CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-395

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	November 13, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-395
Applicant Name	NeurogesX
Proprietary / Established (USAN) Names	Qutenza Capsaicin
Dosage Forms / Strength	patch 8%
Proposed Indication(s)	The prolonged reduction of neuropathic pain associated with postherpetic neuralgia (PHN)
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding capsaicin topic patch 8% (640 mcg/cm^2, 179 mg total) and the reader should refer to the reviews in the action package for a more detailed discussion. Capsaicin, the pungent component of hot chili pepper, is a vanilloid receptor (VR1) agonist classified as a transient receptor potential vanilloid 1 (TRPV1) agonist. TRPV1 receptors are expressed in sensory neurons that detect noxious painful stimuli and the agonist effect of capsaicin at VR1 receptors results in analgesia by causing the death of distal nerve twigs.

Capsaicin can cause substantial pain when applied to the skin depending on the concentration. As such, the 60-minute application of this product requires pretreatment with a topical local anesthetic and is to be done under the supervision of a health care professional. The proposed frequency for application is every three months.

The efficacy is supported by two adequate and well-controlled trials in subjects with postherpetic neuralgia (PHN). It is interesting to note that the subjects enrolled were required to have pain of at least six months (3-4 years on average) in the face of oral treatments. Therefore, these subjects had refractory PHN that was resistant to oral pain therapy and was not resolving through 'tincture of time'. Patients with this type of PHN can be challenging to treat and a demonstration of efficacy from therapy may be an important advancement.

The primary endpoint was change from baseline in an 11-point numerical pain rating scale (NPRS). The trials demonstrated efficacy when evaluated by both a landmark and AUC assessment. Please see the reviews of Drs. Rappaport, Shibuya and Gibbs for a very thorough discussion of the findings. The change between the to-be-marketed product and a low concentration capsaicin comparator was LSMeans of 0.3-0.6, which gives some sense of the mean magnitude of benefit. An important secondary endpoint was the proportion of

responders experiencing either a 30% or 50% decrease in pain from baseline. In both studies, this favored the full strength capsaicin patch (10% difference and 4% difference from low-dose capsaicin respectively for study C116). While these may seem to be small differences, the results must be viewed in the context of the duration of symptoms and how resistant the disease had been to other therapies.

It would be hard to predict how the average patients with less refractory disease will respond to this agent, in that the results from this refractory group of subjects may be quite different from the majority of patients where the symptoms resolve quickly (comparatively) on their own. Other data submitted indicates that repeat patch application will be of benefit to an additional small percentage of the subjects, although this wasn't evaluated in a randomized, blinded, fashion.

Principal safety findings were application site pain, erythema, pain-induced transient blood pressure increases and airway irritation and coughing due to aerosolizing the capsaicin with patch removal.

Advisory Committee Meeting

An advisory committee meeting was not held for as capsaicin has been marketed for many years, has well-defined adverse effects, has limited absorption in this dosage form, trials clearly demonstrating efficacy and no unexpected or concerning safety signals.

Conclusions and Recommendations

Dr. Rappaport's review is very complete and I am in complete agreement with his assessment. This product should receive an approval action.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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/s/

CURTIS J ROSEBRAUGH
11/13/2009

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	October 13, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-395
Applicant Name	NeurogesX
Date of Submission	October 13, 2008
PDUFA Goal Date	August 13, 2009; with three-month clock extension for major amendment November 16, 2009
Proprietary Name / Established (USAN) Name	Qutenza (Capsaicin) 8% patch
Dosage Forms / Strength	8% (179 mg/patch = 640 mcg/cm^2)
Proposed Indication	For the prolonged reduction of neuropathic pain associated with postherpetic neuralgia
Recommendation for action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Neville Gibbs, M.D., M.P.H.
Statistical Review	Katherine Meaker, M.S.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	L. Steven Leshin, D.V.M., Ph.D.; Adam Wasserman, Ph.D.; Paul C. Brown, Ph.D.
CMC Review	Roswitha Kelly, Ph.D.; Theodore Carver, Ph.D.; Ali Al-Hakim, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	David J. Lee, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda Fienkeng, Pharm.D.; Samuel Skariah, Pharm.D.; Kendra Jones
DSI	Susan Liebenhaut, M.D.; Constance Lewin, M.D., M.P.H.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Cathy Miller, M.P.H., R.N.; Kellie Taylor, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DAEA N/A	
OSE/DRISK N/A	
OSE/DEPI N/A	
DDDP	Joanna Ku, M.D.; Jill Lindstrom, M.D.; Susan Walker, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
DDDP=Division of Dermatology and Dental Products

