

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-395

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-395	Submission Date: 10/13/08
Submission Type; Code:	7S
Brand/Code Name:	Qutenza™
Generic Name:	Capsaicin Patch 8%
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
ORM Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	NeurogesX, Inc.
Relevant IND(s):	63,354
Formulation; Strength(s):	8% capsaicin (640 µg/cm ²); Each patch contains a total of 179 mg of capsaicin.
Proposed Indication:	Prolonged reduction of neuropathic pain associated with postherpetic neuralgia (PHN)
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Single patch, 60-minute application of up to four patches;• After removal of Qutenza, generously apply Cleansing Gel to the treatment area and leave on for approximately one minute. Remove Cleansing Gel with a dry wipe and gently wash the area with mild soap and water and dry thoroughly.

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the NDA 22-395 submitted on 10/13/08. From OCP perspective, the information contained in the Application is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

NeurogesX, Inc. has submitted NDA 22-395 for Qutenza™, capsaicin patch 8%, for the management of neuropathic pain associated with postherpetic neuralgia (PHN), as 505(b)(1) application. It is noted that the Applicant has requested Orphan Drug designation for Qutenza. The proposed Qutenza patch area is 280 cm² (20 cm x 14 cm; it contains 179 mg of capsaicin, 640 µg of capsaicin per cm² of adhesive (8% w/w)). Qutenza will be co-packaged with Cleansing Gel, which is used to remove the local anesthetic applied prior to Qutenza patch and the residual capsaicin on the skin after the Qutenza patch is removed. Qutenza can be used up to 4 patches applied to cover the treatment area in a single application session. Patches can be cut to fit the treatment area. In clinical trials, treatment times varied between 30 and 90 minutes but the recommended treatment time is 60 minutes. The treatment may be repeated every three months or as warranted by the return of pain. Qutenza will be applied to the patient in a treatment facility by a physician.

Qutenza clinical development program consisted of 14 clinical studies comprising 2 Phase 1 studies in healthy volunteers (Studies C101 and C115) and 12 Phase 2 or Phase 3 studies in PHN subjects (Studies C102, C106, C108, C110, C111, C116, C117, C118), HIV-associated neuropathy subjects (HIV-AN; Studies C107, C109, C111, C112, C118, C119), and painful diabetic neuropathy subjects (PDN; Study C111). Two studies (Studies C111 and C118) were conducted in a mixed patient population (PHN, HIV-AN, or PDN). However, as indicated above, this Application is being submitted to support the use of Qutenza in the prolonged reduction of neuropathic pain associated with PHN.

The majority of the Qutenza trials, including the pivotal Phase 3 studies, were conducted with the final formulation, CAP 72.

Regarding the capsaicin exposure information, since the patch is applied at the local site(s) associated with PHN for a local pain control, the critical clinical pharmacology aspect of this NDA was to focus on the capsaicin systemic exposure from the systemic safety purpose.

The majority of the capsaicin exposure information reviewed for the capsaicin systemic exposure used the final formulation, CAP 72, except for Study 102, which used the clinical formulation. However, looking at the two formulations, there were minimal differences between the clinical and final formulations, and, the findings from Study 102 will have no impact on the overall findings. The following studies were reviewed from the clinical pharmacology perspective: P2 studies: C102, C108 and C111; P3 studies: C107 and C116. Additionally, the Applicant submitted a population pharmacokinetic (PK) analysis using Studies 108, 111, and 116.

Exposure-Response Relationship

Summary: There is no exposure-response relationship for Qutenza. However, there are several clinical trials, include two pivotal Phase 3 clinical trials, which assessed the safety and efficacy of Qutenza (i.e., duration of patch application; 30, 60 or 90 minutes). The overall data indicated that Qutenza was more effective than the control treatment. The treatment effect was similar regardless of gender, age, or PHN duration.

Efficacy:

Studies 116 and 117 were the 2 pivotal, Phase 3 randomized, double-blind, controlled, multi-center evaluations of the efficacy, safety, and tolerability of Qutenza in PHN patients. Subjects in both studies were randomized in a 1:1 ratio to receive Qutenza or control treatment for 60 minutes. The control group did not receive placebo, rather, the control group had a ‘low’ level capsaicin patch, capsaicin 3.2 µg/cm². This was allowed to mask the pain due to the capsaicin when the patch is applied to the patients. The required minimum duration of PHN for patients enrolled in most studies was 6 months post-vesicle crusting. The primary efficacy endpoint for pivotal studies (the 12-week controlled studies) was the mean percent change in “average pain for the past 24 hours” NPRS score from Baseline during Weeks 2 to 8. Week 1 NPRS scores were not analyzed for the primary endpoint to avoid the potential for bias due to the 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 Qutenza and Control groups over the primary analysis period (i.e., during Weeks 2 to 8). Mean percent change from Baseline in NPRS scores was also evaluated during Weeks 2 to 12 as a secondary endpoint. Additional analyses were performed using a gender-stratified ANCOVA model with Baseline pain score as the only covariate. Subgroup analyses were conducted to determine the potential impact of gender, age, Baseline pain score, duration of PHN, concomitant neuropathic pain medication use, and rescue medication use on the efficacy profile of Qutenza for Studies (C108, C110, C116, and C117). Race and ethnicity were not included in the assessment of subgroups because the overall study populations were predominantly Caucasian and non-Hispanic.

The overall data indicated that Qutenza was more effective than the control treatment. The treatment effect was similar regardless of gender, age, or PHN duration. However, it was noted that females and younger subjects reported larger percent reductions in pain scores compared with males and older subjects, respectively. Rescue medication use did not appear to affect the efficacy of Qutenza.

Safety:

The most notable treatment-emergent adverse reaction incidences from two Phase 3 clinical trials were application site erythema and pain. The Applicant reported that the majority of application site reactions were transient and self-limited. Pain was commonly observed on the day of patch treatment due to capsaicin and usually resolved after patch removal.

QT

No clinical trials were conducted to evaluate the prolongation of QT interval. Although capsaicin is a new chemical entity, a thorough QT study is necessary since capsaicin systemic bioavailability after Qutenza patch application is minimal and capsaicin is used as locally acting drug.

Capsaicin systemic exposure from Qutenza patch

Summary: Overall, only limited and transient systemic exposure to capsaicin occurs following topical applications of Qutenza. The highest observed capsaicin concentration was 17.8 ng/mL.

The following studies were reviewed for capsaicin systemic concentrations after Qutenza application. As stated previously, since the patch is applied at the local site(s) associated with PHN for a local pain control, the critical clinical pharmacology aspect of this NDA was to focus on the capsaicin systemic exposure from the systemic safety purpose. The following 5 studies were reviewed for capsaicin's systemic concentrations: Phase 2 studies, C102, C108, and C111; and, P3 studies, C107 and C116.

Study 102 was a Phase 2 double-blind, randomized, controlled, multi-center study investigating the feasibility, tolerability, safety and efficacy of treatment of pain with Qutenza in subjects with PHN. The study included an initial small open-label phase (all 6 subjects were treated with Qutenza), followed by a double-blind treatment phase in which the subjects were randomized to receive either Qutenza or low-concentration control patch (3.2 µg capsaicin per cm²) for 60 minutes in a 2:1 ratio. Blood samples (10 mL in K₃EDTA coated tubes) were collected at the following time-points: (1) immediately prior to application of capsaicin patches, (2) immediately after removal of capsaicin patches (within 5 minutes), (3) at 1 hour post-patch removal, and (4) 3 hours post-patch removal. Potassium EDTA was used as an anticoagulant. This study was conducted with clinical trial formulation 1. The results indicated that plasma levels of capsaicin in all subjects in this study were below the LLOQ (2.5 ng/mL) at all time-points.

Study C108 was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of PHN, with an open-label extension phase. Subjects were randomized to receive either Qutenza or low-concentration control patches (3.2 mcg capsaicin cm²) for 30, 60 or 90 minutes. Efficacy was assessed over a period of 12 weeks. Subjects who completed study evaluations through Week 12 had the option of receiving a maximum of 3 additional open-label 60 minute re-treatments with Qutenza no more often than once every 12 weeks. During the initial 12 week double-blind phase, blood samples were collected (5 mL in K₃EDTA coated tubes) in subjects assigned to the 90-minute treatment group at selected study sites. A preliminary assessment of plasma lidocaine levels was also performed. Blood samples were also collected in the same cohort of subjects if they elected to receive one or more 60-minute Qutenza treatments during a 40 week open-label extension period.

Sample collection time-points were as follows: (1) immediately before topical lidocaine-based (4%) local anesthetic (L.M.X.4™) application, (2) after topical anesthetic removal but before patch application, (3) upon patch removal, (4) 1 hour post-patch removal and (5) 3 hours post-patch removal. Plasma samples from this study were analyzed by (b) (4). Overall, less than 50% of the subject-treatments had detectable capsaicin levels at any time-point. Forty-eight percent of the PHN subjects had detectable levels of capsaicin in the double-blind phase and 47% of subject-treatments had detectable levels during the three open-label treatment phases cumulatively. Capsaicin: Capsaicin levels were below LLOQ (0.5 ng/mL) at all time-points during the 3rd retreatment period. On the double-blind Treatment Day (Day 0), for those in the 90-minute group with quantifiable levels, capsaicin values ranged from **0.57 to 17.8 ng/mL** (17.8 ng/mL in Subject# 022-03 at 1-hour post-patch removal). Quantifiable levels following 60-minute Qutenza applications ranged from **0.52 to 4.26 ng/mL**. No capsaicin metabolites were detected in any of the samples at any time-point in either treatment phase. Lidocaine: On the double-blind Treatment Day (Day 0), lidocaine levels were assessed in plasma samples of 39 patients in this study. Treated areas ranged from 32 to 948 cm². Lidocaine levels were detectable following topical lidocaine application in plasma samples ranged from 0.57 to 494 ng/mL (topical anesthetic L.M.X.4™), with the majority of the lidocaine levels measured below 50 ng/mL. The maximum lidocaine level detected (Subject 2305; 494 ng/mL) was measured at the time of patch removal. This subject received a double-blind 90-minute Qutenza treatment over an area of 948 cm². Two subjects (Subject 204 and 2502) in the Qutenza group had plasma lidocaine levels ≥ 1000 ng/mL prior to L.M.X.4™ application. The Applicant stated that these were probably due to sample contamination: Subject 204 had plasma lidocaine levels of 60.4, 49.3, 64.0, and 81.5 ng/mL at after L.M.X.4™ removal / before patch application, at patch removal, and at 1 and 3 hours after patch removal, respectively; and Subject 2502 had plasma lidocaine levels of 75.9, 106, 80.4, and 91.1 ng/mL at after L.M.X.4™ removal / before patch application, at patch removal, and at 1 and 3 hours after patch removal, respectively. During the open-label re-treatment phase, plasma levels of lidocaine were quantifiable in the plasma of all 11 subjects analyzed. The maximum plasma lidocaine concentrations during the open-label re-treatment phase ranged from 10.7 to 282 ng/mL measured at after L.M.X.4™ removal / before patch application through 3 hours after patch removal. Treatment areas ranged from 27 to 1000 cm².

Study C111 was a randomized, open-label, multi-center study to assess the tolerability of Qutenza applied for 60 or 90 minutes when used in conjunction with pre-patch topical application utilizing one of three different topical lidocaine-based (4%) local anesthetics (L.M.X.4™, Topicaine® and Betacaine®) in subjects with PDN, HIV-AN or PHN. Subjects were randomly assigned to receive 60 or 90 minute treatments with Qutenza patches, and allocated to one of three topical local anesthetic groups. At selected study sites, blood samples were collected (5 mL in K₃EDTA-coated tubes) from PHN or PDN patients at the following timepoints: (1) after topical anesthetic removal and before patch application, (2) immediately after patch removal, (3) 1 hour post-patch removal, (4) 3 hours post-patch removal, (5) 6 hours post-patch removal, and (6) 24 hours post-patch removal. Quantifiable plasma levels of capsaicin were observed in a total of three

subjects (3 of 39, 8%), ranging from **0.52 to 1.9 ng/mL**; all other subjects evaluated were below the LLOQ (0.5 ng/mL) at all time-points. Plasma levels were detected in 1 (Subject# 038-12) out of 3 PHN subjects receiving a 90-minute Qutenza application and in 1 (Subject# 080-03) of 3 PHN subjects receiving a 60-minute application. Among PDN subjects, none of the 22 subjects treated for 90 minutes had a plasma level of capsaicin greater than the LLOQ, one subject (Subject# 080-06) of 11 receiving a 60-minute application had a quantifiable plasma capsaicin level. No subjects had a quantifiable plasma capsaicin metabolite level detected at any time-point.

