic neuralgia (PHN)”
Recommended:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Primary Medical Officer Review	Neville Gibbs, M.D., MPH
Statistical	Katherine Meaker, M.S. Dionne Price, Ph.D.
Pharmacology Toxicology Review	L. Steven Leshin, D.V.M, Ph.D. Adam Wasserman, Ph.D.
CMC Review	Theodore Carver, Ph.D. Ali Al-Hakim, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. Suresh Doddapaneni, Ph.D.
DSI	Susan Liebenhaut, M.D. Constance Lewin, M.D.
OSE/DMEPA	Cathy Miller, MPH, RN Kellie Taylor, PharmD Denise Toyer, PharmD Carol Holquist, RPh

1. Introduction

Qutenza™ (identified as NGX-4010 during development) is a topical patch that contains a high concentration (8%) of capsaicin. Several lower concentration (0.025% to 0.25%) capsaicin-containing drug products, predominantly creams, are legally marketed as over-the-counter (OTC) drugs under a monograph. However, this is the first high-concentration, high-purity, fully synthetic capsaicin-containing prescription drug to undergo a formal NDA review. Therefore, this product is considered a New Molecular Entity. This product is copackaged with a cleansing gel, used to remove residual capsaicin from the patient's skin following application.

The OTC capsaicin-containing products are labeled with the OTC indication of, "the temporary relief of minor muscle and joint pain". Qutenza is a prescription drug with the proposed indication of, "...the prolonged reduction of neuropathic pain associated with postherpetic neuralgia (PHN)." The method of use for Qutenza is substantially different from the OTC products which are applied by the patient as often as three or four times per day for an unspecified duration. Qutenza is to be administered, following topical local anesthesia, by a health care professional as a single 60-minute application in a healthcare provider's office. The drug application procedure is to be performed no more frequently than every three months.

The efficacy of Qutenza was supported by two adequate and well-controlled studies in patients with pain due to postherpetic neuralgia. The clinical pharmacology program established that the systemic exposure to capsaicin following dosing with Qutenza was limited and transient which predicted little systemic toxicity. The principal safety findings were both local and systemic. Local adverse events included most prominently application site pain and dermatologic findings (erythema). Systemic effects include a transient increase in blood pressure correlated with the pain of the procedure as well as coughing and airway irritation for both patient and healthcare provider if the patch is removed too quickly, aerosolizing the capsaicin. Pain, local skin irritation, and blood pressure changes all resolved within hours (blood pressure changes) to days (pain and skin reactions). The aerosolization is entirely preventable. The Applicant submitted data to support repeat dosing at 3-month intervals.

2. Background

Capsaicin-containing products are legally marketed under Tentative Final Monograph (FR, Vol. 48, No. 27, February 8, 1983) as external analgesics at concentrations ranging from 0.025% to 0.25%. Capsaicin is a TRPV1 agonist and is thought to affect analgesia at high concentrations (such as 8% in this product) by excessive stimulation of cutaneous TRPV1 nerve endings, causing the death of distal nociceptive nerve terminals with preservation of the cell body of the neuron. Qutenza was developed to provide analgesia for pain due to postherpetic neuralgia (PHN). PHN is an uncommon consequence of an acute herpes zoster episode (reactivated varicella) whereby the pain associated with zoster persists after the skin

lesions heal. Because of the severity of the pain associated with PHN, the Applicant hypothesized that a higher concentration of capsaicin would be necessary than for the OTC indication and developed this product as a prescription drug.

(b) (4)

Over the course of product development, several meetings were held with the Applicant and several advice letters were sent. The regulatory history is summarized in Dr. Neville Gibbs' (primary clinical reviewer) review. Key communications are summarized here:

- Two adequate and well-controlled studies would be required (b) (4)
(Advice Letter, 9 February 2004).
- Given the data collected to date, Nerve Conduction Testing is not necessary (EOP2 meeting, 26 October 2005).
- To ensure blinding, a low-dose control (as opposed to a placebo control) was acceptable (EOP2 meeting, 9 November 2004).
- Trials in postherpetic neuropathy may be 8-weeks in duration (EOP1 meeting, 6 March 2003).
- The Applicant's strategy to demonstrate the ability of the cleansing gel to remove residual capsaicin is adequate (Pre-NDA meeting, 6 March 2008).
- It is important to note that the Applicant was not advised to conduct special dermatologic studies (cumulative irritancy, photoallergenicity, sensitization) during development.

Capsaicin causes substantial pain when applied to the skin. Throughout the Qutenza development program, the Applicant consistently used L.M.X.4, an unapproved, marketed 4% topical lidocaine cream, to affect anesthesia of the skin at the application site prior to application of Qutenza. The issue of the use of an unapproved drug, presumably critical in the application procedure, was not addressed during development.

The Applicant has requested, and was granted, Orphan Drug status late in the review cycle (22 May 2009).

The Applicant has provided a rationale to support why the special dermatology studies (i.e. cumulative irritancy) are not required. This submission was consulted to the Division of Dermatology and Dental Products. That consult is pending at this time.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Theodore Carver, Ph.D. with a secondary review by Ali Al-Hakim, Ph.D.

The drug substance is capsaicin, a moiety with poor water solubility. The Applicant has formulated the capsaicin into a matrix reservoir delivery system. (b) (4)

. Approximately 0.9% of the capsaicin content is absorbed into the dermis over a 60-minute application time.

The patch itself is thin, translucent, and of a rectangular shape. It measures 20 cm by 14 cm and contains 179 mg of capsaicin (640 mcg/cm²). Common pharmaceutical-grade excipients and manufacturing processes are used.

The topical cleansing gel is a clear semisolid consisting of polyethylene glycol as the capsaicin (b) (4) and standard pharmaceutical-grade ingredients in an aqueous base. The gel is packaged in a high-density polyethylene tube. The Applicant demonstrated that the gel was 89% effective in removing capsaicin from a stainless steel surface for spike levels up to 400 mcg.

Inspections of the manufacturing, testing, and packaging sites are all acceptable with the exception of (b) (4) which is pending at this time.

Please see Dr. Carver's excellent review for further details regarding the CMC aspects of this product. Both Drs. Carver and Al-Hakim have recommended approval, pending the acceptability of the last cGMP inspection by the Office of Compliance. The Applicant will submit a rationale for decreasing the frequency of microbial testing after approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by L. Steven Leshin, Ph.D., D.V.M. with a secondary review by Adam Wasserman, Ph.D.. As a New Molecular Entity, the Applicant submitted a substantial pharmacology/toxicology package. The finalized pharmacology/toxicology review is pending at this time.

Safety pharmacology and toxicology studies were conducted both via the intended route of administration and via the intravenous route. Capsaicin, administered topically as a liquid or patch formulation, caused reversible skin irritation. Since a topical anesthetic is applied prior to capsaicin application, no behavioral changes were noted compared with placebo patches. When administered intravenously to anesthetized dogs transient vital sign changes (elevated blood pressure, tachycardia) occurred consistent with a pain/sympathomimetic response. The major toxicological findings were dermal erythema and irritation, similar to that seen in the clinical studies. A hypersensitivity study was conducted in a species that is considered insensitive to capsaicin and although capsaicin patches were considered to be mild sensitizers in this study, it likely underestimated the severity of this effect.