1. Introduction

Qutenza is a topical patch containing an 8% w/w concentration of capsaicin. Capsaicin is a TRPV1 agonist which provides analgesia by excessive stimulation of this receptor found on predominantly small-fiber neurons, which results in the death of the distal nociceptive nerve terminals with preservation of the cell bodies of the neurons. There are several lower concentration (0.025% to 0.25%) capsaicin-containing creams that are legally marketed as over-the-counter drug products for the temporary relief of minor muscle and joint pain under a Tentative Final Monograph. Qutenza will be the first capsaicin prescription product and, due to the fact that the monographic remains in tentative final form, is therefore considered a new molecular entity. The proposed indication for this product is "for the prolonged reduction of

neuropathic pain associated with postherpetic neuralgia (PHN)." Qutenza is applied by a health care professional following administration of a topical local anesthetic. The product will be co-packaged with a cleansing gel consisting of polyethylene glycol in an aqueous base which is used to remove residual Qutenza from the patient's skin following application. The sponsor was granted orphan indication status for PHN.

2. Background

PHN is an uncommon consequence of an acute herpes zoster episode (commonly known as shingles). Patients with PHN develop severe pain which continues after the zoster skin lesions have healed, in some cases persisting for as long as months or years. The pain of PHN can be debilitating and is often unresponsive to oral analgesics. (b) (4) As Qutenza itself results in application-related pain, often quite severe, the sponsor pre-treated the subjects in the clinical studies with L.M.X.4, a marketed but unapproved topical cream-formulation of lidocaine. Their use of this unapproved drug in the development studies was found to be unacceptable by the review team as we would not be able to reference the unapproved product in the Qutenza label and it remained unclear whether the available approved topical anesthetic products would provide adequate analgesia in the setting of Qutenza administration. This was of particular concern as even with the administration of the local anesthetic the majority of subjects experienced substantial pain during Qutenza application and required analgesic treatment with oral opioids. Therefore, the sponsor was required to provide data from a clinical study employing an approved local anesthetic product. The sponsor performed an open-label study employing an approved local anesthetic product during the course of the review and submitted it on July 30, 2009. This submission was considered to be a major amendment and, as it was submitted within three months of the original PDUFA date, the review clock was extended for three months in order to allow for a thorough evaluation of this new data. The new study demonstrated that the approved anesthetic, EMLA cream, resulted in tolerability that approximated what was seen throughout the clinical development program.

Including one study conducted during the review cycle (Study C123), the sponsor submitted data from fifteen clinical studies, thirteen conducted with patients and two with healthy volunteers. The following table summarizes those studies:

Protocol #	Phase	Study Design*/Objective	Treatment groups**	Treatment duration	Population^ N		Comments
C101	1	R, DC, OL To determine the relationship between treatment time and loss of cutaneous nociceptors, immunohistochemical changes, etc.	HC LC	30, 60, 120 minutes	HV 20		
C115	1	R, DC, OL To assess the effect of Qutenza on epidermal nerve fiber density and quantitative sensory testing	HC 60	minutes	HV	36	
C102	2	R, DB, DC Efficacy and exploration of anesthesia and analgesia requirements	HC LC	60 minutes	PHN	44	
C107	3	R, DB, DC Efficacy, safety, and tolerability for 3 treatment durations	HC LC	30, 60, 90 minutes	HIV-AN	307	Up to three repeat treatments permitted
C108	2/3	R, DB, DC Efficacy, safety, and tolerability for 3 treatment durations	HC LC	30, 60, 90 minutes	PHN	299	Up to three repeat treatments permitted
C110	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	155	
C112	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	HIV-AN	5	Terminated early for business reasons
C116	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	402	Primary support for efficacy
C117	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	418	Primary support for efficacy
C119	3	R, DB, DC Efficacy, safety, tolerability	HC LC	30 or 60 minutes	HIV-AN 494		
C106	2	OL, extension study To obtain information on repeat dosing in patients with PHN	HC	60 minutes	PHN	24	OL extension of C102. Up to three repeat treatments permitted
C109 2		OL Proof of concept study	HC 60	minutes	HIV-AN	12	
C111 2		R, OL To evaluate three local anesthetic formulations used prior to Qutenza	HC	60 or 90 minutes	PHN/DPN 117		All local anesthetics tested were unapproved.
C118 2		OL To assess safety and "efficacy" of repeat treatments of Qutenza	HC	60 minutes (a few patients received a single 90 minute application)	PHN/HIV-AN	106	
C123 N	/A	OL To assess whether a 60-minute Qutenza application was tolerable when used in conjunction with an approved topical local anesthetic [2.5% lidocaine/2.5% prilocaine cream (EMLA)]	HC 60	minutes	PHN	24	

*R = randomized; DC = dose-controlled; OL = open-label; DB = double-blind;
**HC = high concentration (8%, active) patch; LC = low concentration (control) patch
^HV = healthy volunteer; PHN = postherpetic neuralgia; DPN = diabetic peripheral neuropathy; HIV-AN = HIV-associated neuropathy

The sponsor provided substantial evidence of the efficacy of Qutenza from two adequate and well-controlled studies. Repeat treatment, however, was not evaluated in controlled studies. While Drs. Gibbs and Shibuya concluded that there was adequate evidence of repeat-dose

efficacy, I disagree with that conclusion as per my discussion below in Section 7. The clinical pharmacology studies of Qutenza demonstrated that the systemic absorption of capsaicin from the product was extremely low and, therefore, systemic toxicity was considered to be unlikely. Nevertheless, elevations of blood pressure and cardiac rate were noted in proximity to patch application. The clinical review team has concluded that these events were related to the pain associated with patch application and that they can be addressed in the clinical setting with monitoring and proper pain management, and via cautions in the product labeling. While there was significant local toxicity, it did not result in any severe or persistent adverse events.

3. CMC

The Qutenza patch is a matrix delivery system. (b) (4) (b) (4) (b) (4) Approximately 0.9% of the capsaicin is absorbed into the dermis over a 60-minute application. The cleansing gel contains polyethylene glycol to (b) (4) the capsaicin. The sponsor provided data demonstrating that the gel was 89% effective in removing capsaicin from a stainless steel surface. Adequate stability data was submitted to support a 36-month shelf-life. All facility inspections were found to be acceptable.

I concur with the review team that there are no outstanding CMC issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The sponsor performed an extensive battery of nonclinical pharmacology and toxicology studies. The major toxicological findings were dermal erythema and irritation. A hypersensitivity study was conducted in a species that is considered insensitive to capsaicin. However, based on the conclusions of the dermatology consultants regarding the need for a clinical hypersensitivity study, further nonclinical evaluations would be superfluous. The sponsor's in vitro mouse lymphoma assay results were positive. However, the sponsor noted that this would be the expected result with capsaicin as it is structurally similar to endogenous compounds such as the catecholamines which also test positive in this assay. Drs. Leshin and Wasserman determined that the weight of evidence from all of the genetic toxicology studies supports the sponsor's conclusion that capsaicin is not genotoxic.