Study C107 was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of HIV-AN. Patients were randomized to receive Qutenza or low-concentration control patches (3.2 µg capsaicin per cm²) for 30, 60 or 90 minutes. During the initial 12-week double-blind phase, blood samples were collected (5 mL in K₃EDTA-coated tubes) from subjects assigned to the 90-minute treatment group at selected study sites. A preliminary assessment of plasma lidocaine levels was also performed. Plasma samples were also collected in the same cohort of subjects if they elected to receive one or more 60-minute Qutenza treatments during a 40 week open-label extension period. Sample collection timepoints were as follows: (1) immediately before topical lidocaine-based (4%) local anesthetic (L.M.X.4™) application, (2) after topical anesthetic removal/before patch application, (3) upon patch removal, (4) 1 hour post-patch removal and (5) 3 hours post-patch removal. Capsaicin: In the initial double-blind phase (90-minute treatment), plasma levels of capsaicin were quantifiable in three of 37 subjects (8%), with values ranging from **0.57 to 1.75 ng/mL** which were only detected at patch removal or 1 hour after removal. All other subjects, including the subjects receiving the low-concentration control treatment, were below the LLOQ (0.5 ng/mL). In the open-label re-treatment phases (60-minute treatment), no quantifiable levels of capsaicin were detected in any sample. No metabolites were detected in any of the samples at any timepoint in either phase of the study. Lidocaine: Lidocaine levels were assessed in plasma samples of 27 patients in this study. Treated areas ranged from 252 to 1120 cm². Lidocaine levels were detectable following topical lidocaine application in plasma samples of 19 of 27 patients sampled and the majority of lidocaine levels were below 50 ng/mL. The maximum lidocaine level detected in any subject was 93.5 ng/mL (Subject 4607); this sample was collected immediately following lidocaine removal. This subject received a double-blind 90-minute Qutenza treatment over an area of approximately 930 cm².

Study C116 was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of PHN when applied for 60 minutes. Patients were randomized to receive either Qutenza (640 µg capsaicin cm²) or low-concentration control patches (3.2 µg capsaicin cm²) for 60 minutes. Efficacy was assessed over a period of 12 weeks. At selected sites, blood samples (5 mL in K₃EDTA-coated glass tubes) were collected as follows: (1) after anesthetic removal and before patch application, (2) immediately after patch removal, (3) 1 hour post-patch removal, (4) 3 hours post-patch removal, (5) 6 hours post-patch removal and (6) 24 hours post-patch removal. Plasma samples were analyzed by (b) (4) using HPLC with MS/MS detection. Quantifiable plasma capsaicin levels (LLOQ = 0.5 ng/mL) were detected in 10 of the 49 subjects (20%) who received the 60-minute Qutenza treatment. The highest

concentration of capsaicin detected in any subject plasma sample was **4.64 ng/mL** (Subject# 130-0096). This concentration was observed immediately after patch removal. The capsaicin level in the same subject declined to **2.39 ng/mL** at the one-hour post-patch removal timepoint and was below the LLOQ 3 and 24 hours post-patch removal. No capsaicin metabolites at or above the LLOQ were detected in any of the study samples at any time-point.

Capsaicin absorption, distribution, metabolism, and elimination information

Skin permeation:

The in vitro skin permeation study demonstrated that only a small percentage, approximately 0.9%, of the total capsaicin in the Qutenza is transferred from the patch into the skin during 60-minute applications.

Protein binding:

Trans-[14C]Capsaicin was 92.8 to 94.3% bound to human plasma proteins over the concentration range of 50 to 500 ng/mL at 37°C for 4 hours. The binding was independent of the concentration.

Metabolism:

The majority of capsaicin in the skin was not metabolized; however, there were two metabolites identified in the skin, vanillylamine and vanillic acid. Capsaicin is a substrate of CYP 2C9 (capsaicin to 16-hydroxy-capsaicin and 16, 17-dehydro-capsaicin) and 2C19 (may be involved in the formation of capsaicin to 16-hydroxy-capsaicin). Three notable metabolites of capsaicin were 16-hydroxy-capsaicin, 16,17-dehydro-capsaicin and 17-hydroxy-capsaicin. As well, vanillin, vanillylamine and vanillic acid were observed.

Excretion:

There is no human excretion information available for capsaicin. However it is speculated that capsaicin and its metabolites will be excreted via the liver and kidneys, although the amount absorbed into the systemic circulation is minimal. In rat, of the absorbed radioactivity from the 14C-radiolabeled Qutenza, > 3.36% of the dose was excreted in urine and > 2.42% in feces. In minipigs, two weeks after patch application, the absorbed radioactivity recovered in urine was 2.80% and 0.49% in feces.

Induction/Inhibition

The results from in vitro experiments indicate that *trans*-capsaicin does not have inhibition capability, as well as induction.

Special populations

Pediatrics:

The safety and efficacy of Qutenza in children and adolescents younger than 16 years of age has not been studied. The Applicant submitted a Request for Waiver of Pediatric Studies for the entire pediatric population including patients' age birth to 16 years. The reason for waiving pediatric assessment requirements is that the incidence of PHN in this age group is extremely low and, is therefore not likely to be used in this group. At the End-of-Phase 2 meeting for Qutenza, the Agency agreed that deferral of pediatric studies was appropriate.

Impairments/Elderly:

No studies in patients with renal impairment, hepatic impairment, or elderly subject were conducted with Qutenza. Qutenza is used as a single dose. For the possible re-administration, the patients may be re-dosed with Qutenza every three months or as warranted by the return of pain. Since Qutenza is used as a single dose application, a dosage adjustment in patients with renal or hepatic impairments and in elderly may not be necessary.

Population PK analysis

The impact of demographic covariates, e.g., body weight (BW), age, gender and race, on PK parameter estimates of capsaicin was assessed by the Applicant using the population pharmacokinetic modeling. Covariates such as treated surface area (cm²), dose levels of capsaicin (mg) and application times (60 or 90 minutes) were also evaluated. Data in PHN patients from the following studies were used for the population PK analysis of capsaicin: Studies C108, C111 and C116. Overall, a total of 96 PHN patients receiving Qutenza for 60 or 90 minutes in the above three studies had plasma samples drawn for the determination of capsaicin levels and its metabolites. Of these, 31% (30 patients, 19 males and 11 females) displayed quantifiable levels of capsaicin at one or more time points. No metabolites were detected. The following demographic variables were observed in these patients.

Considering the relatively small number of patients with limited capsaicin observed systemic levels making the utility of these findings questionable.

Drug-Drug interactions

No formal drug interaction studies have been performed. The in vitro data indicated that capsaicin does not inhibit or induce enzymes. Additionally, there is minimal to no capsaicin skin metabolism. Finally, low levels of systemic capsaicin concentrations were observed. Therefore, drug-drug interaction is not expected with capsaicin.

With the exception of the use of topical anesthetic products, e.g., lidocaine, the use of other topical analgesic products was prohibited in the clinical studies. Therefore, it is recommended and should be reflected in the Product Insert that patients do not apply

topical analgesic products immediately prior to treatment, such as NSAIDs, methyl salicylate, corticosteroids, or other capsaicin-containing products to the treatment areas.

Labeling proposal

It is recommended that information from the population PK report be removed in the package insert.

<p>12.3 Pharmacokinetics</p> <p>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 Qutenza. The highest plasma concentration of capsaicin detected was 4.64 ng/mL and occurred immediately after Qutenza removal. Most quantifiable levels were observed at the time of Qutenza removal and were below the limit of quantitation 3 to 6 hours after Qutenza removal. No detectable levels of metabolites were observed in any subject.</p>	<p>Study C108</p>
 <p>(b) (4)</p>	

In all, the information submitted in this Application is acceptable, provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What is Qutenza™?

Qutenza™, capsaicin patch 8%, is a topical patch indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN). The proposed patch area

is 280 cm² (20 cm x 14 cm; it contains 179 mg of capsaicin equaling 640 µg of capsaicin per square centimeter of adhesive (8% w/w)). Qutenza will be co-packaged with Cleansing Gel, which is used to remove the local anesthetic applied prior to Qutenza patch and the residual capsaicin on the skin after the Qutenza patch is removed.

Qutenza can be used up to 4 patches applied to cover the treatment area in a single application session. Patches can be cut to fit the treatment area. In clinical trials, treatment times varied between 30 and 90 minutes but the recommended treatment time is 60 minutes. The treatments may be repeated every three months or as warranted by the return of pain. During clinical trials, the application area was pretreated with a topical anesthetic. Qutenza will be applied to a patient in a treatment facility by a physician.

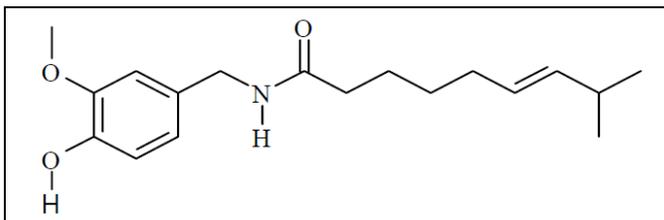
2.1.2 What is postherpetic neuralgia (PHN)?

Neuropathic pain is defined as pain that is “initiated or caused by a primary lesion or dysfunction in the nervous system.” Neuropathic pain can originate in the peripheral nervous system or the central nervous system (CNS), although both systems are commonly involved in most conditions. Almost 4 million people in the U.S. are afflicted with neuropathic pain syndromes. Peripheral neuropathy generally refers to conditions in which there is a predominant abnormality or disease of the sensory afferent fibers. Clinical features of peripheral neuropathy may include disabling symptoms of burning, stinging, shooting pain or electrical sensations, paresthesias, and sensitivity to light touch or noxious stimuli (i.e., allodynia and hyperalgesia, respectively). These clinical features are most often associated with an underlying disease state such as diabetes mellitus, a history of herpes zoster outbreak, malnutrition, or human immunodeficiency virus (HIV) infection and therapy.

Postherpetic neuralgia (PHN) is a painful disorder that stems from an acute herpes zoster, which the pain persists during (initiation and crusting of the skin lesions) or recurring (the pain in the affected area persists months after crusting of the skin lesions) with healing of acute herpes zoster. Herpes zoster or shingles is caused by reactivation of the varicella zoster virus usually contracted in childhood (chickenpox). Acute herpes zoster is a localized infection that begins in the dorsal root ganglia of the cranial or spinal nerves and spreads as a rash over the corresponding dermatome. The duration of PHN is defined as from beginning as short as 1 month to as long as 6 months after lesion crusting.

2.1.3 What is the formulation of the drug product?

The capsaicin is completely dissolved in the adhesive matrix, which contains diethylene glycol monoethyl ether (DGME), ethylcellulose, dimethicone, and (b) (4) (b) (4) silicone adhesives (b) (4). DGME is present as a drug (b) (4) at a target concentration of (b) (4) in the adhesive. Ethylcellulose is added to (b) (4) the DGME. The adhesive layer, (b) (4)



Capsaicin's empirical formula is C₁₈H₂₇NO₃, with a molecular weight of 305.42. The chemical name is (E)-8-methyl-N-vanillyl-6-nonenamide.

Several prototype patches with various capsaicin concentrations (i.e., 4%, 6%, 6.4%, and 8% w/w) were tested (drug permeation rates over 8 hours) using the Franz diffusion cell method. From this analysis, the capsaicin patch prototype containing 8% capsaicin was chosen as the basis for clinical development.

Qutenza™ 8% Formulations used in clinical trials

Ingredient	Weight %			
	Experimental Formulation 1 (CAP 21)	Clinical Formulation 1	Experimental Formulation 2 (CAP 61)	Clinical Formulation 2 (CAP 72)
Capsaicin	8.0	8.0	8.0	8.0
DGME	(b) (4)			
Ethylcellulose (b) (4)				
(b) (4)				
Dimethicone				
(b) (4)				

Original formulation or Clinical Formulation 1 was used in Studies C101, C102, C106, and C109. Over time, Clinical Formulation 1 exhibited a slight tendency for “cold flow”, which refers to the tendency of the matrix material to slowly spread out during storage. The “cold flow” does not generally affect the drug delivery characteristics of patches, but can cause them to stick to the pouch or other packaging materials. To resolve this problem, several modified formulations were tested, and, based on stability studies and comparable performance in *in vitro* release tests, a modified formulation (CAP 61) was selected to replace the original formulation. Both Clinical Formulation 1 and CAP 61 were tested by the disk-over-paddle method for drug release profiles and by the Franz diffusion cell method for permeation properties, using both heat-separated human epidermis and an EVA membrane (an ethylene-vinyl acetate co-polymer membrane commonly used as a skin substitute for quick screening of transdermal products in the Franz diffusion cell model). It is noted that *in vitro* studies demonstrated comparable performance of the original formulation and CAP 61. Subsequently, CAP 61 formulation was slightly modified further in order to facilitate the precision of the weighing and

measurement steps used during the manufacturing process and this formulation was designated as CAP 72, which is the final formulation.