The nonclinical pharmacokinetic program is worthy of further mention. Absorption/distribution/metabolism/excretion studies were performed in both rats (two

studies) and minipigs (one study). One rat study and the minipig study showed a small amount of absorption (2% to 6%) with transient measurable blood concentrations of capsaicin. The other rat study showed substantial absorption (~70%) with radioactivity detectable in the plasma up to 72 hours post-dose. The difference in the rat studies is felt to be due to a difference in the patches used. The patches used were developmental, not the to-be-marketed product. As noted in Section 5, systemic absorption using the to-be-marketed patch was low.

The genotoxicity evaluation was negative with the exception of the in vitro mouse lymphoma assay. The Applicant provided evidence that structurally similar endogenous compounds (catecholamines) also had positive mouse lymphoma assays. Mixed positive and negative test results are reported in the literature for this assay.

The Applicant conducted a carcinogenicity study that was unacceptable due to inadequate data collection and analysis. However, because of the infrequent dosing of this product, a carcinogenicity assessment is not required for approval.

Segment I, II, and III reproductive toxicity studies were conducted in rats and rabbits. Key findings include decreased fertility, abnormal testes, delays in skeletal ossification, and the expected dermatologic abnormalities of the dams at higher doses. There were no teratogenic or adverse effects on embryo-fetal development, other than delayed in ossification of a few bones.(metatarsals and sternebrae)

Drs. Leshin and Wasserman have recommended approval from the pharmacology/toxicology perspective for Qutenza.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by David Lee, Ph.D. with a secondary review by Suresh Doddapaneni, Ph.D.

The systemic absorption of capsaicin from this product has been a critical piece of information because it would have affected the nonclinical and clinical programs, specifically, requirements for safety database size, the requirement for carcinogenicity assessment, and a thorough QT study. The Applicant addressed this question via five clinical studies that assessed the systemic capsaicin concentration following topical application.

These five studies (C102, C108, C111, C107, and C116) are all described in detail in Dr. Lee's excellent review. Briefly these studies assessed plasma capsaicin concentrations after single- and repeat-dose (no more frequent than once every 12 weeks) patch applications ranging from 30 to 90 minutes in duration and following the use of several unapproved local anesthetics. Collectively, these data show:

- A small percentage (0.9%) of the total capsaicin is transferred into the skin during a 60-minute application.
- Any systemic capsaicin is heavily protein bound (~93%).

- Limited and transient systemic capsaicin exposure occurs following topical administration of Qutenza in some individuals.
 - Most of the patients and subjects had capsaicin levels that were below the level of detection of the assay. Most of the quantifiable capsaicin concentrations were less than 5 ng/mL.
 - The highest capsaicin concentration measured was 17.8 ng/mL which occurred immediately following a 90-minute application.
 - Capsaicin was undetectable by 3 hours post patch removal.

The Applicant did not conduct an exposure-response relationship. However, Dr. Lee found that Qutenza was more effective than the low-dose control treatment in the controlled clinical studies in PHN. Drs. Lee and Doddapaneni are recommending approval from the clinical pharmacology perspective for this product.

6. Clinical Microbiology

Clinical microbiology is not applicable for this product.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Neville Gibbs, M.D., MPH and the primary statistical review was conducted by Katherine Meaker, M.S.. Dionne Price, Ph.D. conducted the secondary statistical review.

The Applicant submitted a substantial clinical development program consisting of a total of 14 clinical studies, 12 of which were conducted in patients and two in healthy volunteers.

(b) (4)
A total of six studies are relevant to the evaluation of efficacy for this application since they were conducted in patients with PHN.

Of the six studies conducted in patients with PHN, two were considered adequate and well-controlled, Studies C116 and C117. Dr. Gibbs has described these nearly identical studies in detail. Briefly, these studies were randomized, double-blind, low-dose controlled, parallel-group designs that enrolled adults with PHN of at least 6-months duration and a pain score of at least 3/10 on an 11-point numerical pain rating scale (NPRS). It is important to note that patients had to experience pain upon screening when they might have been taking conventional oral therapies and those therapies were continued at stable dose throughout the study. Approximately 50% of patients were taking oral prescription medications at screening. Topical treatments were prohibited and the only analgesics permitted besides the permitted stable-dose oral therapies were opioid analgesics to manage the pain associated with patch application, for up to 5 days following patch application and acetaminophen as needed (“aches and pains”) with a daily limit of 2 grams.

Following a 60-minute application of L.M.X.4, an unapproved, marketed topical anesthetic containing 4% lidocaine as the active ingredient, eligible patients were treated with a single, 60-minute application of either Qutenza or a low-concentration (1/20 the capsaicin

concentration) comparator. Adverse events including pain, application site abnormalities, and vital signs were monitored throughout the treatment episode and for two hours following the removal of the Qutenza patch. Patients were followed for efficacy (11-point NPRS) and safety for an additional 12 weeks.

The Applicant specified a primary efficacy endpoint of the percent change from baseline to the average of 2-8 weeks post treatment for the NPRS score. Conceptually, this endpoint is a summed pain intensity difference (SPID) or area-under-curve (AUC) analysis which is not consistent with the approach to analyzing efficacy data currently considered appropriate for chronic therapy. An AUC analysis may demonstrate efficacy for a product that is effective only for the early part of the treatment period, without sustained effects through the entire treatment period. For this reason, the standard endpoint for a chronic pain indication is a landmark analysis where the difference between the baseline and end-of-study pain intensity is compared.

The Applicant showed a statistically significant difference between Qutenza and the control using the AUC approach. Ms. Meaker confirmed that result and also conducted a landmark analysis by both percent change from baseline and actual change from baseline. Her results are summarized in Tables 1 and 2, for Studies C116 and C117, respectively.

Table 1: Primary efficacy analysis, “landmark,” Study C116

Change in Average Pain from Baseline		Low concentration 3.2 mcg/cm ² [CONTROL] n=196	Qutenza [®] High concentration 640 mcg/cm ² n=206
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 stratified by gender with terms for treatment + baseline pain

Source: Ms. Meaker’s review, page 10/21

Table 2: Primary efficacy analysis, “landmark,” Study C117

Change in Average Pain from Baseline		Low concentration 3.2 mcg/cm ² [CONTROL] n=196	Qutenza [®] High concentration 640 mcg/cm ²
DAARP Preferred Analysis:*	LSMeans (SE)	-26.3 (2.4)	-32.9 (2.3)
Percent Change from Baseline to Week 8	Diff. p-value vs. control		6.6 0.046
DAARP Alternative Analysis:*	LSMeans (SE)	-1.4 (0.1)	-1.7 (0.1)
Actual Change from Baseline to Week 8	Diff. p-value vs. control		0.3 0.125