The sponsor's reproductive toxicology studies demonstrated adverse effects on sperm parameters and a reduction in the size of the testes in a fertility evaluation, as well as delays in skeletal ossification in the offspring of pregnant rats treated with the capsaicin patch in a study of embryofetal development. However, these findings were observed with doses much higher than the proposed clinical doses and they were also noted after significantly more intense administration regimens than the single use clinical regimen. Therefore, Drs. Leshin and Wasserman have concluded that there is limited risk to patients under the conditions of labeled use.

I agree with the review team that there are no outstanding pharmacology or toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted five clinical pharmacology studies. The following summary of Dr. Lee's findings is from pages 5 and 6 of Dr. Shibuya's 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.

Based on the limited systemic absorption, studies in special populations and drug-drug interaction studies were not performed. I agree with the review team that there are no outstanding clinical pharmacology issues that would preclude approval of this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

Two of the studies submitted by the sponsor in support of efficacy, studies C116 and C117, were considered adequate and well-controlled by the clinical/statistical review team, Both studies were randomized, double-blind, low-dose controlled, parallel-group trials that compared the Qutenza patch to a patch that contained five percent of the capsaicin dose in the Qutenza patch in adults with PHN of at least six-months duration and a pain score of at least 3 on an 11-point numerical rating scale (NRS). Approximately 50% of the subjects were taking prescription oral analgesics at screening and those enrolled were required to maintain stable doses of those analgesics throughout the studies. The subjects were pretreated with the L.M.X.4 topical anesthetic discussed above in Section 2. During patch application and for five days following treatment the subjects were allowed rescue analgesia with opioid analgesics, as well as up to 2 gm of acetaminophen daily as needed for "aches and pains."

The primary outcome measure in both studies was the percent change from baseline to the average over Weeks 2 through 8 post-treatment on the NRS. This "AUC-type" analysis is not consistent with the Agency's approach to analyzing efficacy data for chronic pain treatment

and the sponsor was informed that they should employ a "landmark" type analysis by the clinical reviewer during development. As the sponsor chose not to submit this type of analysis, Ms. Meaker performed landmark analyses on the data from each of the studies, including analyses of both percent change from Baseline to Week 8 and actual change from Baseline to Week 8. Both the sponsor's AUC-type analyses and Ms. Meaker's landmark analyses demonstrated a statistically significant treatment effect for the Qutenza patch with the exception of Ms. Meaker's analysis of the actual change from Baseline to Week 8 for Study C117. The latter analysis did demonstrate a strong trend and, considering the results of all of the other analyses, the clinical and statistical review teams concluded that there was substantial evidence of efficacy for the Qutenza patch. Ms. Meaker also conducted continuous responder analyses for both studies which demonstrated a clear separation of the cumulative responder curves. The following tables from pages 41 and 58 of Dr. Gibbs' review summarize the sponsor's analyses:

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

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)

The following tables and graphs summarizing Ms. Meaker's analyses have been reproduced from pages 7, 8 and 9 of Dr. Shibuya's review:

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)	-19.2 (2.3)	-29.9 (2.3)
	Diff.		10.7
	p-value vs. control		0.001
DAARP Alternative Analysis:** Actual Change from Baseline to Week 8	LSMeans (SE)	-1.1 (0.1)	-1.7 (0.1)
	Diff.		0.6
	p-value vs. control		0.002