With respect to clinical pharmacology, the majority of the capsaicin exposure information reviewed for the clinical pharmacology information used the final formulation, CAP 72, except, one P2 Study, 102, which utilized the original formulation.

Formulation	Studies
Original formulation or Clinical Formulation 1	Phase I healthy - C101, Phase II/III PHN - <u>C102</u> , C106 Phase II/III HIV-AN [#] - C109
CAP 72	Phase I healthy - C115 Phase II/III PHN - <u>C108</u> , C110, <u>C111</u> , <u>C116*</u> , C117*, C118 Phase II/III HIV-AN [#] - <u>C107</u> , C109, C111, C112, C118, and C119

*: Pivotal P3 PHN studies.

_ : Clinical Pharmacology capsaicin exposure information

#: Studies conducted in HIV-associated neuropathy, (b) (4)

2.1.4 What is the proposed mechanism of action?

Capsaicin 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 on those nociceptors that primarily deal in the detection of painful or noxious sensations. TRPV1 is expressed selectively on C-fibers, and, to a lesser extent, on A δ -fibers. Following exposure to capsaicin, it is thought that cutaneous nociceptors become less sensitive to a variety of stimuli. There are 2 isomers of capsaicin. Only *trans*-capsaicin occurs naturally and is the most abundant pungent molecule contained in chili peppers. The rationale for the development of Qutenza for the management of chronic pain syndromes comes from the fact that after a prolonged exposure to capsaicin, reduced spontaneous and evoked painful sensations occur, referred to as “desensitization” or “defunctionalization” of the sensory neurons.

2.1.5 What are the proposed dosage and route of administration?

QutenzaTM, capsaicin patch 8%, is a topical patch. The proposed patch area is 280 cm² (20 cm x 14 cm; it contains 179 mg of capsaicin equaling 640 μ g of capsaicin per square centimeter of adhesive (8% w/w)). Qutenza will be co-packaged with Cleansing Gel, which is used to remove the *local anesthetic applied prior to Qutenza patch and the residual capsaicin on the skin after the Qutenza patch is removed.*

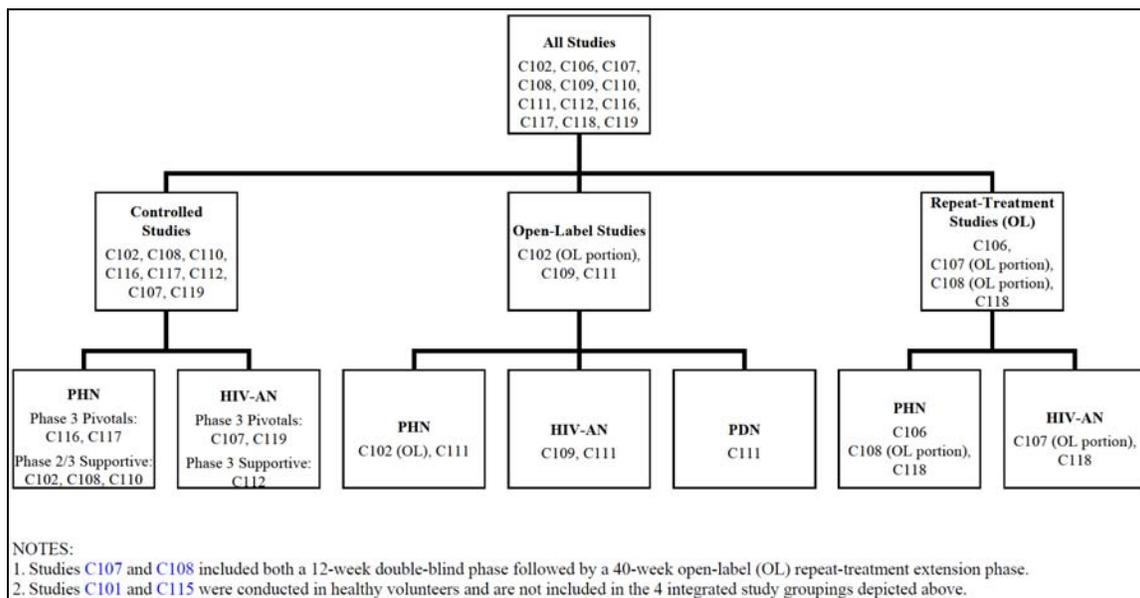
Qutenza can be used up to 4 patches applied to cover the treatment area in a single application session. Patches can be cut to fit the treatment area. In clinical trials, treatment times varied between 30 and 90 minutes but the recommended treatment time is 60 minutes. The patients may be repeated with Qutenza every three months or as

warranted by the return of pain. During clinical trials, the application area was pretreated with a topical anesthetic.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

Qutenza clinical development program (see figure below) consisted of 14 clinical studies comprising 2 Phase 1 studies in healthy volunteers (Studies C101 and C115) and 12 Phase 2 or Phase 3 studies in PHN subjects (Studies C102, C106, C108, C110, C111, C116, C117, C118), HIV-Associated Neuropathy subjects (HIV-AN), Studies C107, C109, C111, C112, C118, C119, and Painful Diabetic Neuropathy (PDN) subjects, Study C111. Two studies (Studies C111 and C118) were conducted in a mixed patient population (PHN, HIV-AN, or PDN). As stated previously, this Application is being submitted to support the use of Qutenza in the prolonged reduction of neuropathic pain associated with PHN.



Typical primary efficacy variable for the studies in the Qutenza clinical program was the change in Numeric Pain Rating Scale (NPRS) scores from Baseline. The NPRS is a uni-dimensional, 11-point scale (0 to 10), with 0 indicating no pain and 10 indicating the worst possible pain. Subjects used this scale to rate “pain now”, “worst pain”, and/or “average pain for the past 24 hours” for their painful area(s). For pivotal studies (the 12-week controlled studies) the primary efficacy variable was the mean percent change in “average pain for the past 24 hours” NPRS score from Baseline during Weeks 2 to 8. Week 1 NPRS scores were not analyzed for the primary endpoint to avoid the potential for bias due to the 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 Qutenza and Control groups over the primary analysis period (i.e., during Weeks 2 to 8). Mean

percent change from Baseline in NPRS scores was also evaluated during Weeks 2 to 12 as a secondary endpoint.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

There is no exposure-response relationship for Qutenza. The clinical endpoints used for Qutenza did not stem from clinical pharmacology characteristics. Therefore there was no relationship between clinical pharmacology measurement and the clinical endpoints.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The patch is applied at the local site(s) associated with PHN, for local pain reduction. With respect to clinical pharmacology the capsaicin systemic exposure was assessed from the systemic safety purpose. Capsaicin (and its metabolites) in the plasma was appropriately identified for this purpose. See Analytical Section for the assay methodology.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

There is no exposure-response relationship for Qutenza. However, there are several clinical trials, include two pivotal Phase 3 clinical trials, which assessed the efficacy of Qutenza (i.e., duration of patch application; 30, 60 or 90 minutes).

Study C108 was a Phase 2/3, a 12 week, randomized, double-blind, controlled (low concentration 3.2 $\mu\text{g}/\text{cm}^2$), multicenter evaluation of the efficacy, safety, and tolerability of Qutenza (high-concentration capsaicin, 640 mcg/cm^2), with an open-label extension phase, and assessed durations of 30, 60 and 90 minutes; the primary efficacy variable was the percent change in “average pain for the past 24 hours” NPRS scores from Baseline to Weeks 2–8. Week 1 NPRS scores were not analyzed in the primary endpoint to avoid the potential for bias from allowed rescue medication use; subgroup analysis was conducted for age and gender differences. A cursory review of the Study C108 results indicated that the patch application duration was associated with similar reductions in NPRS scores from Baseline (–26.2% for the 30-minute group, –25.6% for the 60-minute group, and –27.8% for the 90-minute group). The differences between 30- and 60-minute treatment with Qutenza and control did not reach statistical significance. When a post-hoc, analysis including a gender-stratified ANCOVA model was applied to the data (it was noted that the 60-minute duration group had a larger percentage of males (61%) compared with the other groups (43% to 50%), and male subjects were found to report smaller changes in

pain scores than female subjects in both the Qutenza and control groups), the LS mean percent reduction in pain was similar in the 60- and 90-minute groups (60-minute: -28.0%, 90-minute: -27.7%) and the difference between the Qutenza 60-minute group and the pooled Control group was significant ($p = 0.0331$). The 60-minute dose had a small, numerical advantage compared to the 30-minute Qutenza dose after the study results were adjusted for baseline gender imbalances (30-minute -25.6%, 60-minute -28.0%). The conclusion was that although Qutenza failed to meet the primary efficacy endpoints according to pre-defined statistical analyses, taking into consideration the effects of gender imbalance on the 60 minute Qutenza group, 60 minute treatment was slightly better than 30 minute, and both 60 and 90 minute treatments were better than controlled group.

Study C111 was an open-label mixed population study (i.e., subjects with PHN, HIV-AN, or PDN) conducted to assess the tolerability of Qutenza in conjunction with pre-patch topical application of 1 of 3 lidocaine-based local anesthetic products (non-U.S. approved local anesthetics: L.M.X.4® and Topicaine® or Betacaine® groups), assessed durations of 60 and 90 minutes. The primary efficacy variable included the percent change in mean NPRS scores for “average pain for the past 24 hours” from Baseline to Weeks 2–12. As secondary endpoints of this study, proportion of subjects achieving at least a 30% decrease in “average pain for the past 24 hours” NPRS scores from Baseline to Weeks 2–12 was also included in the analysis. The brief review of the results indicated that there were 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 following pre-patch topical application of 1 of 3 lidocaine-based local anesthetic products. A summary of average pain scores (NPRS) for “average pain for the past 24 hours” at Baseline and Weeks 2–12 is presented in below table. All groups had similar pain scores for “average pain for the past 24 hours” at Baseline ranging from 5.2 to 6.0. At Weeks 2–12, the mean decrease from Baseline across all anesthetic groups was approximately 30%. Within local anesthetic groups, responses ranged from 18.2% to 50.4% decrease from Baseline at Weeks 2–12. The difference in percent change of mean NPRS scores for “average pain for the past 24 hours” from Baseline between L.M.X.4® and Topicaine® or Betacaine® groups were not statistically significant.

NPRS Score	L.M.X.4 [®]			Topicaine [®] Gel			Betacaine [®] Enhanced Gel 4		
	90 Min. (n = 20)	60 Min. (n = 19)	Total (n = 39)	90 Min. (n = 19)	60 Min. (n = 19)	Total (n = 38)	90 Min. (n = 20)	60 Min. (n = 20)	Total (n = 40)
Baseline									
LS Mean ± SE	5.3 ± 0.32	5.9 ± 0.33	5.6 ± 0.23	5.8 ± 0.33	6.0 ± 0.33	5.9 ± 0.23	5.2 ± 0.32	5.6 ± 0.32	5.4 ± 0.23
Weeks 2–12									
Actual (LS Mean ± SE)	3.6 ± 0.45	4.2 ± 0.46	3.9 ± 0.32	4.9 ± 0.46	2.8 ± 0.46	3.8 ± 0.33	3.8 ± 0.45	4.1 ± 0.45	4.0 ± 0.32
Change from Baseline (LS Mean ± SE)	-2.0 ± 0.45	-1.4 ± 0.46	-1.7 ± 0.32	-0.7 ± 0.46	-2.8 ± 0.46	-1.8 ± 0.33	-1.8 ± 0.45	-1.5 ± 0.45	-1.6 ± 0.32
Percent Change from Baseline (LS Mean ± SE)	-34.9 ± 7.87	-28.6 ± 8.07	-31.8 ± 5.61	-18.2 ± 8.04	-50.4 ± 8.09	-34.3 ± 5.72	-31.3 ± 7.89	-23.2 ± 7.83	-27.2 ± 5.56
P-value ^a						0.757			0.563
Subjects with ≥ 30% Decrease from Baseline to Weeks 2–12									
Yes (n, %)	10 (50%)	8 (42%)	18 (46%)	5 (26%)	14 (74%)	19 (50%)	12 (60%)	6 (30%)	18 (45%)
P-value ^b						0.588			0.864
Subjects with ≥ 50% Decrease from Baseline to Weeks 2–12									
Yes (n, %)	8 (40%)	5 (26%)	13 (33%)	3 (16%)	11 (58%)	14 (37%)	5 (25%)	6 (30%)	11 (28%)
P-value ^b						0.610			0.608

LS Mean = Least Squares Mean; SE = Standard Error

Note: Baseline pain level was defined as the mean of all available non-biased Screening NPRS scores in that category (see Section 9.7.1.2). Missing scores during Days 8–84 were estimated using the previous non-missing score.