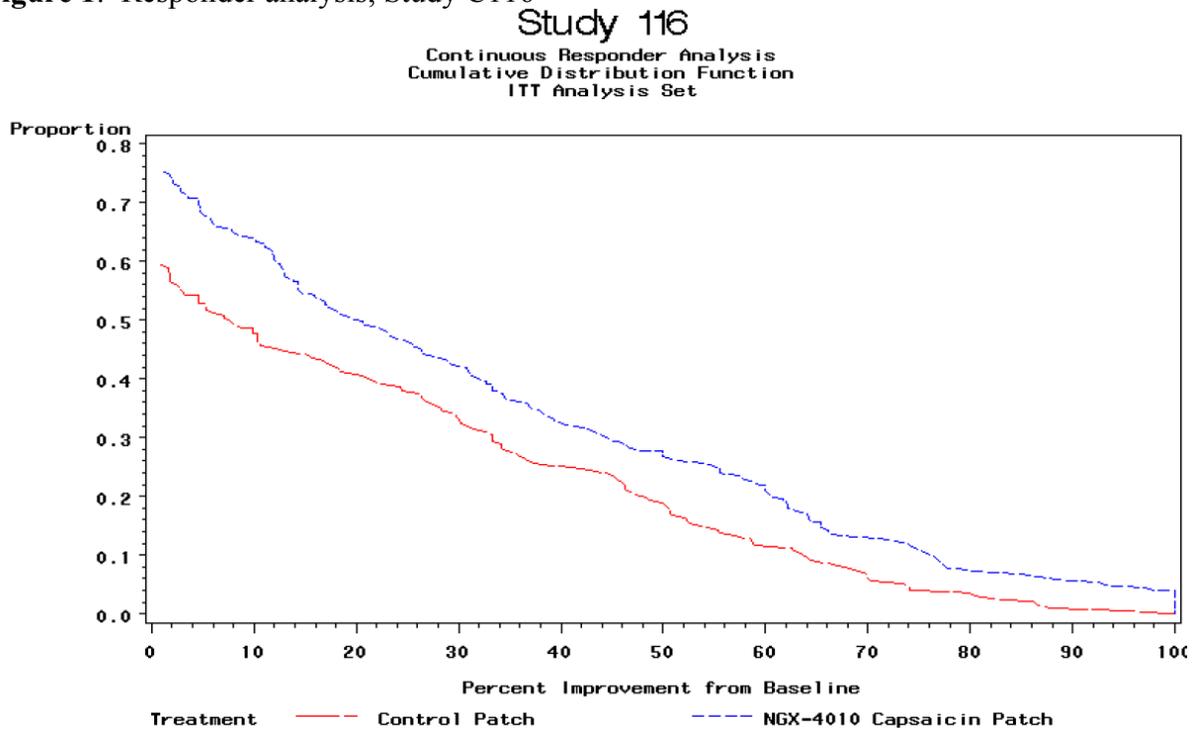
* P-value from ANCOVA model with terms for treatment + gender + baseline pain score (as planned in protocol)

Source: Ms. Meaker’s review, page 15/21

Ms. Meaker showed that the results from the reanalysis were consistent with the Applicant’s protocol-specified AUC analysis. She notes that one of the four comparisons (actual change from baseline in Study C117) did not meet criteria for statistical significance. However, the trend was consistent with the conclusion that Qutenza has an analgesic benefit and Ms. Meaker opined that this finding did not affect her recommendation that the drug is efficacious. I concur with Ms. Meaker’s conclusion.

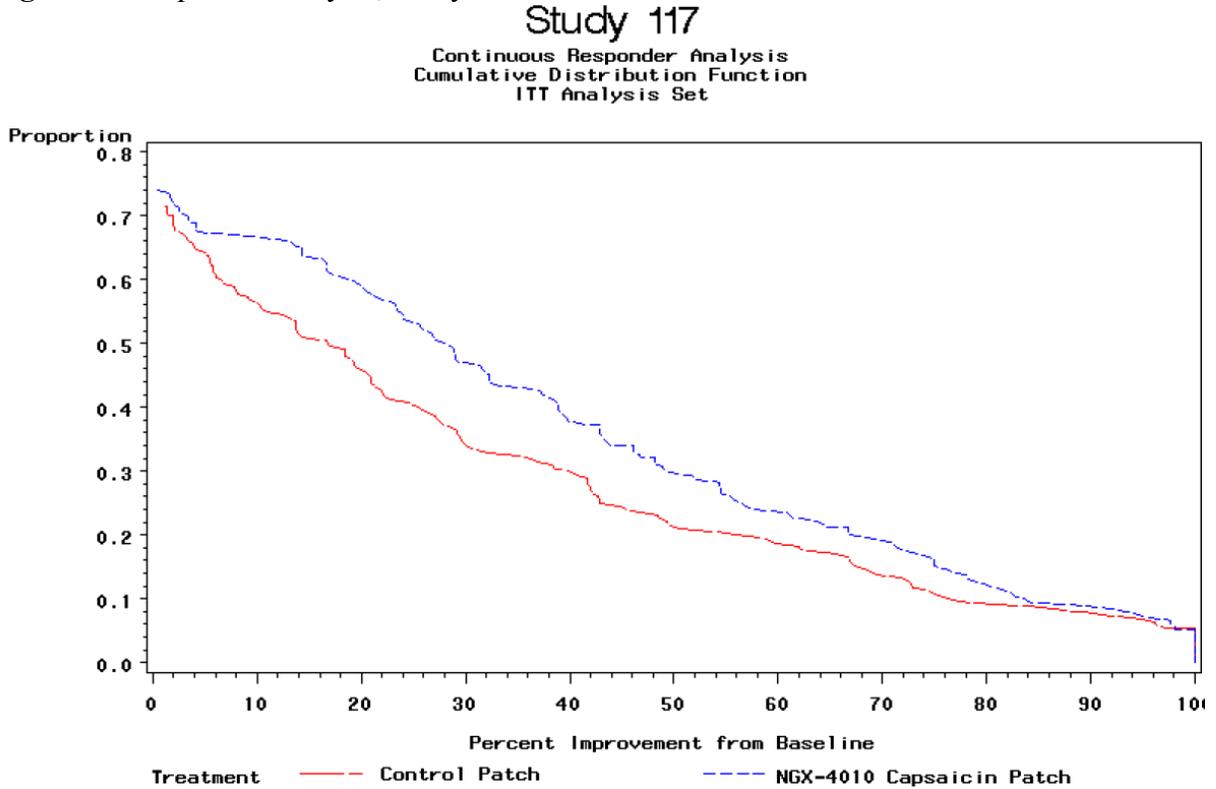
Ms. Meaker also conducted continuous responder analyses for Studies C116 and C117, shown in Figures 1 and 2, respectively. These analyses show a clear difference between the active and control groups that tends to diminish when the responder definition (percent decrease in pain intensity) is set to very high levels.

Figure 1: Responder analysis, Study C116



Source: Ms. Meaker's review, page 11/21

Figure 2: Responder analysis, Study C117



Source: Ms. Meaker's review, page 16/21

The study results are impressive given the duration of pain due to PHN (3-4 years on average) and severity of pain at baseline (while the protocol only required a NPRS score of 3/10, the mean baseline pain score was ~6) in the patients enrolled in the studies.