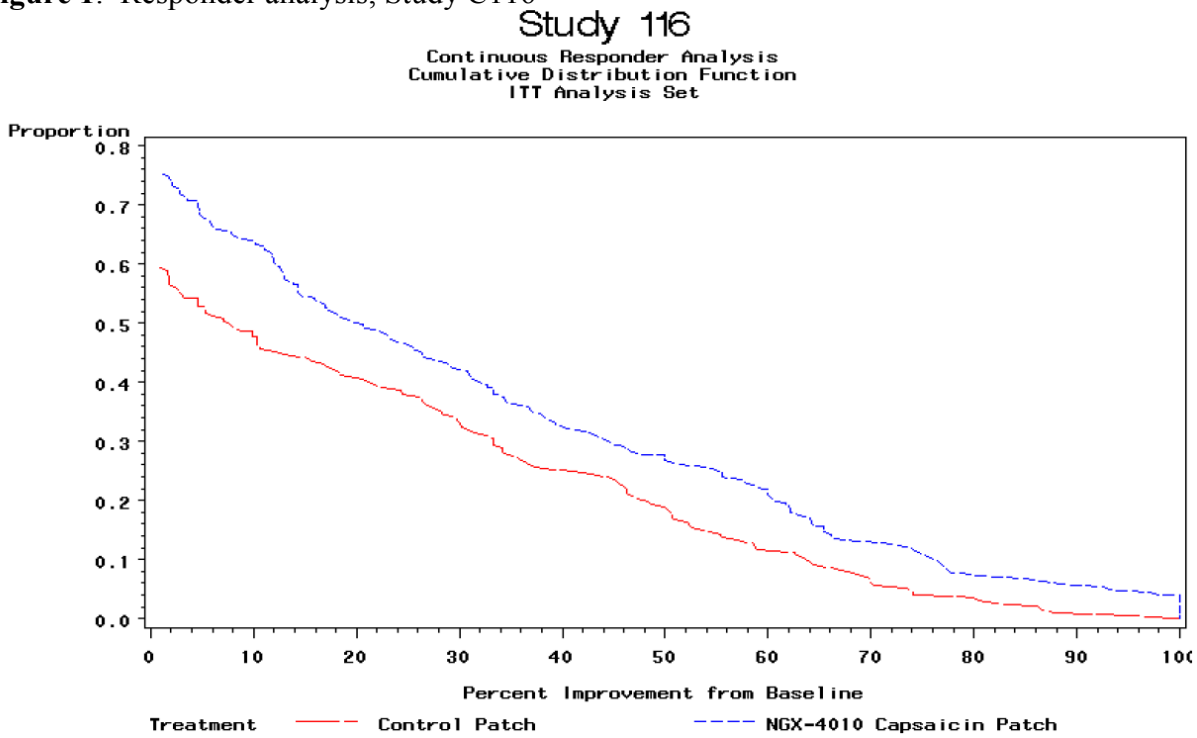
** P-value from ANCOVA model stratified by gender with terms for treatment + baseline pain
Source: Ms. Meaker's review, page 10/21

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:* 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