^a P-value was computed using ANCOVA to test for difference between pooled L.M.X.4[®] group and the other 2 local anesthetic groups.

^b P-value was computed using logistic regression to test for difference between pooled L.M.X.4[®] group and the other 2 local anesthetic groups.

Source: Table 14.2.1

Phase 3 pivotal trials

Studies 116 and 117 were the 2 pivotal, Phase 3 randomized, double-blind, controlled, multi-center evaluations of the efficacy, safety, and tolerability of Qutenza in PHN patients. Subjects in both studies were randomized in a 1:1 ratio to receive Qutenza or control treatment for 60 minutes. The control group did not receive placebo, rather, the control group had a ‘low’ level capsaicin patch, capsaicin 3.2 µg/cm². This was allowed to mask the pain due to the capsaicin when the patch is applied to the patients. The required minimum duration of PHN for patients enrolled in most studies was 6 months post-vesicle crusting. The primary efficacy endpoint for pivotal studies (the 12-week controlled studies) was the mean percent change in “average pain for the past 24 hours” NPRS score from Baseline during Weeks 2 to 8. Week 1 NPRS scores were not analyzed for the primary endpoint to avoid the potential for bias due to the 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 Qutenza and Control groups over the primary analysis period (i.e., during Weeks 2 to 8). Mean percent change from Baseline in NPRS scores was also evaluated during Weeks 2 to 12 as a secondary endpoint.

The following table contains the efficacy results from the 2 Phase 3 pivotal studies.

Summary of Mean Change and Mean Percent Change in NPRS Scores from Baseline in Individual Studies, Weeks 2 to 8 (ITT Population)

Study	Treatment	N	Weeks 2 to 8		
			Mean Change	Mean % Change ^{a,b}	
<i>Phase 3 Pivotal Controlled Studies</i>					
C117	60 minutes	NGX-4010	212	-1.7	-32.0
		Control	204	-1.3	-24.4
		<i>p-value</i> ^c		0.0344	0.0108
C116	60 minutes	NGX-4010	206	-1.7	-29.6
		Control	196	-1.2	-19.9
		<i>p-value</i> ^c		0.0024	0.001

Additional analyses were performed using a gender-stratified ANCOVA model with Baseline pain score as the only covariate. An analysis of the integrated data using the same model was also performed. Results from these analyses using last observation carried forward (LOCF) imputation are presented below looking at weeks 2 to 8 and weeks 2 to 12.

Summary of Mean Change and Mean Percent Change in NPRS Scores from Baseline (LOCF), Weeks 2 to 8 and Weeks 2 to 12

Study	Treatment	N	Weeks 2 to 8		Weeks 2 to 12	
			Mean Change	Mean % Change	Mean Change	Mean % Change
<i>Phase 3 Pivotal Controlled Studies</i>						
C117	NGX-4010	212	-1.7	-32.0	-1.7	-32.3
	Control	204	-1.3	-24.4	-1.4	-25.0
	<i>p-value</i>		0.0344	0.0108	0.0581	0.0172
C116	NGX-4010	206	-1.7	-29.7	-1.7	-29.9
	Control	196	-1.2	-19.9	-1.2	-20.4
	<i>p-value</i>		0.0021	0.0009	0.0028	0.0015

Responders, defined as subjects who achieved a mean percent decrease in NPRS score from Baseline of $\geq 30\%$, were evaluated. Additionally, subjects with a mean decrease in NPRS scores from Baseline of ≥ 2 units were assessed. Results of responder analyses during Weeks 2 to 8 and Weeks 2 to 12 using a logistic regression analysis with Baseline pain score and gender as covariates are presented below.

Summary of Percent Responders from Baseline (LOCF), Weeks 2 to 8 and Weeks 2 to 12

Study	Treatment	N	Weeks 2 to 8		Weeks 2 to 12	
			$\geq 30\%$ Response	≥ 2 Unit Decrease	$\geq 30\%$ Response	≥ 2 Unit Decrease
<i>Phase 3 Pivotal Controlled Studies</i>						
C117	NGX-4010, n (%)	212	97 (45.8)	88 (41.5)	100 (47.2)	92 (43.4)
	Control, n (%)	204	69 (33.8)	54 (26.5)	72 (35.3)	59 (28.9)
	<i>p-value</i>		0.0196	0.0017	0.0212	0.0029
C116	NGX-4010, n (%)	206	86 (41.7)	83 (40.3)	90 (43.7)	86 (41.7)
	Control, n (%)	196	63 (32.1)	51 (26.0)	68 (34.7)	55 (28.1)
	<i>p-value</i>		0.0343	0.0025	0.0487	0.0038

Subgroup efficacy analysis in of 12-week controlled studies

Subgroup analyses were conducted to determine the potential impact of gender, age, Baseline pain score, duration of PHN, concomitant neuropathic pain medication use, and rescue medication use on the efficacy profile of Qutenza for Studies (C108, C110, C116, and C117). Race and ethnicity were not included in the assessment of subgroups because the overall study populations were predominantly Caucasian and non-Hispanic.

Overall, improvements in NPRS scores, as assessed by mean percent change data and the achievement of either a $\geq 30\%$ response or a ≥ 2 unit decrease in NPRS score from Baseline during Weeks 2 to 8 or Weeks 2 to 12 in Qutenza patients compared with Control subjects, were similar regardless of gender, age, or PHN duration. However, it was noted that females and younger subjects reported larger percent reductions in pain scores compared with males and older subjects, respectively (see below).

Summary of Mean Percent Changes in NPRS Scores from Baseline During Weeks 2 to 8 (Integrated Data; LOCF)

	Males	Females	Age \geq median ^a	Age $<$ median ^a	Con Pain Med Use	No Con Pain Med Use
NGX-4010 ^b						
n	286	311	305	292	302	295
LS Mean % Change	-26.7	-35.3	-25.7	-37.0	-26.1	-36.5
Control ^b						
n	251	279	277	253	250	280
LS Mean % Change	-17.2	-27.0	-17.2	-27.9	-18.1	-26.2
Treatment difference						
LS Mean % Change	-9.5	-8.4	-8.5	-9.1	-8.0	-10.3

LOCF: Last observation carried forward; LS: Least Squares.

Note: Baseline pain level was defined as the mean of all available Screening NPRS scores from Day -14 to Day -1 for C117 and C116. Baseline pain level is defined as the mean of all available non-biased Screening NPRS scores in that category for C110 and C108. If NPRS scores were missing on any of Days 0 to 8, or on Day 8 and any consecutive days, or if all post-treatment NPRS scores are missing, then Baseline score was used for imputation. If NPRS Score was missing after Day 8, the previous non-missing score was used for imputation.

a. The median age for all studies combined (C117, C116, C110, and C108) was 73 years; this median age was used for the integrated data.

b. The Qutenza group contains all subjects in Studies C117, C116, and C110, but only those subjects from Study C108 that were treated for 60 minutes during the double-blind phase. The Control group contains all subjects treated with control in all 4 studies.

The potential impact of rescue medication use was also assessed by evaluating mean percent change in NPRS score from Baseline during Weeks 2 to 8 and Weeks 2 to 12 in subjects who did and did not use rescue medication. Rescue medication use did not appear to affect the efficacy of Qutenza. Mean percent change in NPRS score from Baseline during Weeks 2 to 8 and Weeks 2 to 12 was similar in subjects who did and did not use rescue medication in both the Qutenza and Control groups. The results of this analysis support a lack of an interaction between rescue medication and efficacy of Qutenza treatment, and also support a lack of any potential long-term opioid effect.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

There is no exposure-response relationship for Qutenza. The following table lists the treatment-emergent adverse reaction incidences from two Phase 3 clinical trials. The Applicant reported that the majority of application site reactions were transient and self-limited. Pain was commonly observed on the day of patch treatment due to capsaicin and usually resolved after patch removal.

Body system Preferred Term	Qutenza 60 minutes (N = 622) %	Control 60 minutes (N = 495) %	Total Qutenza ¹ (N = 767) %	Total Control ^{1,2} (N = 543) %
General Disorders and Administration Site Conditions				
Application Site Erythema	63	54	51	50
Application Site Pain	42	21	35	19
Application Site Pruritus	6	4	7	5
Application Site Papules	6	3	6	3
Application Site Oedema	4	1	3	1
Application Site Swelling	2	1	2	1
Application Site Dryness	2	1	2	1
Infections and Infestations				
Nasopharyngitis	4	2	4	2
Bronchitis	2	1	2	1
Sinusitis	3	1	2	1
Gastrointestinal Disorders				
Nausea	5	2	5	3
Vomiting	3	1	3	1
Skin and Subcutaneous Tissue Disorder				
Pruritus	2	< 1	2	< 1
Vascular Disorders				
Hypertension	2	1	3	1

¹ Combined 30, 60, and 90-minutes dose groups.

² Control contained a low concentration of the active ingredient, capsaicin (3.2 mcg/cm², 0.04% w/w) to retain blinding.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No clinical trials were conducted to evaluate the prolongation of QT interval. Although capsaicin is a new chemical entity, a thorough QT study is necessary since capsaicin systemic bioavailability after Qutenza patch application is minimal and capsaicin is used as locally acting drug.

2.2.4.4 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

There is no exposure-response relationship for Qutenza, as the systemic capsaicin levels do not reflect the capsaicin levels at the local site of action.

2.2.5 What are the PK characteristics of the drug and its metabolites?

2.2.5.1 Skin absorption/permeation information

The *in vitro* skin permeation study demonstrated that only a small percentage (approximately 0.9%) of the total capsaicin in the Qutenza is transferred from the patch into the skin during 60-minute applications. The extent of *in vitro* capsaicin delivery from Qutenza is approximately linear with the patch application time. The delivered dose of capsaicin will be directly related to the duration of exposure to Qutenza.

2.2.5.2 Distribution

Trans-[14C]Capsaicin was highly bound to human plasma proteins in all four species over the concentration range of 50 to 500 ng/mL at 37°C for 4 hours. Over this range, the mean percentage of *trans*-[14C]capsaicin bound to plasma proteins ranged from 92.8 to 94.3%. The binding was independent of the concentration.

Species	Concentration (ng/mL)	Percentage of Radioactivity						
		Bound			Unbound		Recovered ^a	
		Individual	Mean	SD	Individual	Mean	Individual	Mean
Human	50	94.6	94.3	0.3	5.40	5.75	100	102
		94.2			5.83		102	
		94.0			6.02		103	
	200	94.6	94.3	0.5	5.39	5.66	98.9	99.5
		94.7			5.35		99.3	
		93.8			6.25		100	
	300	92.4	92.8	0.5	7.64	7.23	96.3	98.3
		93.3			6.75		99.7	
		92.7			7.28		98.9	
	500	93.1	93.8	0.7	6.94	6.24	96.2	98.0
		94.4			5.58		99.9	
		93.8			6.22		98.0	

SD Standard deviation.
a Based on the radioactivity recovered in the plasma, buffer, and dialysis membrane at the end of dialysis.

2.2.5.3 Capsaicin metabolism

Summary: Three significant metabolites were identified, 16-hydroxy-capsaicin, 16,17-dehydro-capsaicin and 17-hydroxy-capsaicin. Capsaicin is a substrate of CYP 2C9 and 2C19. The majority of capsaicin in the skin was not metabolized; however, there were two metabolites identified in the skin, vanillylamine and vanillic acid..