Repeat Patch Application

The Applicant has proposed to include labeling regarding repeat dosing and believes that data support redosing at 3-month intervals for return of pain. Studies C106, C108, and C118 permitted repeat dosing at intervals no more frequent than every 3 months.

Study C106

Briefly, Study C106 was an open-label extension of Study 102 which was a Phase 2 safety and efficacy study in patients with PHN. Study 106 was designed to provide information for repeat treatments (up to a total of three) of Qutenza regarding the effects on pain as well as safety and tolerability. Pain intensity was assessed via a NPRS. Table 3 shows the change from baseline in pain scores for the different applications in Study 106.

Table 3: Percent change from baseline, mean NPRS scores, applications 1-3, Study C106

NPRS Score (Weeks 2–End)	Study C106 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 $100 * [(Mean Rating at Time Point) - (Mean Baseline Rating)] \div (Mean Baseline Rating)$.

Source: Clinical Study Report, page 47-143 of pdf file

Study C106 supports the notion that patients continue to experience a benefit from repeated applications of Qutenza.

Study C108

Briefly, Study C108 was a randomized, double-blind, controlled safety and efficacy study in patients with PHN. The study design contained an open-label extension phase whereby repeat treatments (up to a total of four) could be applied no less than 12 weeks apart. Pain intensity was assessed via a NPRS. Table 4 shows the percentage of responders (defined as either a $\geq 30\%$ or $\geq 50\%$ reduction in pain intensity from baseline) by treatment episode.

Table 4: Summary data, responders by treatment episode, Study C108

	Total Number of NGX-4010 Treatments			
	1	2	3	4
“Average Pain for the past 24 hours” NPRS Score	n = 101	n = 69	n = 54	n = 19
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%)
≥ 50% Decrease from Baseline	40 (40%)	12 (17%)	8 (15%)	3 (16%)
“Worst Pain for the past 24 hours” NPRS Score	n = 101	n = 69	n = 54	n = 19
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%)
≥ 50% Decrease from Baseline	37 (37%)	14 (20%)	10 (19%)	3 (16%)
“Pain Now” NPRS Score	n = 101	n = 69	n = 54	n = 19
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%)
≥ 50% Decrease from Baseline	39 (39%)	14 (20%)	10 (19%)	4 (21%)

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 9–84 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 2–8 after the last treatment were excluded.

Source: Clinical Study Report, page 94/705 of pdf

Similar to Study C106, these data support a continued benefit to repeat treatment although, in this analysis, the benefit appears to diminish with repeated treatments.

Study C118

Briefly, Study C118 was an open-label study designed to inform the safety and tolerability of repeated applications (up to a total of 4) of Qutenza in patients with both HIV neuropathy and PHN. The study design did not require retreatment every 12 weeks, rather retreatment was dictated based upon the return of pain. Pain intensity was assessed via a NPRS. A total of 106 patients entered the study of which 25% received one treatment, 10% received two treatments, 29% received three treatments, and 36% received four treatments. The Applicant did not present the data per treatment, instead it provided a statistical summary at 12 and 48-weeks.

Table 5 shows the percent responders where “responder” is defined as either a $\geq 30\%$ decrease from baseline or a $\geq 50\%$ decrease from baseline at either 12-weeks (following one application) or 48-weeks (following as many as 4 applications).

Table 5: Responders at Weeks 12 and 48, Study C118

Subjects, n (%)	TOTAL (N = 106)	PHN (N = 54)	HIV-AN (N = 52)
Week 12			
$\geq 30\%$ Decrease from Baseline			
Yes	16 (18%)	11 (24%)	(b) (4)
No	74 (82%)	35 (76%)	
$\geq 50\%$ Decrease from Baseline			
Yes	8 (9%)	7 (15%)	
No	82 (91%)	39 (85%)	
Week 48			
$\geq 30\%$ Decrease from Baseline			
Yes	28 (37%)	21 (51%)	
No	48 (63%)	20 (49%)	
$\geq 50\%$ Decrease from Baseline			
Yes	17 (22%)	14 (34%)	
No	59 (78%)	27 (66%)	

Source: Clinical Study Report, page 62/380 of pdf

These data appear to show that as needed treatments, no more frequently than every 12 weeks, are associated with higher responder rates with more time on drug. The results could also be explained by spontaneous resolution of the PHN or HIV neuropathy. However, it is important to note that patients were treated based on the return of pain so that seems less likely.

While it is important to note that none of the studies contributing repeat-dose efficacy data were controlled, the data do support the efficacy of repeated applications of Qutenza when dictated by the return or persistence of pain. I note that even though different metrics were used (% change and responder status), the effect was consistent across studies.

8. Safety

The review of clinical safety was conducted by Dr. Gibbs.

A total of 1,696 patients and subjects were exposed to Qutenza in the development program. Of those persons, approximately 74% received a single administration and approximately 26% received two or more administrations. One hundred and seven patients received four treatments. Follow-up was up to one year. As discussed previously, because of the limited systemic exposure, a thorough QT study was not required.

Major Safety Findings

With the exception of one patient who experienced severe hypertension, the major safety findings (deaths, serious adverse events (SAEs), and adverse events leading to discontinuation) did not appear to be related to the use of Qutenza. As described in Dr. Gibbs' review, one patient (with a history of hypertension) experienced a pronounced increase in blood pressure during and shortly following the procedure. Three days post procedure, he presented to an Emergency Department with a blood pressure of 230/120 (baseline blood pressure 150-170/90-100). He was admitted for management of the hypertension. While his capsaicin level was quite low (1.9 ng/mL 1 hour post patch removal and undetectable at other times), given the blood pressure signal noted with the use of Qutenza (discussed later in this section), this SAE appears reasonably related to the use of the product.

Common Adverse Events and Adverse Events of Interest

Five key issues were identified in the safety review: application site pain, blood pressure elevations around the time of dosing, cardiac adverse events, skin reactions at the application site and respiratory irritation (coughing and sneezing) following patch removal.

1. Application site pain

The application of Qutenza causes substantial pain at the application site, even after pretreatment with a topical local anesthetic.

In the pivotal clinical trials, C116 and C117, nearly 60% of patients treated with Qutenza reported application site pain as an adverse event and 5.3% of patients reported the pain as severe. Patients were permitted treatment for the pain caused by the patch application with physical measures such as an ice pack or a narcotic analgesic (either immediate-release single-ingredient oxycodone or hydrocodone/acetaminophen). In the first 24 hours after dosing (when pain due to Qutenza application is maximal), approximately 40% and approximately 20% of

patients dosed with Qutenza required treatment with oxycodone or hydrocodone/acetaminophen, respectively. In the large majority of cases, the pain associated with patch application returned to baseline or below by three days post application. In conjunction with the in vitro testing of the cleansing gel, the adverse event profile supports a conclusion that the gel is adequate to remove excess capsaicin.

The rates of nausea and vomiting in patients treated with Qutenza were 4.6% and 2.9%, respectively, compared to 1.7% and 0.7%, respectively, in the patients treated with control. This appears due to the higher rate of narcotic rescue required in the active arms.