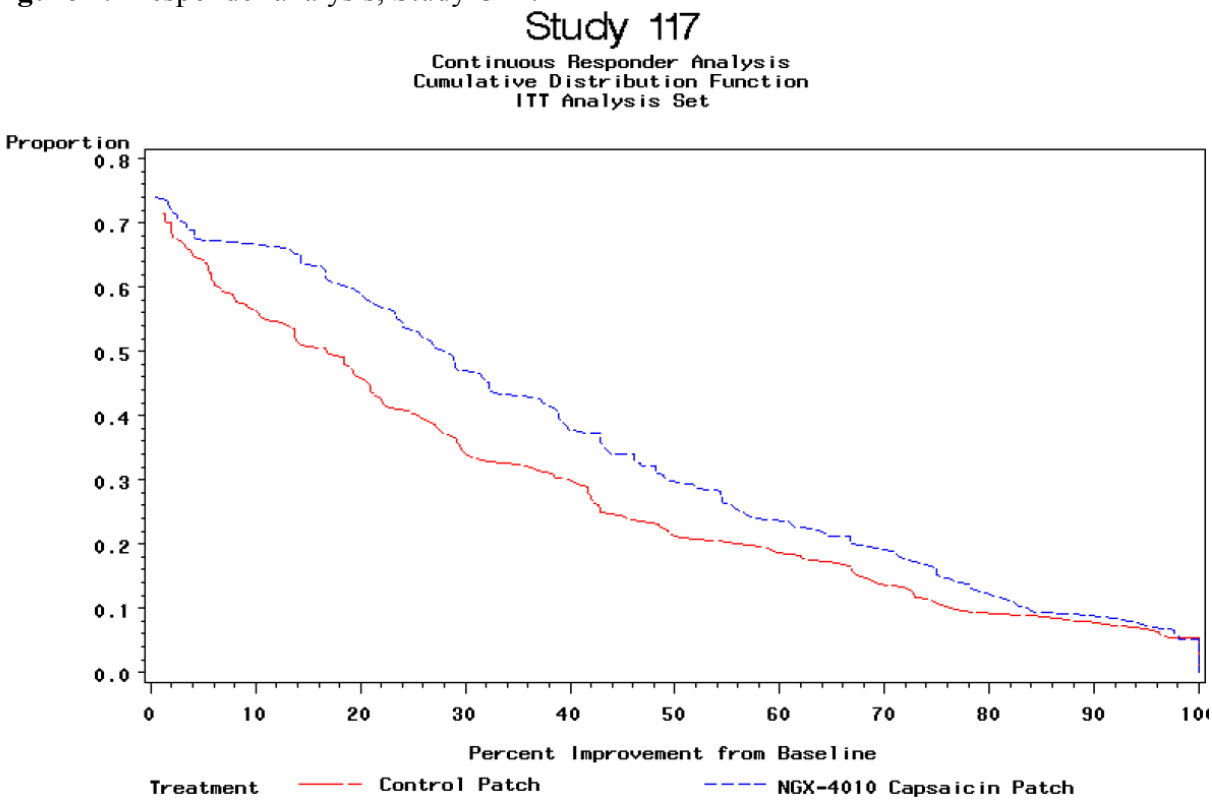
* P-value from ANCOVA model with terms for treatment + gender + baseline pain score (as planned in protocol)
Source: Ms. Meaker's review, page 15/21

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 sponsor has proposed that repeat patch application be allowed at no earlier than three-months after a prior treatment. The data supporting the efficacy of repeat dosing is numerically quite strong, but comes from open-label studies only. Retreatment was only initiated with the reoccurrence of pain, thus it is unlikely that the positive results could be explained by resolving PHN. However, a placebo effect cannot be ruled out. Drs. Gibbs and Shibuya have concluded that there is adequate data to support labeling for repeat dosing. I do not agree with this conclusion as there are no data to support repeat dosing from adequately controlled studies.

8. Safety

A total of 1,696 subjects were exposed to Qutenza in the clinical development program. Approximately 74% of those subjects received two or more administrations, with 107 subjects receiving four treatments. Drs. Gibbs and Shibuya have concluded that the deaths, serious adverse events and adverse events leading to discontinuation were not related to study drug exposure with one possible exception and I agree with their conclusion. The exception was a subject with a history of hypertension who experienced a pronounced increase in blood pressure during patch application which then persisted post-procedure. Three days after patch application he was admitted to hospital with a blood pressure of 230/120. His capsaicin levels were 1.9 ng/mL at one hour post patch removal and undetectable at other times. However, as blood pressure increases were not uncommon with Qutenza application and were most likely due to the pain associated with the procedure, this event must be considered drug-related and does suggest the need for caution in the use of this product in at risk patients.

As noted above, mild to moderate elevations in blood pressure were noted in the clinical studies. The only other significant adverse events noted in the clinical studies were application site reactions such as pain, erythema and papules, and coughing. While the application site reactions occurred frequently, other than the pain they were mild to moderate and resolved completely within a reasonable period of time post-treatment. The coughing was noted in both patients and health care practitioners and was associated with aerosolization of the capsaicin when the Qutenza patch was removed too quickly. The labeling now includes a caution against too rapid removal of the patch.