Summary table:

	Enzyme Substrate		Capsaicin with specific CYP inhibitor
	Recombinant CYP*	Human liver microsomes [#]	Specific inhibitor ^{\$}
16-hydroxy-capsaicin	2C9, 2C19	2C9, 2C19	2C9
16,17-dehydro-capsaicin	2C9	2C9	2C9
17-hydroxy-capsaicin	3A4 (weak)	2D6 (weak) 2E1 (weak)	2B6 3A4

*[14C] *trans*-Capsaicin concentrations: 2 and 20 μ M; rCYP concentrations: 25 pmol P450 per incubation

[#][14C] *trans*-Capsaicin concentration: 2 μ M

^{\$} [14C] *trans*-capsaicin concentration: 2 μ M

Metabolite identification by in vitro microsomes and S-9 fractions

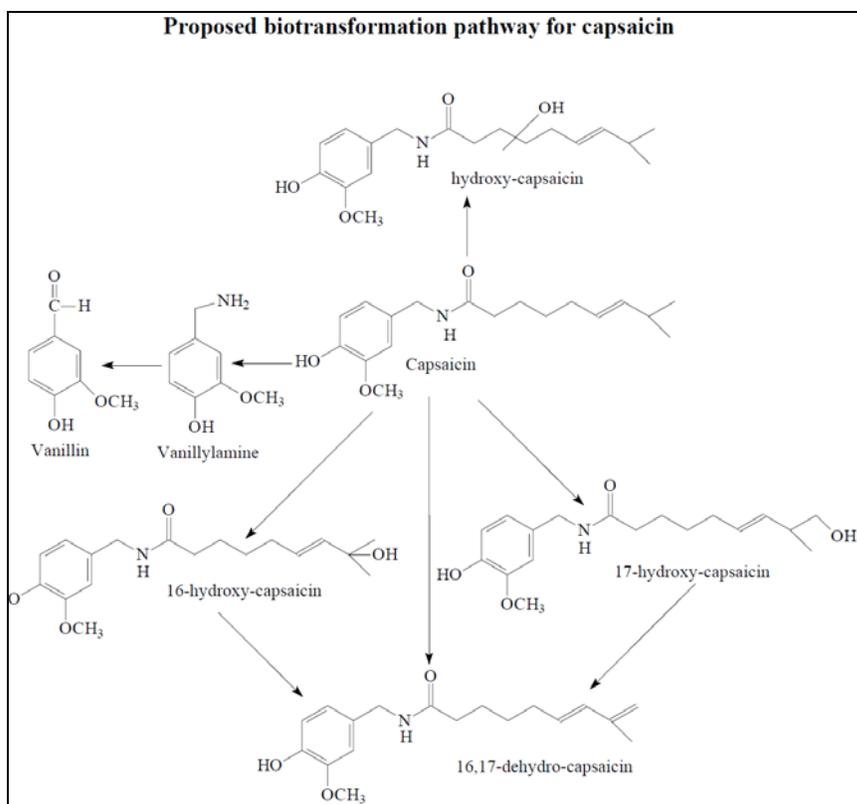
The metabolism of [14C]capsaicin was assessed *in vitro* following incubation with human hepatic microsomes and S-9 fraction. Biotransformation was determined at 1 and 10 μ M [14C]capsaicin with 1 mg microsomal protein/mL for 0, 5, 10, 20, and 30 minutes. Microsomal and S-9 fraction incubations were performed in 0.1 M phosphate buffer (pH 7.4) containing a NADPH-generating system. Incubations were terminated by the addition of acetonitrile and analyzed for capsaicin and metabolites by high-performance liquid chromatography (HPLC) with radiochemical detection. Radioactive peaks in samples were further identified by liquid chromatography/mass spectrometry (LC/MS). [14C]capsaicin was rapidly metabolized by human microsomal and S-9 fractions. As many as five metabolites were also detected. At both the 1 and 10 μ M concentrations, 16-hydroxy-capsaicin and 17-hydroxy-capsaicin were the major metabolites, while vanillin, 16,17-dehydro-capsaicin, and M5 (not identified) were detected as minor metabolites. In human S-9 fraction, metabolism of [14C]capsaicin was slower than in microsomes. The major metabolites were 16-hydroxy-capsaicin, 17-hydroxy-capsaicin, and 16,17-dehydro-capsaicin. Biotransformation in both human microsomes and S-9 fraction was qualitatively similar at both concentrations, although metabolism of [14C]Capsaicin was less extensive in S-9 fraction compared to microsomes. [14C]Capsaicin was not metabolized in the absence of NADPH and Phase II metabolites were not detected in S-9 fraction.

Matrix	Conc.	Timepoint (Minutes)	% of Radioactivity in the Sample					Capsaicin (33.1)
			M5 (20.2-20.4)	Vanillin (20.5-20.7)	M8 (23.9)	M9 (24.6-24.7)	M11 (31.2-31.3)	
Microsomes	1 μ M	0	ND	ND	ND	ND	ND	95.9
		5	ND	ND	16.8	42.8	6.72	26.7
		10	2.15	ND	22.7	52.4	4.84	5.54
		20	4.90	ND	23.5	56.1	ND	ND
		30	1.28	2.27	24.8	63.5	ND	ND
Medium Control		0	ND	ND	ND	ND	ND	94.2
		30	ND	ND	ND	ND	ND	94.3
Negative Control (without NADPH)		0	ND	ND	ND	ND	ND	97.4
		30	ND	ND	ND	ND	ND	96.4
Microsomes	10 μ M	0	ND	ND	ND	ND	ND	93.2
		5	ND	ND	14.2	27.4	7.95	46.9
		10	ND	1.36	19.9	42.6	8.81	21.7
		20	ND	7.90	23.8	54.2	4.33	4.03
		30	ND	10.3	27.0	55.6	ND	ND
Medium Control		0	ND	ND	ND	ND	ND	97.5
		30	ND	ND	ND	ND	ND	99.1
Negative Control (without NADPH)		0	ND	ND	ND	ND	ND	98.5
		30	ND	ND	ND	ND	ND	95.4

Conc. Concentration.
Note: M8 tentatively identified as 16-hydroxy-capsaicin.
M9 tentatively identified as 17-hydroxy-capsaicin.
M11 tentatively identified as 16,17-dehydro-capsaicin.
ND Not detected.

Matrix	Conc.	Timepoint (Minutes)	% of Radioactivity in the Sample					Capsaicin (33.1)
			M2 (18.6-19.0)	Vanillin (20.5-20.7)	M8 (23.9)	M9 (24.6-24.7)	M11 (31.2-31.3)	
S-9	1 μ M	0	ND	ND	ND	ND	ND	96.0
		5	ND	ND	8.34	16.5	9.92	61.7
		10	ND	ND	12.5	29.1	13.0	37.6
		20	ND	1.51	25.9	40.6	11.4	10.5
		30	ND	ND	27.7	49.0	4.47	5.10
Medium Control		0	ND	ND	ND	ND	ND	96.5
		30	ND	ND	ND	ND	ND	96.6
Negative Control (without NADPH)		0		ND	ND	ND	ND	96.8
		30	1.09	ND	ND	ND	ND	94.6
S-9	10 μ M	0	ND	ND	ND	ND	ND	98.5
		5	ND	ND	3.21	6.42	4.04	83.6
		10	ND	ND	6.33	12.0	6.84	71.7
		20	ND	ND	13.2	25.4	12.3	44.5
		30	ND	ND	20.6	31.6	13.8	28.1
Medium Control		0	ND	ND	ND	ND	ND	98.4
		30	ND	ND	ND	ND	ND	99.1
Negative Control (without NADPH)		0	ND	ND	ND	ND	ND	98.8
		30	ND	ND	ND	ND	ND	97.2

Conc. Concentration.
Note: M8 tentatively identified as 16-hydroxy-capsaicin.
M9 tentatively identified as 17-hydroxy-capsaicin.
M11 tentatively identified as 16,17-dehydro-capsaicin.
ND Not detected.



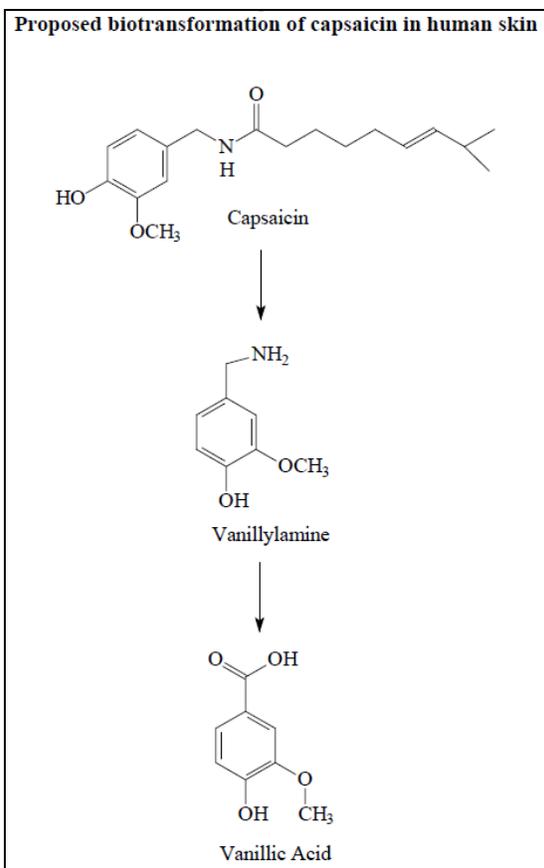
Capsaicin human skin metabolism

Human skin disks were incubated in the presence (capsaicin concentrations were 1, 3, and 10 μM) or absence of [^{14}C]capsaicin for 20 hours. The viability of representative skin disks was evaluated by assessing their mitochondrial function using a tetrazolium dye 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT). The viability controls indicated that the skin used in the incubations was viable; conversion of MTT to MTT formazan was observed with skin disks incubated for 0 and 20 hours.

The results showed that the majority of the sample radioactivity was associated with unchanged capsaicin; however, some of capsaicin was converted to vanillylamine and vanillic acid. Capsaicin was stable in the medium used for the study. In incubation medium and skin, capsaicin, vanillylamine, and vanillic acid ranged from 74.0 to 95.6%, 4.37 to 19.8%, and 0.11 to 7.97%, respectively, of the radioactivity in each sample at all concentrations.

		% Radioactive Dose at 20 hours (Range of Mean Values)	
		Incubation Medium	Skin Samples
Capsaicin (Parent)		91–95.6	74–78.7
Vanillylamine (Metabolite 1)	Conc. tested 1, 3, 10 μM	4.37–8.77	12.9–19.8
Vanillic Acid (Metabolite 2)		0.11–0.15	5.25–7.97

Additional Information: In control incubations (without skin) for 0 or 20 hours with 1, 3, and 10 μM ^{14}C -capsaicin, 99 to 100% of the radioactivity consisted of unchanged capsaicin, indicating stability of the test article in control medium under the incubation conditions.



2.2.5.4 Excretion

There is no human excretion information available for capsaicin. However it is speculated that capsaicin and its metabolites will be excreted via the liver and kidneys. In rat, administered with labeled capsaicin, most of the radioactivity remained in the dermal patch, dermal wrap, and skin wipe after 3 hours of application (accounted for 80.8 and 90.9% of the dose for males and females, respectively) indicating that a limited amount of radioactivity was absorbed. Of the absorbed radioactivity, in males, mean of 3.36% of the dose was excreted in urine, 2.42% in feces, and 1.05% retained in skin (test site) and carcass (residual). In females absorbed radioactivity resulted in a mean of 2.24% of the dose being excreted in urine, 1.35% in feces, and 0.27% retained in skin (test site) and carcass (residual). The radioactivity was excreted through 336 hours postdose. A total mean mass balance for males and females was 88.2 and 95.1%, respectively. In urine samples, two metabolites and low levels of unchanged capsaicin were observed. Vanillic acid-sulfate (M2A) was the major metabolite in male urine and accounted for 1.26% of the dose, while in female the metabolite accounted for 0.67% of the dose. Vanillylamine was the major metabolite in female urine, and accounted for 1.09% of the dose, while in male the metabolite accounted for 1.07% of the dose. Unchanged parent drug in urine through 96 hours postdose in male and female rats accounted for 0.04 and 0.03% of the dose, respectively. In feces samples, six metabolites and unchanged capsaicin were observed through 96 hours postdose. O-demethyl-capsaicin (M6A) was the major

metabolite in male and female feces and accounted for 0.88 and 0.45% of the dose, respectively. Unchanged parent drug in male and female feces through 96 hours postdose accounted for 0.09 and 0.05% of the dose, respectively. Vanillylamine, vanillic acid, and vanillin were also detected in male and female feces; none of the metabolites were >0.1% of the dose at any single time point profiled. The unidentified metabolites, M4 and M5, were each <0.1% of the dose through 96 hours postdose.

In minipigs, two weeks after patch application, a total of 4.2% of the dose was recovered, which radioactivity recovered in urine was 2.80%, 0.49% in feces, and 0.94% in samples of pan/screen rinse, cage wipe, and cage wash. Skin at the application site contained 1.23% of the administered dose. Metabolite analysis was not conducted due to the low concentrations in samples.

2.2.5.5 What is the available pharmacokinetic information?

The following studies were reviewed for capsaicin systemic concentrations after Qutenza application. As stated previously, since the patch is applied at the local site(s) associated with PHN for a local pain control, the critical clinical pharmacology aspect of this NDA was to focus on the capsaicin systemic exposure from the systemic safety purpose. The following 5 studies were reviewed for capsaicin's systemic concentrations: Phase 2 studies, C102, C108, and C111; and, P3 studies, C107 and C116.