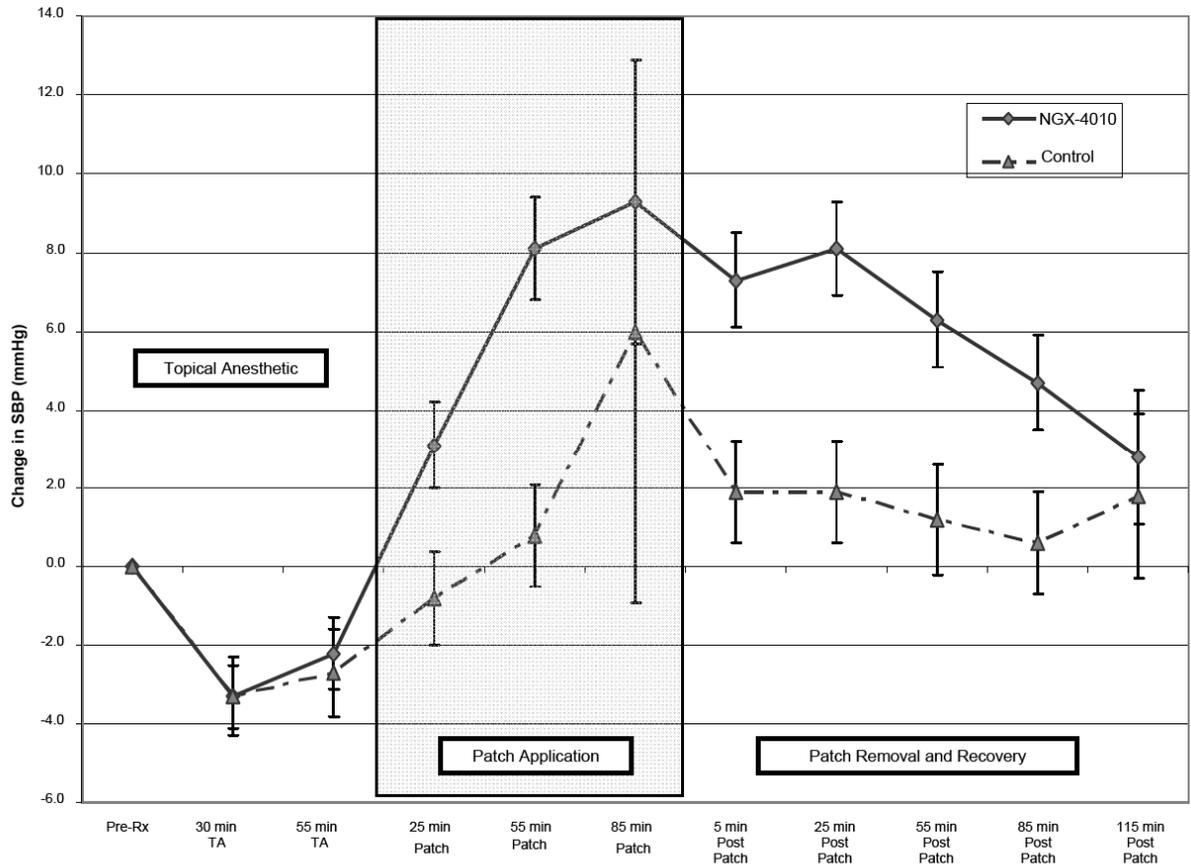
The anesthetic used in the Phase 3 studies, L.M.X.4, is an unapproved product. To provide support for the use of Qutenza following application of an approved topical anesthetic, the Applicant is conducting a small, open-label study with an approved topical anesthetic (EMLA) presently.

2. Blood pressure elevations around the time of dosing

Vital signs were measured periodically throughout the studies at scheduled visits (screening, Week 4, Week 8, etc.) and showed no treatment-related effects.

On the day of treatment, vital signs were monitored at baseline, during pretreatment with the topical anesthetic, during treatment with Qutenza or control, and for two-hours post patch removal. Figure 3 shows aggregate systolic blood pressure data from Studies C102, C108, C116, and C117 (controlled PHN studies).

Figure 3: Mean change from baseline in systolic blood pressure, all controlled PHN studies



SP=patch with study medication (NGX-4010 or Control); TA=topical anesthetic.

Source: ISS, page 243/330

The figure shows elevation in mean systolic blood pressure starting at the first blood pressure measurement after patch application. The systolic blood pressure peaks around the time of patch removal and gradually normalizes over the two hours following patch removal.

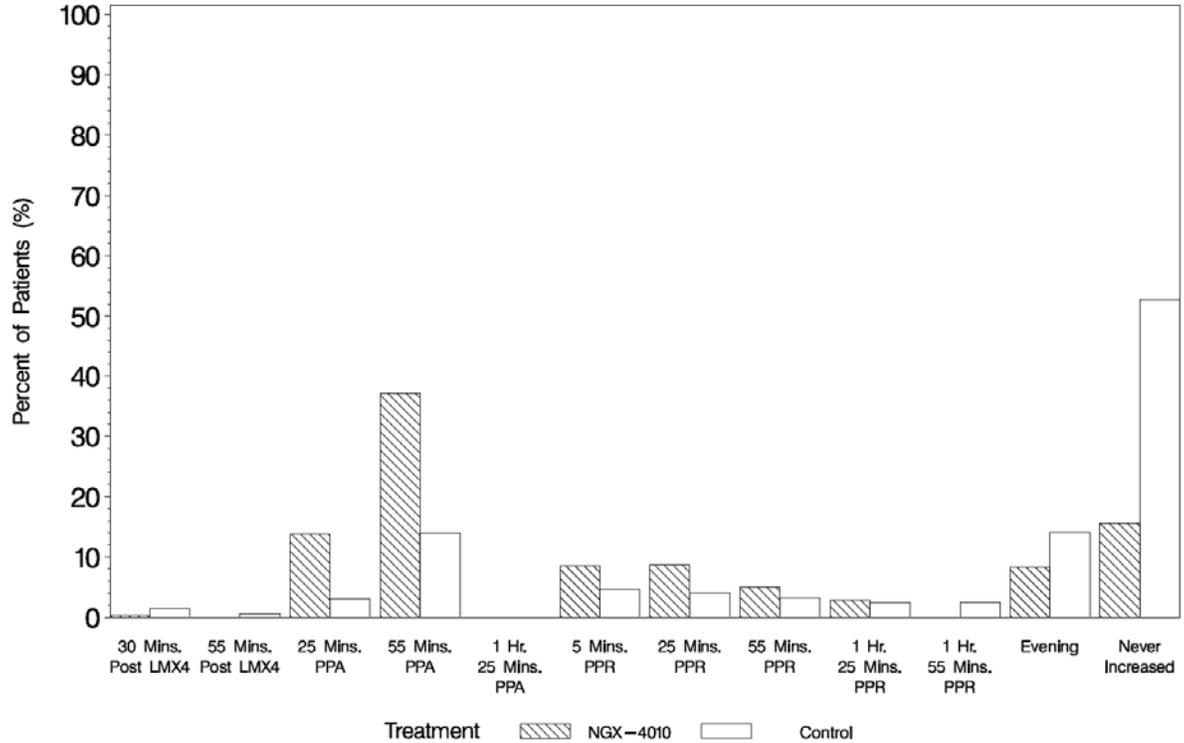
Because of the effects on blood pressure and heart rate observed in dogs in the safety pharmacology study, a further analysis of the effects of Qutenza on vital signs was requested from the Applicant. Specifically, the Applicant was asked to assess whether there was a temporal association between application site reactions, including pain, and changes in vital signs, and whether the pain was associated with the anatomic site of application.