The Division of Dermatology and Dental Products was consulted to assess the absence of certain standard dermal safety studies in this application and they have provided the following conclusions and recommendations in their response:

- Given that existing clinical data already demonstrate that Qutenza is a dermal irritant, the Applicant has proposed a waiver of the requirement of a cumulative irritancy study, and to use labeling to warn users about the irritation potential of the product, as well as to state the incidence of AEs associated with application site reactions. DDDP finds this approach acceptable, based on the following rationale. Cumulative irritancy study may be waived, as the purpose of conducting such test is to determine whether irritancy potential exist for a product. Where the product formulation has already been shown to be significantly irritating, and will be identified as such in proposed labeling, cumulative irritancy study could be waived. We recommend, however, 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 Reactions

section of labeling should clearly state that the incidence of pain reflects the incidence of pain *after* pre-treatment with topical lidocaine anesthetics, since without pre-treatment with anesthesia, incidence of pain would certainly have been higher. [from page 5 of Dr. Ku's consult response]

- [The] clinical data, together with the pre-clinical data in the guinea pig, suggest that Qutenza may be an allergic sensitizer in a subset of patients. The evidence is not conclusive but suggestive. The Sponsor could include in the labeling a warning that Qutenza may be a sensitizing agent, in which case a formal sensitization study could be waived. However, if the Sponsor does not wish to include that in the labeling, a formal sensitization study should be pursued to rule out the risk of sensitization. [from page 7 of Dr. Ku's consult response]

- Assuming that the Applicant's claim with regards to Qutenza's absorption spectrum is accurate… DDDP concur that phototoxicity and photoallergenicity studies may be waived. In general, if no components of the drug product absorb light corresponding to wavelengths of 290 to 700 nm (UVA, UVB, and visible), then an Applicant may request these tests to be waived. Also, in general, phototoxicity studies may be waived if the use of the topical product is to be in an area not normally exposed to light, or under an opaque dressing, both which of which appear to be the case with Qutenza administration. It may be reasonable to include instructions in the labeling for limiting sun/light exposure to the area after Qutenza application. [from page 8 of Dr. Ku's consult response]

9. Advisory Committee Meeting

Capsaicin is consumed daily by millions of people around the world. In addition, as there are legally marketed over-the-counter products containing capsaicin in the US, there is limited systemic absorption of capsaicin from the Qutenza patch, the sponsor has clearly demonstrated efficacy, and there were no clinically concerning safety signals, this application was not presented at an advisory committee.

10. Pediatrics

Qutenza received orphan indication designation for PHN, thus the requirements of the Pediatric Research Equity Act do not apply. Furthermore, PHN is extremely rare in children.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The Agency and the sponsor have concurred on appropriate language for the product labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Approval

- Risk Benefit Assessment

  The sponsor has provided data that support their conclusion that Qutenza is safe and effective when used according to the product labeling. I disagree with the clinical review team's conclusion that the application included adequate data to demonstrate that the product is effective with repeat-dosing, as repeat-dosing was only evaluated in open-label studies. Therefore, I recommend that the dosing and administration section of the product label not explicitly state that repeat dosing is acceptable. However, I do think it is acceptable to state that the product was found to be safe with repeat dosing, particularly as practitioners are likely to employ repeated dosing for persistent pain. The sponsor's new study of the use of EMLA as a pre-treatment anesthetic has addressed the review team's concerns regarding the use of an unapproved product in the earlier studies, and will allow appropriate recommendations for pre-treatment in the product label. The elevations in blood pressure and heart rate noted in the clinical studies in association with Qutenza application appear to be related to the pain associated with application, particularly given the absence of any significant systemic absorption of capsaicin as documented in the clinical pharmacology studies. However, in spite of the fact that these elevations were generally mild and did not result in serious outcomes for the most part, there did appear to be some evidence that patients with poorly controlled hypertension or cardiac disease may be at risk for complications from these effects. Therefore, appropriate cautions, and recommendations for monitoring and adequate analgesic treatment during patch application, should be included in the product label. Finally, I agree with the DDDP consultants and the clinical review team that post-marketing studies of dermal safety are not necessary, for the reasons explicated in Dr. Ku's consult response.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

  None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22395	ORIG-1	NEUROGESX INC	Qutenza

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/s/

BOB A RAPPAPORT
11/13/2009