Phase 2 trials:

Study C102: Title: A Double-Blind Controlled Pilot Study of High-Concentration Capsaicin Patches in the Treatment of Pain Associated with Postherpetic Neuralgia

This study was conducted with clinical trial formulation 1. This was a double-blind, randomized, controlled, multi-center study investigating the feasibility, tolerability, safety and efficacy of treatment of pain with Qutenza in subjects with PHN. The study included an initial small open-label phase (all 6 subjects were treated with Qutenza), followed by a double-blind treatment phase in which the subjects were randomized to receive either Qutenza or low-concentration control patch (3.2 µg capsaicin per cm²) for 60 minutes in a 2:1 ratio. Blood samples (10 mL in K₃EDTA coated tubes) were collected at the following time-points: (1) immediately prior to application of capsaicin patches, (2) immediately after removal of capsaicin patches (within 5 minutes), (3) at 1 hour post-patch removal, and (4) 3 hours post-patch removal. Potassium EDTA was used as an anticoagulant.

Distribution of Subjects in Clinical Study C102 for Plasma Analysis

Total No. of Subjects	Qutenza	Low-Concentration Control
24	16	8

Plasma samples were analyzed by (b) (4) and the lower limit of quantitation (LLOQ) for capsaicin in plasma was 2.5 ng/mL. This method measured only capsaicin levels.

The results indicated that plasma levels of capsaicin in all subjects in this study were below the LLOQ (2.5 ng/mL) at all time-points.

Study C108: Title: A Randomized, Double-Blind, Controlled Dose Finding Study of Qutenza for the Treatment of Postherpetic Neuralgia

This study was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of PHN, with an open-label extension phase. Subjects were randomized to receive either Qutenza or low-concentration control patches (3.2 mcg capsaicin cm²) for 30, 60 or 90 minutes. Efficacy was assessed over a period of 12 weeks. Subjects who completed study evaluations through Week 12 had the option of receiving a maximum of 3 additional open-label 60 minute re-treatments with Qutenza no more often than once every 12 weeks.

During the initial 12 week double-blind phase, blood samples were collected (5 mL in K₃EDTA coated tubes) in subjects assigned to the 90-minute treatment group at selected study sites. A preliminary assessment of plasma lidocaine levels was also performed. Blood samples were also collected in the same cohort of subjects if they elected to receive one or more 60-minute Qutenza treatments during a 40 week open-label extension period. Sample collection time-points were as follows: (1) immediately before topical lidocaine-based (4%) local anesthetic (L.M.X.4™) application, (2) after topical anesthetic removal but before patch application, (3) upon patch removal, (4) 1 hour post-patch removal and (5) 3 hours post-patch removal. Plasma samples from this study were analyzed by (b) (4). Plasma samples for lidocaine levels were analyzed only by (b) (4). Concentrations were determined by using HPLC with MS/MS detection. The lower limit of quantitation (LLOQ) for capsaicin, capsaicin metabolites and lidocaine in plasma was 0.5 ng/mL.

Distribution of Subjects in Clinical Study C108 for Plasma Analysis

Double-Blind Phase		Open-Label Re-Treatment Phase
Qutenza 90 min	Low-Concentration Control 90 min.	Qutenza 60 min.
27	11	First re-treatment = 15
		Second re-treatment = 14
		Third re-treatment = 3

Summary of Treatment Administration During Double-Blind Treatment

	NGX-4010				Control			
	Total (n = 222)	90 min (n = 73)	60 min (n = 77)	30 min (n = 72)	Total (n = 77)	90 min (n = 25)	60 min (n = 29)	30 min (n = 23)
Total Surface Area Treated (cm ²)								
Mean ± SD	383.6 ± 252.16	400.4 ± 282.56	387.8 ± 252.38	361.9 ± 219.07	339.6 ± 211.05	278.6 ± 191.66	385.3 ± 234.03	348.4 ± 192.41
Median	316.5	318.0	330.0	302.5	325.0	222.0	371.0	290.0
Min, Max	21, 1092	43, 1092	21, 1000	38, 873	32, 893	32, 705	33, 871	44, 893
p-value ^a	0.172	0.136	0.201	0.528				
Duration of Patch Application (min)								
Mean ± SD	59.9 ± 24.14	89.2 ± 5.19	59.8 ± 1.86	30.2 ± 0.94	60.9 ± 23.96	90.3 ± 1.17	60.0 ± 0.89	30.0 ± 0.00
Median	60.0	90.0	60.0	30.0	60.0	90.0	60.0	30.0
Min, Max	27, 95	60, 95	45, 63	27, 35	30, 95	89, 95	57, 62	30, 30
95% CI	56.67, 63.06	88.02, 90.44	59.38, 60.23	29.93, 30.37	55.43, 66.31	89.80, 90.76	59.66, 60.34	30.00, 30.00

^a P-value was computed from t-test comparing the mean value between each NGX-4010 group and the pooled Control group.

Summary of Treatment Administration by Number of NGX-4010 Treatments Received

	Number of NGX-4010 Treatments				
	0	1	2	3	4
Number of Subjects	17	112	87	63	20
Total Surface Area Treated (cm ²)					
Mean ± SD	348.5 ± 236.08	412.2 ± 254.80	340.7 ± 228.16	334.9 ± 241.75	375.0 ± 269.71
Median	266.0	372.0	299.0	248.0	232.5
Min, Max	39, 871	44, 1000	22, 1000	38, 1054	38, 1092
Duration of Patch Application (min)					
Mean ± SD	59.8 ± 21.23	59.5 ± 19.31	60.0 ± 0.99	59.3 ± 4.21	60.1 ± 0.45
Median	60.0	60.0	60.0	60.0	60.0
Min, Max	30, 90	27, 92	55, 65	30, 62	60, 62

Plasma Capsaicin Levels in Subjects from Clinical Study C108

90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47%)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
006-02 ^C _H	Before L.M.X.4	ND	006-02	Did not give blood	ND	006-02	Before L.M.X.4	< LLOQ
	Before Patch	ND					Before Patch	< LLOQ
	At PR	ND					At PR	< LLOQ
	1 hr post-PR	ND					1 hr post-PR	< LLOQ
	3 hr post-PR	(b) (4)					3 hr post-PR	< LLOQ
014-04 _H	Before L.M.X.4	< LLOQ	014-04	Before L.M.X.4	< LLOQ	014-04	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	(b) (4)		At PR	(b) (4)		At PR	< LLOQ
	1 hr post-PR	(b) (4)		1 hr post-PR	(b) (4)		1 hr post-PR	(b) (4)
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ
018-16 _H	Before L.M.X.4	< LLOQ	018-16	Did not give blood	ND	018-16	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ					Before Patch	< LLOQ
	At PR	(b) (4)					At PR	(b) (4)
	1 hr post-PR	(b) (4)					1 hr post-PR	(b) (4)
	3 hr post-PR	(b) (4)					3 hr post-PR	(b) (4)

90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47%)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
018-39 _H	Before L.M.X.4	< LLOQ	018-39	Did not give blood ^b	ND	018-39	Did not give blood	ND
	Before Patch	< LLOQ						
	At PR	ND (b) (4)						
	1 hr post-PR	█						
	3 hr post-PR	ND						
019-11 _H	Before L.M.X.4	< LLOQ	019-11	Before L.M.X.4	< LLOQ	019-11	Did not give blood	ND
	Before Patch	< LLOQ		Before Patch	< LLOQ			
	At PR	(b) (4)		At PR	< LLOQ			
	1 hr post-PR	█		1 hr post-PR	< LLOQ			
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ			
019-12 _H	Before L.M.X.4	< LLOQ	019-12	Before L.M.X.4	< LLOQ	019-12	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	< LLOQ		At PR	< LLOQ		At PR	< LLOQ
	1 hr post-PR	< LLOQ		1 hr post-PR	< LLOQ		1 hr post-PR	(b) (4)
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ
90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47%)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
022-03 _H	Before L.M.X.4	< LLOQ	022-03	Did not give blood	ND	022-03	Did not give blood	ND
	Before Patch	< LLOQ						
	At PR	(b) (4)						
	1 hr post-PR	█						
	3 hr post-PR	█						
022-04 _H	Before L.M.X.4	< LLOQ	022-04	Before L.M.X.4	< LLOQ	022-04	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	(b) (4)		At PR	(b) (4)		At PR	(b) (4)
	1 hr post-PR	█		1 hr post-PR	█		1 hr post-PR	█
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ		3 hr post-PR	█
023-05 _H	Before L.M.X.4	< LLOQ	023-05	Before L.M.X.4	< LLOQ	023-05	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	(b) (4)		At PR	(b) (4)		At PR	(b) (4)
	1 hr post-PR	█		1 hr post-PR	ND		1 hr post-PR	█
	3 hr post-PR	< LLOQ		3 hr post-PR	ND		3 hr post-PR	< LLOQ

90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47 %)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
024-06 _H	Before L.M.X.4	< LLOQ	024-06	Did not give blood	ND	024-06	Did not give blood	ND
	Before Patch	< LLOQ						
	At PR	< LLOQ						
	1 hr post-PR	< LLOQ						
	3 hr post-PR	< LLOQ (b) (4)						
024-07 _H	Before L.M.X.4	< LLOQ	024-07	Did not give blood	ND	024-07	Did not give blood	ND
	Before Patch	< LLOQ						
	At PR	< LLOQ (b) (4)						
	1 hr post-PR	< LLOQ						
	3 hr post-PR	< LLOQ						
025-02 _H	Before L.M.X.4	< LLOQ	025-02	Before L.M.X.4	< LLOQ	025-02	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	< LLOQ (b) (4)		At PR	< LLOQ (b) (4)		At PR	< LLOQ
	1 hr post-PR	< LLOQ		1 hr post-PR	< LLOQ		1 hr post-PR	< LLOQ
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ
90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47 %)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
036-09 _H	Before L.M.X.4	< LLOQ	036-09	Before L.M.X.4	< LLOQ	036-09	Before L.M.X.4	< LLOQ
	Before Patch	< LLOQ		Before Patch	< LLOQ		Before Patch	< LLOQ
	At PR	< LLOQ (b) (4)		At PR	< LLOQ (b) (4)		At PR	< LLOQ (b) (4)
	1 hr post-PR	< LLOQ		1 hr post-PR	< LLOQ		1 hr post-PR	ND
	3 hr post-PR	ND		3 hr post-PR	ND		3 hr post-PR	ND
037-06 _H	Before L.M.X.4	< LLOQ	037-06	Before L.M.X.4	< LLOQ	037-06	Did not give blood	ND
	Before Patch	< LLOQ		Before Patch	< LLOQ			
	At PR	< LLOQ (b) (4)		At PR	< LLOQ			
	1 hr post-PR	< LLOQ		1 hr post-PR	< LLOQ			
	3 hr post-PR	< LLOQ		3 hr post-PR	< LLOQ			
017-04 _L	Before L.M.X.4	ND	017-04	Before L.M.X.4	ND	017-04	Did not give blood	ND
	Before Patch	ND		Before Patch	< LLOQ			
	At PR	ND		At PR	< LLOQ			
	1 hr post-PR	ND		1 hr post-PR	< LLOQ (b) (4)			
	3 hr post-PR	ND		3 hr post-PR	< LLOQ			

90 min. Initial Treatment (Double-Blind Phase) C _{max} : 17.8 ng/mL n = 13/27 (48%)			60 min. First Re-Treatment (Open-Label Phase) C _{max} : 3.17 ng/mL n = 7/15 (47%)			60 min. Second Re-Treatment (Open-Label Phase) C _{max} : 4.26 ng/mL n = 8/14 (57%)		
Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)	Subject	Blood Sample Timepoint	Conc. (ng/mL)
018-23 _L	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ < LLOQ < LLOQ < LLOQ	018-23	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ < LLOQ (b) (4) ND	018-23	Did not give blood	ND
022-01 _L	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ < LLOQ < LLOQ < LLOQ	022-01	Did not give blood	ND	022-01	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ (b) (4) ND ND
037-02 _L	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ < LLOQ < LLOQ < LLOQ	037-02	Did not give blood	ND	037-02	Before L.M.X.4 Before Patch At PR 1 hr post-PR 3 hr post-PR	< LLOQ < LLOQ (b) (4) < LLOQ < LLOQ

^a Represents only those subjects (except one subject with unknown ID) that had detectable levels of capsaicin at any timepoint during either the double-blind phase or subsequent re-treatment phases.

^b Gave blood only before L.M.X.4 application. Capsaicin level at that time was < LLOQ.