Unfortunately, for the most part, the data collected were too coarse (i.e. data collection points were too far apart) or were qualitatively not helpful to assess this issue.

The analyses generally supported the conclusion that the changes in blood pressure are likely to be due to the pain of the procedure and not due to a direct effect on the

cardiovascular system. Figure 4 is a histogram showing the time to maximum increase in pain score on the day of treatment.

Figure 4: Time to maximum increase in pain score, aggregated, controlled PHN studies (PPA=post patch application; PPR=post patch removal)



Source: 13 April 2009 submission

Examined in conjunction with Figure 3, the data from Figure 4 support the idea that the elevated blood pressure is temporally associated with the pain of patch application. This finding should be addressed in labeling. Patients with poorly controlled hypertension may be at some degree of risk from an increase in blood pressure so there should be adequate vital sign monitoring during and after the procedure, and the practitioner should be prepared to aggressively treat the pain associated with the procedure.

Table 6 was submitted by the Applicant in response to a request to assess whether there was any difference in the pain of drug application based on the treatment site. These data show that the pain associated with patch application, except for the leg, where pain scores were lower, was independent of treatment site.

Table 6: Mean maximum increases in pain, systolic blood pressure, and heart rate by site treated

Treated Site	Mean Maximum Increase in Pain Intensity* (NPRS Score)		Mean Maximum Increase in Systolic Blood Pressure* (mmHG)		Mean Maximum Increase in Heart Rate* (beats/min)	
	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: 13 April 2009 submission

These data also support that vital sign changes are correlated with the level of pain experienced. Figures 5 and 6 are scattergrams of the maximum increase in pain versus systolic blood pressure and heart rate, respectively. While largely driven by the data for application to the leg, the correlation coefficient for these relationships is 0.78 and 0.86, respectively, consistent with a reasonable correlation between pain and vital sign changes.

Figure 5: Maximum increase in pain intensity versus increase in blood pressure, controlled PHN studies

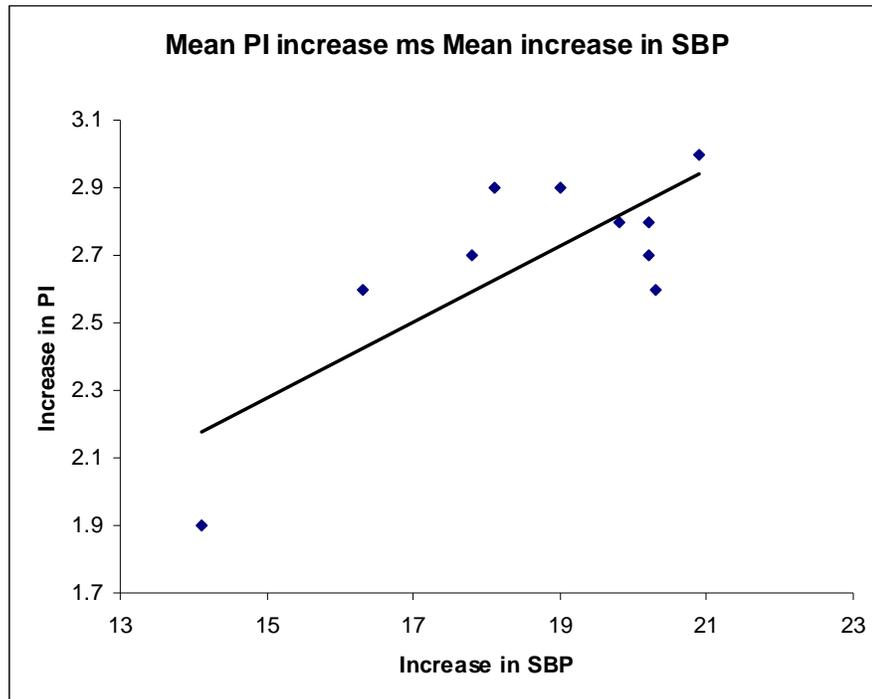
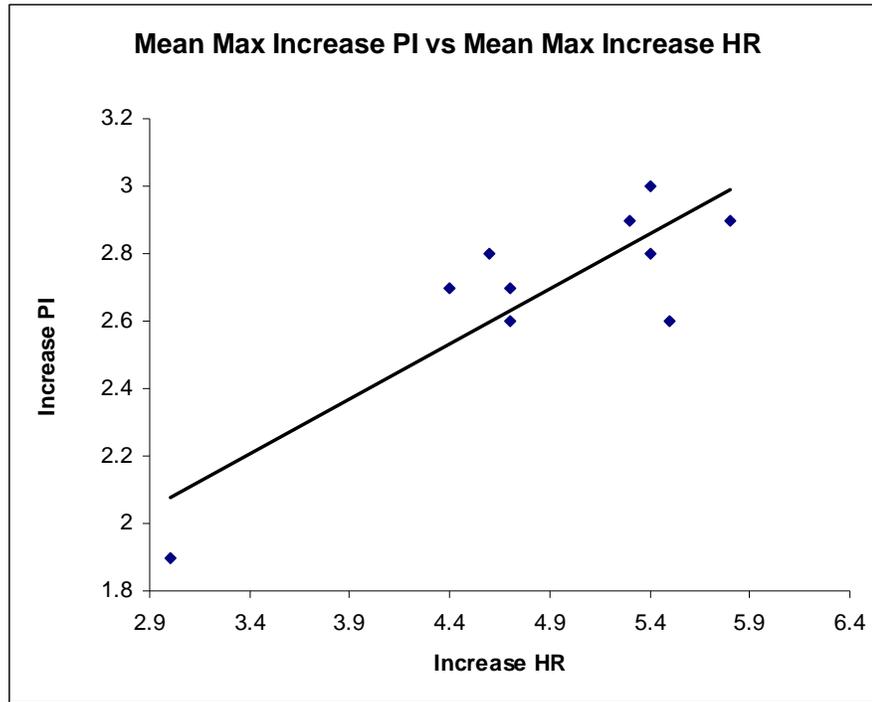


Figure 6: Maximum increase in pain intensity versus increase in heart rate, controlled PHN studies



3. Cardiac Events

While, in all controlled studies (b) (4) the incidence of adverse events coded to the “cardiac disorders” system organ class (SOC) was approximately equal (2.9% in patients treated with Qutenza; 2.7% in patients treated with control), in the controlled PHN studies, patients treated with Qutenza had a higher rate (4.6% to 2.9%) of cardiac AEs. The Applicant provided data that indicated that the cardiac events were related to pre-existing cardiac risk factors and did not appear to be related to systemic capsaicin exposure or to treatment-related pain or changes in blood pressure.