^c Underwent four treatments all together (initial 90 minute treatment and then 3 subsequent 60 minute re-treatments); blood samples were drawn at 3rd open-label re-treatment. Data from the 3rd re-treatment is not shown here as no blood levels were detected.

n = Number of subjects with quantifiable values/total number of subjects treated with NGX-4010 patches who gave blood for analysis. ND = Not done
PR = Patch removal

H = Subject received NGX-4010 during the initial double-blind treatment phase

L = Subject received low-concentration capsaicin patches (control) during the initial double-blind treatment phase. LLOQ = Lower Limit of Quantitation

Capsaicin levels

Overall, less than 50% of the subject-treatments had detectable capsaicin levels at any time-point. Forty-eight percent of the PHN subjects had detectable levels of capsaicin in the double-blind phase and 47% of subject-treatments had detectable levels during the three open-label treatment phases cumulatively. Capsaicin levels were below LLOQ at all time-points during the 3rd retreatment period. On the double-blind Treatment Day (Day 0), for those in the 90-minute group with quantifiable levels, capsaicin values ranged from 0.57 to 17.8 ng/mL ((b) (4) in Subject# 022-03 at 1-hour post-patch removal). Quantifiable levels following 60-minute Qutenza applications ranged from 0.52 to 4.26 ng/mL.

During the open-label re-treatment phase, when subjects received 60 minute Qutenza treatments, 7 of 15 subjects (47%) had quantifiable plasma capsaicin levels ranging from 0.77 to 3.17 ng/mL at patch removal through 3 hours after patch removal after the first re-treatment and 8 of 14 subjects (57%) had quantifiable plasma capsaicin levels ranging from 0.52 to 4.26 ng/mL at patch removal through 3 hours after patch removal after the second re-treatment. None of the 3 subjects after the third re-treatment had quantifiable plasma capsaicin levels.

None of the 11 control subjects (low capsaicin dose patch) had quantifiable levels following 90-minute double-blind treatment. No capsaicin metabolites were detected in any of the samples at any time-point in either treatment phase.

Lidocaine levels

On the double-blind Treatment Day (Day 0), lidocaine levels were assessed in plasma samples of 39 patients in this study. Treated areas ranged from 32 to 948 cm². Lidocaine levels were detectable following topical lidocaine application in plasma samples ranged from 0.57 to 494 ng/mL (topical anesthetic L.M.X.4™), with the majority of the lidocaine levels measured below 50 ng/mL. The maximum lidocaine level detected (Subject 2305; (b) (4)) was measured at the time of patch removal. This subject received a double-blind 90-minute Qutenza treatment over an area of 948 cm². Two subjects (Subject 204 and 2502) in the Qutenza group had plasma lidocaine levels \geq 1000 ng/mL prior to L.M.X.4™ application. The Applicant stated that these were probably due to sample contamination: Subject 204 had plasma lidocaine levels of (b) (4) at after L.M.X.4™ removal / before patch application, at patch removal, and at 1 and 3 hours after patch removal, respectively; and Subject 2502 had plasma lidocaine levels of (b) (4) at after L.M.X.4™ removal / before patch application, at patch removal, and at 1 and 3 hours after patch removal, respectively.

During the open-label re-treatment phase, plasma levels of lidocaine were quantifiable in the plasma of all 11 subjects analyzed. The maximum plasma lidocaine concentrations during the open-label re-treatment phase ranged from 10.7 to 282 ng/mL measured at after L.M.X.4™ removal / before patch application through 3 hours after patch removal. Treatment areas ranged from 27 to 1000 cm².

Study C111: Title: A Randomized, Open-Label Study of the Tolerability of Three Local Anesthetic Formulations in Conjunction with Qutenza for the Treatment of Neuropathic Pain

This was a randomized, open-label, multi-center study to assess the tolerability of Qutenza applied for 60 or 90 minutes when used in conjunction with pre-patch topical application utilizing one of three different topical lidocaine-based (4%) local anesthetics (L.M.X.4™, Topicaine® and Betacaine®) in subjects with PDN, HIV-AN or PHN. Subjects were randomly assigned to receive 60 or 90 minute treatments with Qutenza patches, and allocated to one of three topical local anesthetic groups. At selected study sites, blood samples were collected (5 mL in K₃EDTA-coated tubes) from PHN or PDN patients at the following timepoints: (1) after topical anesthetic removal and before patch application, (2) immediately after patch removal, (3) 1 hour post-patch removal, (4) 3 hours post-patch removal, (5) 6 hours post-patch removal, and (6) 24 hours post-patch removal. Plasma samples were analyzed by (b) (4) using HPLC

with MS/MS detection. The lower limit of quantitation (LLOQ) for capsaicin and capsaicin metabolites in plasma was 0.5 ng/mL.

Distribution of Subjects in Clinical Study C111 for Plasma Analysis

Indication	Qutenza Application Time (min.)	Total No. of Subjects
PHN	90	3
	60	3
PDN	80	22
	60	11

Quantifiable plasma levels of capsaicin were observed in a total of three subjects (3 of 39, 8%), ranging from 0.52 to 1.9 ng/mL; all other subjects evaluated were below the LLOQ (0.5 ng/mL) at all time-points. Plasma levels were detected in 1 (Subject# 038-12) out of 3 PHN subjects receiving a 90-minute Qutenza application and in 1 (Subject# 080-03) of 3 PHN subjects receiving a 60-minute application. Among PDN subjects, none of the 22 subjects treated for 90 minutes had a plasma level of capsaicin greater than the LLOQ, one subject (Subject# 080-06) of 11 receiving a 60-minute application had a quantifiable plasma capsaicin level. No subjects had a quantifiable plasma capsaicin metabolite level detected at any time-point.

Table 9: C111 Subjects^a with Detectable Plasma Capsaicin Levels

Subject #	Indication	NGX-4010 Application Time (min.)	Anesthetic Used	Blood Sampling Timepoints	Capsaicin Conc. (ng/mL)
080-03	PHN	60	Topicaine®	Before patch	< LLOQ
				At PR	(b) (4)
				1 hr post-PR	< LLOQ
				3 hr post-PR	< LLOQ
				6 hr post-PR	< LLOQ
				24 hr post-PR	< LLOQ
080-06	PDN	60	L.M.X.4™	Before patch	< LLOQ
				At PR	< LLOQ
				1 hr post-PR	< LLOQ
				3 hr post-PR	(b) (4)
				6 hr post-PR	< LLOQ
				24 hr post-PR	< LLOQ
038-12	PHN	90	L.M.X.4™	Before patch	< LLOQ
				At PR	(b) (4)
				1 hr post-PR	(b) (4)
				3 hr post-PR	< LLOQ
				6 hr post-PR	< LLOQ
				24 hr post-PR	< LLOQ

^a Represents only those subjects that had detectable levels of capsaicin at any timepoint.
PR = Patch removal

Phase 3 trials:

Clinical Trial C107: Title: A Randomized, Double-Blind, Controlled Dose Finding Study of Qutenza for the Treatment of Painful HIV-Associated Distal Symmetrical Polyneuropathy

This study was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of HIV-AN. Patients were randomized to receive Qutenza or low-concentration control patches (3.2 mcg capsaicin per cm²) for 30, 60 or 90 minutes. During the initial 12-week double-blind phase, blood samples were collected (5 mL in K₃EDTA-coated tubes) from subjects assigned to the 90-minute treatment group at selected study sites. A preliminary assessment of plasma lidocaine levels was also performed. Plasma samples were also collected in the same cohort of subjects if they elected to receive one or more 60-minute Qutenza treatments during a 40 week open-label extension period. Sample collection timepoints were as follows: (1) immediately before topical lidocaine-based (4%) local anesthetic (L.M.X.4™) application, (2) after topical anesthetic removal/before patch application, (3) upon patch removal, (4) 1 hour post-patch removal and (5) 3 hours post-patch removal.

Plasma samples were analyzed by (b) (4) using HPLC with MS/MS detection. The lower limit of quantitation (LLOQ) for capsaicin, capsaicin metabolites and lidocaine in plasma was 0.5 ng/mL.

Distribution of Subjects in Clinical Study C107 for Plasma Analysis

Double-Blind Phase		Open-Label Re-Treatment Phase
Qutenza 90 min	Low-Concentration Control 90 min.	Qutenza 60 min.
37	14	First re-treatment = 13
		Second re-treatment = 8
		Third re-treatment = 1

In the initial double-blind phase (90-minute treatment), plasma levels of capsaicin were quantifiable in three of 37 subjects (8%), with values ranging from 0.57 to 1.75 ng/mL which were only detected at patch removal or 1 hour after removal. All other subjects, including the subjects receiving the low-concentration control treatment, were below the LLOQ (0.5 ng/mL). In the open-label re-treatment phases (60-minute treatment), no quantifiable levels of capsaicin were detected in any sample. No metabolites were detected in any of the samples at any timepoint in either phase of the study.

Subject Number	Treatment Group	Blood Sampling Timepoint	Capsaicin Conc. (ng/mL)
012-03	NGX-4010 90 min.	Before L.M.X.4	< LLOQ
		Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
048-04	NGX-4010 90 min.	Before L.M.X.4	< LLOQ
		Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
053-01	NGX-4010 90 min.	Before L.M.X.4	< LLOQ
		Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ

^a Represents only those subjects that had detectable levels of capsaicin at any timepoint.
PR = Patch removal

Lidocaine levels were assessed in plasma samples of 27 patients in this study. Treated areas ranged from 252 to 1120 cm². Lidocaine levels were detectable following topical lidocaine application in plasma samples of 19 of 27 patients sampled and the majority of lidocaine levels were below 50 ng/mL. The maximum lidocaine level detected in any subject was 93.5 ng/mL (Subject 4607); this sample was collected immediately following lidocaine removal. This subject received a double-blind 90-minute Qutenza treatment over an area of approximately 930 cm².

Clinical Study C116: Title: A Randomized, Double-Blind, Controlled Study of Qutenza for the Treatment of Postherpetic Neuralgia

This study was a randomized, double-blind, controlled multi-center evaluation of the efficacy, safety and tolerability of Qutenza for the treatment of PHN when applied for 60 minutes. Patients were randomized to receive either Qutenza (640 µg capsaicin cm²) or low-concentration control patches (3.2 µg capsaicin cm²) for 60 minutes. Efficacy was assessed over a period of 12 weeks. At selected sites, blood samples (5 mL in K₃EDTA-coated glass tubes) were collected as follows: (1) after anesthetic removal and before patch application, (2) immediately after patch removal, (3) 1 hour post-patch removal, (4) 3 hours post-patch removal, (5) 6 hours post-patch removal and (6) 24 hours post-patch removal. Plasma samples were analyzed by (b) (4) using HPLC with MS/MS detection. The lower limit of quantitation (LLOQ) for capsaicin and capsaicin metabolites was 0.5 ng/mL.

Distribution of Subjects in Clinical Study C116 for Plasma Analysis

Qutenza	Low-Concentration Control
49	51

Quantifiable plasma capsaicin levels (LLOQ = 0.5 ng/mL) were detected in 10 of the 49 subjects (20%) who received the 60-minute Qutenza treatment. The highest concentration of capsaicin detected in any subject plasma sample was 4.64 ng/mL (Subject# 130-0096). This concentration was observed immediately after patch removal. The capsaicin level in the same subject declined to 2.39 ng/mL at the one-hour post-patch removal timepoint and was below the LLOQ 3 and 24 hours post-patch removal.

No capsaicin metabolites at or above the LLOQ were detected in any of the study samples at any time-point. Of the 51 subjects who received the low-concentration control treatment, none had detectable levels of capsaicin or its metabolites at any time-point.

Study C116 Subjects^a with Detectable Plasma Capsaicin Levels

Subject Number	Treatment Group	Blood Sampling Timepoints	Capsaicin Conc. (ng/mL)
004-1118	NGX-4010	Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
		6 hr post-PR	< LLOQ
		24 hr post-PR	< LLOQ
019-0182	NGX-4010	Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
		6 hr post-PR	< LLOQ
		24 hr post-PR	< LLOQ
019-1018	NGX-4010	Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
		6 hr post-PR	< LLOQ
		24 hr post-PR	< LLOQ
073-1289	NGX-4010	Before patch	< LLOQ
		At PR	< LLOQ
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
		6 hr post-PR	< LLOQ
		24 hr post-PR	(b) (4)
073-1290	NGX-4010	Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	< LLOQ
		3 hr post-PR	< LLOQ
		6 hr post-PR	< LLOQ
		24 hr post-PR	< LLOQ
077-1310	NGX-4010	Before patch	< LLOQ
		At PR	(b) (4)
		1 hr post-PR	(b) (4)
		3 hr post-PR	(b) (4)
		6 hr post-PR	< LLOQ
		24 hr post-PR	< LLOQ

Subject Number	Treatment Group	Blood Sampling Timepoints	Capsaicin Conc. (ng/mL)
125-0041	NGX-4010	Before patch At PR 1 hr post-PR 3 hr post-PR 6 hr post-PR 24 hr post-PR	< LLOQ (b) (4) < LLOQ < LLOQ < LLOQ < LLOQ
125-0110	NGX-4010	Before patch At PR 1 hr post-PR 3 hr post-PR 6 hr post-PR 24 hr post-PR	< LLOQ (b) (4) < LLOQ < LLOQ < LLOQ < LLOQ
128-1032	NGX-4010	Before patch At PR 1 hr post-PR 3 hr post-PR 6 hr post-PR 24 hr post-PR	< LLOQ ND (b) (4) < LLOQ ND < LLOQ
130-0096	NGX-4010	Before patch At PR 1 hr post-PR 3 hr post-PR 6 hr post-PR 24 hr post-PR	< LLOQ (b) (4) < LLOQ < LLOQ ND < LLOQ

^a Represents only those subjects that had detectable levels of capsaicin at any timepoint
PR = Patch removal
ND = Not done

Overall, only limited and transient systemic exposure to capsaicin occurs following topical applications of Qutenza. The highest observed capsaicin concentration is 17.8 ng/mL. An overview of the highest capsaicin concentration observed is depicted in the following table.