The Applicant argued that, due to the transient exposure to capsaicin, the relevant events are limited to those that occurred within 7 days of dosing. Given what is known about the pharmacokinetics of the drug and the pattern of resolution of the adverse events, this limitation is reasonable. When the analysis is limited to a 7-day period, the incidence drops to 1.0% in patients treated with Qutenza versus 0.6% in patients treated with control.

Table 7 shows the adverse event terms related to the cardiac disorders SOC reported in the Qutenza development program.

Table 7: Cardiac adverse events, entire clinical development program, controlled studies

Preferred Term	Qutenza (total) N=1327	Control (total) N=789
All Cardiac	39 (2.9%)	21 (2.7%)
Angina pectoris	4 (0.3%)	2 (0.3%)
Arrythmia	1 (0.3%)	2 (0.3%)
Atrial Fibrillation	5 (0.4%)	2 (0.3%)
AV Block, first degree	2 (0.2%)	2 (0.3%)
Bradycardia	3 (0.2%)	0
Bundle branch block, left	2 (0.2%)	1 (0.1%)
Myocardial infarction	5 (0.4%)	3 (0.4%)
Palpitations	7 (0.5%)	0
Supraventricular extrasystoles	0	3 (0.4%)
Tachycardia	3 (0.2%)	2 (0.3%)
Ventricular extrasystoles	2 (0.2%)	2 (0.3%)

Source: Extracted from Table 52, ISS, page 175/330 of pdf

Table 7 shows no treatment-related pattern to the cardiac adverse events. In addition, examination of the entirety of Table 52 in the Integrated Summary of Safety shows no dose response with regard to duration of application (30, 60 and 90 minutes). However, overall, the cardiac safety data do not exclude the possibility of a cardiac safety signal because, even in the best case analysis (PHN-only, limited to within 7 days of treatment), the cardiac AE rate in patients treated with Qutenza still exceeds that of patients treated with placebo (1.0% to 0.6%). Because of the weakness of the cardiac signal, the cardiac risk can be addressed through adequate cautions in the labeling.

4. Skin reactions at the application site

The most common adverse events were skin reactions at the application site. These data are summarized in Table 8.

Table 8: Application site adverse events (excluding pain), pooled data, Studies C116 and C117

Preferred Term	Qutenza (N = 417)	Control (N = 401)
Erythema	387 (93%)	269 (67%)
Papules	35 (8.4%)	11 (2.7%)
Edema	25 (6.0%)	2 (0.5%)
Pruritis	16 (3.8%)	9 (2.2%)
Eccymosis	4 (1.0%)	0

Source: Summary data from Dr. Gibb’s review, page 100/148

These skin reactions were self-limited. They peaked shortly after patch removal and resolved within 1-3 days post treatment. As described in Dr. Gibbs’ review, some of the studies included qualitative and quantitative sensory testing. There was no evidence of perturbation in sensation of any consequence.

5. Respiratory irritation (coughing and sneezing) following patch removal

When the patch was removed too quickly, there was the potential for capsaicin to aerosolize, resulting in respiratory irritation by both the healthcare provider and patient. This occurred in a small number of patients (25 events that occurred in 19 patients – 0.8%). This event is preventable with appropriately slow removal of the patch.

Repeat Patch Application

Again, to support the language pertaining to repeat dosing at no less than 12-week intervals, the sponsor collected safety data in three trials, Studies C106, C108, and C118.

Table 9 contains summary data from Study C106, an open-label extension following a controlled study. The table reports the adverse event of pain following each application. While this is an indirect measure of tolerability in repeat applications, overall the data suggest that there is not a substantial difference in the pain associated with patch application over three treatment cycles.

Table 9: Assessment of pain, during or immediately following application, Study C106

Subject Responses, n (%)	Study C106 NGX-4010		
	Treatment Cycle 1 (n = 21)	Treatment Cycle 2 (n = 15)	Treatment Cycle 3 (n = 9)
Improved	3 (14)	2 (13)	1 (11)
Remained the same	2 (10)	0	0
Worsened somewhat	7 (33)	8 (53)	6 (67)
Worsened definitely	9 (43)	3 (20)	1 (11)
Not done	0	2 (13)	1 (11)

Source: Clinical Study Report, page 66/143 of pdf

Table 10 shows summary adverse event data from Study 108, an open-label, repeat dose study. The data do not show evidence of any cumulative or increasing toxicity with repeat applications.

Table 10: Most frequent adverse events, Study C108

System Organ Class Preferred Term	NGX-4010 Treatment n (%)			
	First	Second	Third	Fourth
Number of Subjects Receiving NGX-4010 Treatment	282	170	83	20
Number of Subjects Reporting 1 or More Events	159 (56%)	70 (41%)	35 (42%)	3 (15%)
Gastrointestinal Disorders	36 (13%)	16 (9%)	8 (10%)	0
Diarrhea	8 (3%)	2 (1%)	0	0
Nausea	15 (5%)	7 (4%)	1 (1%)	0
Vomiting	10 (4%)	6 (4%)	1 (1%)	0
General Disorders and Administration Site Conditions	57 (20%)	26 (15%)	16 (19%)	3 (15%)
Application Site Burning	6 (2%)	1 (1%)	3 (4%)	0
Application Site Dermatitis	1 (< 1%)	1 (1%)	2 (2%)	0
Application Site Dryness	6 (2%)	5 (3%)	3 (4%)	1 (5%)
Application Site Erythema	1 (< 1%)	0	2 (2%)	0
Application Site Excoriation	1 (< 1%)	0	0	1 (5%)
Application Site Papules	4 (1%)	4 (2%)	1 (1%)	1 (5%)
Application Site Pruritus	22 (8%)	11 (6%)	8 (10%)	1 (5%)
Application Site Swelling	4 (1%)	2 (1%)	1 (1%)	1 (5%)
Application Site Vesicles	1 (< 1%)	1 (1%)	0	2 (10%)
Fatigue	4 (1%)	3 (2%)	1 (1%)	0
Pain Exacerbated	8 (3%)	1 (1%)	0	0
Infections and Infestations	47 (17%)	15 (9%)	10 (12%)	0
Bronchitis	6 (2%)	0	1 (1%)	0
Herpes zoster	1 (< 1%)	3 (2%)	2 (2%)	0
Influenza	5 (2%)	2 (1%)	0	0
Nasopharyngitis	15 (5%)	2 (1%)	2 (2%)	0
Sinusitis	6 (2%)	2 (1%)	0	0
Musculoskeletal and Connective Tissue Disorders	17 (6%)	11 (6%)	4 (5%)	0
Arthralgia	1 (< 1%)	1 (1%)	2 (2%)	0
Back Pain	5 (2%)	4 (2%)	0	0
Nervous System Disorders	19 (7%)	8 (5%)	2 (2%)	0
Dizziness	10 (4%)	3 (2%)	0	0
Headache	7 (2%)	2 (1%)	1 (1%)	0
Psychiatric Disorders	10 (4%)	3 (2%)	2 (2%)	0
Insomnia	5 (2%)	3 (2%)	2 (2%)	0
Respiratory, Thoracic, and Mediastinal Disorders	12 (4%)	7 (4%)	2 (2%)	0
Cough	6 (2%)	3 (2%)	1 (1%)	0
Skin and Subcutaneous Tissue Disorders	9 (3%)	3 (2%)	5 (6%)	0
Rash	2 (1%)	2 (1%)	2 (2%)	0
Vascular Disorders	7 (2%)	4 (2%)	0	0
Hypertension	5 (2%)	3 (2%)	0	0

Source: Clinical Study Report, page 129/705 of pdf

Tables 11 and 12 show summary safety data for Study C118, an open-label, repeat dose study in patients with both HIV neuropathy and PHN. The Dermal Assessment Scores were a composite assessment of skin irritation and, in the data presentation in Table 12, the Applicant has shown percentages of patients who experienced increases in pain intensity > or < 33%.

There is no evidence of cumulative toxicity or increasing adverse event rate or severity with repeated application.

Table 11: Dermal assessment score, day of treatment, Study C118

Dermal Assessment Scores ^{a,b}	Treatments Received PHN				Treatments Received HIV-AN			
	1 st	2 nd	3 rd	4 th	1 st	2 nd	3 rd	4 th
N	54	40	33	19	52	40	36	19
Immediately After Patch Removal								
0	2 (4%)	3 (8%)	2 (6%)	2 (11%)	28 (54%)	17 (43%)	17 (47%)	10 (53%)
1	16 (30%)	8 (20%)	5 (15%)	5 (26%)	13 (25%)	16 (40%)	15 (42%)	8 (42%)
2	35 (65%)	28 (70%)	26 (79%)	12 (63%)	10 (19%)	7 (18%)	3 (8%)	1 (5%)
3	1 (2%)	0	0	0	1 (2%)	0	1 (3%)	0
4	0	1 (3%)	0	0	0	0	0	0
1 hour After Patch Removal								
0	3 (6%)	3 (8%)	2 (6%)	1 (5%)	20 (38%)	18 (45%)	19 (53%)	11 (58%)
1	22 (41%)	14 (35%)	11 (33%)	7 (37%)	20 (38%)	13 (33%)	12 (33%)	7 (37%)
2	28 (52%)	21 (53%)	20 (61%)	11 (58%)	10 (19%)	9 (23%)	5 (14%)	1 (5%)
3	1 (2%)	2 (5%)	0	0	0	0	0	0
4	0	0	0	0	2 (4%)	0	0	0

- a. 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.
- b. No subject in either group after any treatment had a dermal assessment score higher than 4.

Source: Clinical Study Report, page 100/380 of pdf

Table 12: Change in NPRS, day of treatment, Study C118

NPRS Score, n (%)	Treatments Received			
	1 st	2 nd	3 rd	4 th
TOTAL (N = 106)				
5 mins. Prior to Patch Removal				
n	104	80	69	38
Same or No Increase	43 (41%)	39 (49%)	34 (49%)	22 (58%)
< 33% Increase from Baseline	22 (21%)	16 (20%)	13 (19%)	4 (11%)
≥ 33% Increase from Baseline	39 (38%)	25 (31%)	22 (32%)	12 (32%)
1 Hour After Patch Removal				
n	106	80	69	38
Same or No Increase	51 (48%)	47 (59%)	48 (70%)	26 (68%)
< 33% Increase from Baseline	22 (21%)	18 (23%)	11 (16%)	6 (16%)
≥ 33% Increase from Baseline	33 (31%)	15 (19%)	10 (14%)	6 (16%)

Source: Clinical Study Report, page 100/380 of pdf

The repeat dose safety data, while not ideal to make a comprehensive safety assessment, show that, by a variety of metrics, there is no evidence of cumulative or increasing adverse events with repeated applications of Qutenza. These data support the proposed labeling.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for Qutenza.

10. Pediatrics

The Applicant requested a waiver for the Pediatric Research Equity Act requirements because PHN occurs extremely rarely in the pediatric population. The Division agreed with the Applicant as did the Pediatric Research Committee and the requirement for pediatric studies has been waived for the PHN indication.

11. Other Relevant Regulatory Issues

The inspection summary for four clinical investigators requested from the Division of Scientific Investigations (Roy Blay, Ph.D.) is pending at this time although Dr. Blay has verbally informed us that there are no significant findings.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted. The proposed tradename, Qutenza was found to be acceptable. DMEPA had a number of comments regarding the instructions for use that will be addressed in the labeling meetings and negotiations.

12. Labeling

In addition to recommendations from other disciplines, key points to be emphasized in labeling include:

1. Pain is to be expected, beginning at the time of patch application, peaking at patch removal, and may persist for several days following patch removal. Clinicians should be prepared to manage this pain aggressively, during and after the procedure.
2. Elevations in blood pressure, again during and after patch application, are to be expected. Adequate analgesia is expected to mitigate this effect. However, conscientious vital sign monitoring is critical and the clinician should carefully weigh the risks and benefits of this procedure in patients with poorly controlled hypertension.
3. The patch must be handled with caution using nitrile gloves only starting from the time the pouch is opened. The patch must be applied and removed with care and disposed of appropriately. The cleansing gel must be used per directions. DMEPA had a number of labeling recommendations that must be conveyed to the Applicant.
4. Clinicians must carefully consider the benefit-to-risk ratio for patients with substantial cardiac risk factors.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Pending acceptable results from the EMLA tolerability study, Approval

- Risk Benefit Assessment

The Applicant has generated replicated evidence of efficacy in a population of adults with longstanding, clinically significant PHN. The efficacy data have withstood various analyses and support a finding of efficacy for Qutenza.

The clinical trial data identified five areas of concern: application site pain, elevations in blood pressure which appear to be due to the pain of patch application, a weak cardiac safety signal, skin changes at the application site, and respiratory irritation due to aerosolization of capsaicin upon patch removal.

With the exception of the weak cardiac signal, the adverse events are monitorable, manageable, avoidable, and/or self-limited. With regard to the cardiac signal, it is very unclear whether the slight excess incidence (0.4%) in cardiac adverse events observed were due to the study drug, particularly because they were correlated with commonly recognized cardiac risk factors and they were not correlated with systemic exposure to capsaicin.

The current armamentarium for the treatment of PHN is limited and consists of:

- Gabapentin
- Pregabalin
- Topical lidocaine
- Several classes of drugs used off-label including anti-epileptics, antidepressants, and OTC capsaicin

Given that the Applicant has demonstrated replicated efficacy in this group of patients who have long-standing pain on conventional therapies, I believe that the benefits of this drug outweigh the risks. It is important to provide strong labeling warning of the use of this drug in patients with substantial cardiac risk.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

Not applicable.

Cross Discipline Team Leader Review

- Recommended Comments to Applicant

None

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/s/

Robert Shibuya
7/10/2009 08:15:00 AM
MEDICAL OFFICER