Study	C102 (PHN)	C107 (HIV-AN)				C108 (PHN)				C111 (PDN > PHN)		C116 (PHN)
Application Time (min)	60	90	60	60	60	90	60	60	60	90	60	60
Phase of Study	DB Treatment	DB Treatment	OL 1 st RT	OL 2 nd RT	OL 3 rd RT	DB Treatment	OL 1 st RT	OL 2 nd RT	OL 3 rd RT	OL Treatment	OL Treatment	DB Treatment
Number of Subjects ^a	0/16	3/37	0/13	0/8	0/1	13/27	7/15	8/14	0/3	PHN : 1/3 PDN: 0/22	PHN: 1/3 PDN: 1/11	10/49
% ^c	0	8	0	0	0	48	47	57	0	PHN: 33 PDN: 0	PHN: 33 PDN: 9	20
Capsaicin ^b C _{max} ^d (ng/mL)	< LLOQ ^f	1.75	< LLOQ ^e	< LLOQ ^e	< LLOQ ^e	17.8	3.17	4.26	< LLOQ ^e	PHN: 0.74 PDN: < LLOQ ^e	PHN: 1.9 PDN: 0.52	4.64

DB = double blind initial treatment

OL = open label

RT = re-treatment

^a Number of subjects with quantifiable values/total number of subjects treated with NGX-4010 patches who gave blood for analysis.

^b No metabolites of capsaicin were quantifiable in any of these studies.

^c Percent of subjects with detectable levels of capsaicin at any time point

^d Highest concentration of capsaicin detected at any time point

^e Lower limit of quantitation (0.5 ng/mL for capsaicin and its metabolites)

^f Lower limit of quantitation (2.5 ng/mL for capsaicin, no metabolite evaluation)

2.3 Intrinsic Factors

2.3.1 What is the status of pediatric studies and/or any pediatric plan for study?

The safety and efficacy of Qutenza in children and adolescents younger than 16 years of age has not been studied. The Applicant submitted a Request for Waiver of Pediatric Studies for the entire pediatric population including patients' age birth to 16 years. The reason for waiving pediatric assessment requirements is that the incidence of PHN in this age group is extremely low and, is therefore not likely to be used in this group. At the End-of-Phase 2 meeting for Qutenza, the Agency agreed that deferral of pediatric studies was appropriate.

2.3.2 Special populations

No studies in patients with renal impairment, hepatic impairment, or elderly subject were conducted with Qutenza. Since Qutenza is used as a single dose application, a dosage adjustment in patients with renal or hepatic impairments and in elderly may not be necessary.

Population PK analysis:

The impact of demographic covariates, e.g., body weight (BW), age, gender and race, on PK parameter estimates of capsaicin was assessed by the Applicant using the Population pharmacokinetic modeling. Covariates such as treated surface area (cm²), dose levels of capsaicin (mg) and application times (60 or 90 minutes) were also evaluated.

Data in PHN patients from the following studies were used for the population PK analysis of capsaicin: Studies **C108, C111 and C116**. Overall, a total of 96 PHN patients receiving Qutenza for 60 or 90 minutes in the above three studies had plasma samples drawn for the determination of capsaicin levels and its metabolites. Of these, 31% (30 patients, 19 males and 11 females) displayed quantifiable levels of capsaicin at one or more time points. No metabolites were detected. The following demographic variables were observed in these patients.

Count	
Number of PHN patients with measurable capsaicin levels	30
Number of applications with measurable concentrations	40
Males / Females	19 / 11
Ethnicity (White / Asian / Other)	28 / 1 / 1
Study C108 / C111 / C116	18 / 2 / 10
60 minutes / 90 minutes applications	26 / 14
Median (Min – Max)	
Age (years)	72 (42 – 81)
Body weight (kg)	78.7 (49.0 – 118)
Height (cm)	168 (151 – 188)
BMI	28.5 (17.3 – 37.4)
Treatment area (cm2)	375 (32 – 1000)

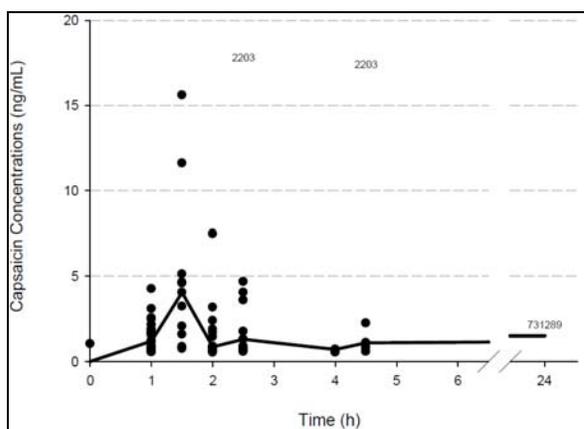
Theoretical dose calculation

The maximum recommended treatment area is 1,120 cm² and hence the maximum recommended single human dose is 717 mg (1120 x 640 µg/cm²), for an adult of 60 kg body weight (11.95 mg/kg). Based on an *in vitro* study, after a 60-minute patch application, only approximately 0.9% of the administered dose is delivered into human skin, and hence the estimated exposure is approximately 107.6 µg/kg per treatment (11.95 mg/kg x 0.009).

Median capsaicin plasma concentration profiles

Prior to performing the population PK analysis, plasma concentrations of capsaicin were explored graphically in order to evaluate potential outliers. Median and individual plasma concentrations of capsaicin after initial patch application (i.e., at time zero) are presented in the figure below.

Median and Individual Plasma Concentrations of Capsaicin



Note: The following patients are noteworthy. One patient had a measureable capsaicin concentration at 24 hours (2.16 ng/mL; Patient 731289; Patient PK ID 124; Study C116; a PHN male subject with body weight of 55.4 kg; capsaicin dose of 541 mg over 60 minutes). The other Patient 2203 (Patient PK ID 110, Study C108) had capsaicin concentration values ranging from 11.6 to 17.8 ng/mL which the capsaicin patches were removed at 1.5 hours, rather at 1 hour. In this analysis, these two patients were considered as “outliers.” Consequently, the Applicant presented the findings in both “All patients” or as “Main Dataset,” which include all patients (N=30) as well as “Without Outliers” or as “Exploratory Dataset,” which exclude these two patients (N=28).

Model building

Model build-up was performed using typical selection criteria such as 1) quality-of-fit, 2) measures of bias, and 3) measures of precision. Patients with detectable concentrations were used in the analysis. Total doses of capsaicin were calculated as the amount delivered (640 µg/cm²) multiplied by the treated area of pain (cm²). Overall, a total of 68

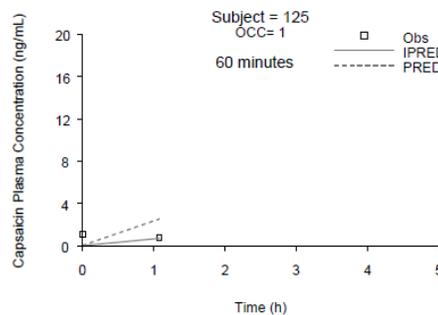
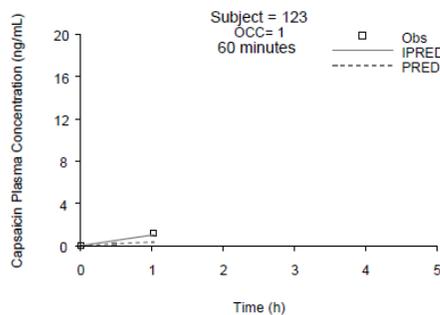
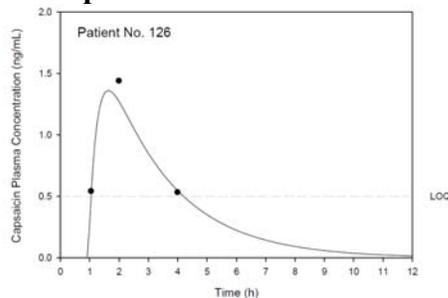
plasma concentrations of capsaicin were fitted simultaneously (actual dosing and sampling times were used) from a main dataset including a total of 30 patients that displayed at least one quantifiable value in a profile. The final population PK model was internally validated using a non-parametric bootstrap re-sampling approach in order to confirm the robustness of the final population PK estimates. A total of approximately 2000 bootstrap runs were performed. Bootstrap re-sampling was performed using Wings for NONMEM (Version 6)(files for the population PK analysis performed using the models listed above are retained on file at (b) (4))

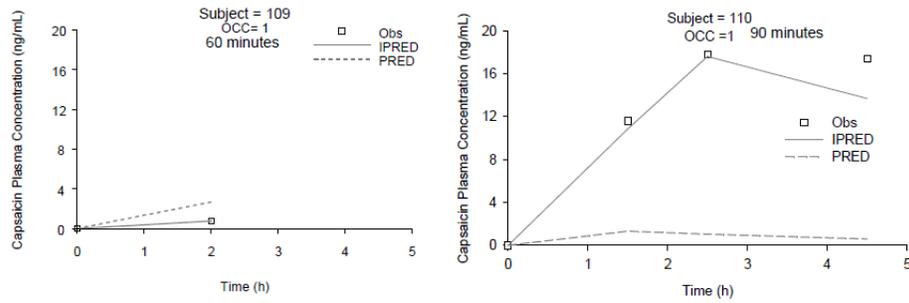
The Applicant stated that “due to the nature of the data,” population PK analysis of the plasma concentration dataset was not subjected to a complete model discrimination procedure. Rather, the following modeling was explored: one-compartment, zero-order rate constant of absorption (taking into account the duration of application), first-order rate constant of absorption, linear elimination, setting BLQ values to missing concentrations was deemed the most conservative approach) and log-transformed PK parameters. The Applicant stated that a one-compartment model with first-order absorption provided a better quality of fit than zero-order absorption models. When BLQ values were set to missing and when a lag time was used, the r^2 was markedly improved. The quality of fit of capsaicin concentration profiles was further improved when an inter-occasion variability (IOV) was added on the apparent volume of distribution, allowing a different V_c/F to be fitted within the same patient during the retreatment period in the open label phase.

Results

The simplest model that best described the plasma concentrations of capsaicin was a one-compartment model with first-order absorption and lag time (see below for examples).

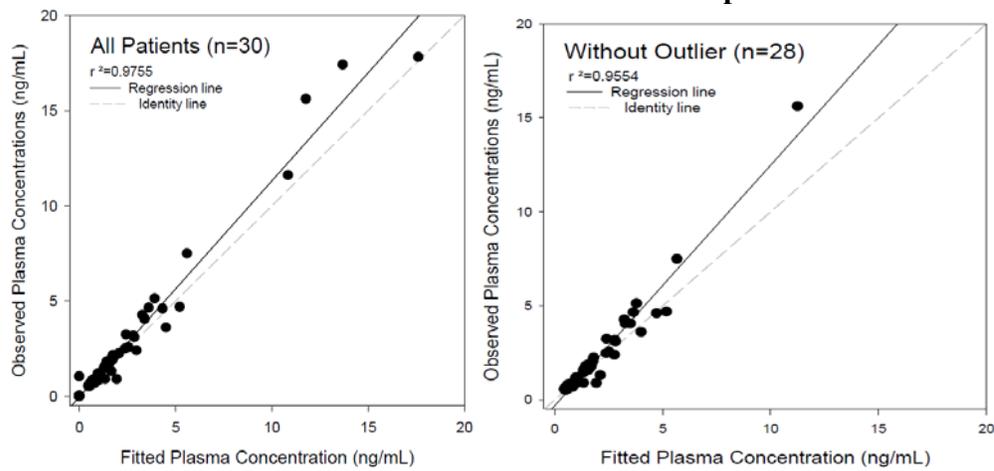
Example of a Fitted PK Profile of Capsaicin:





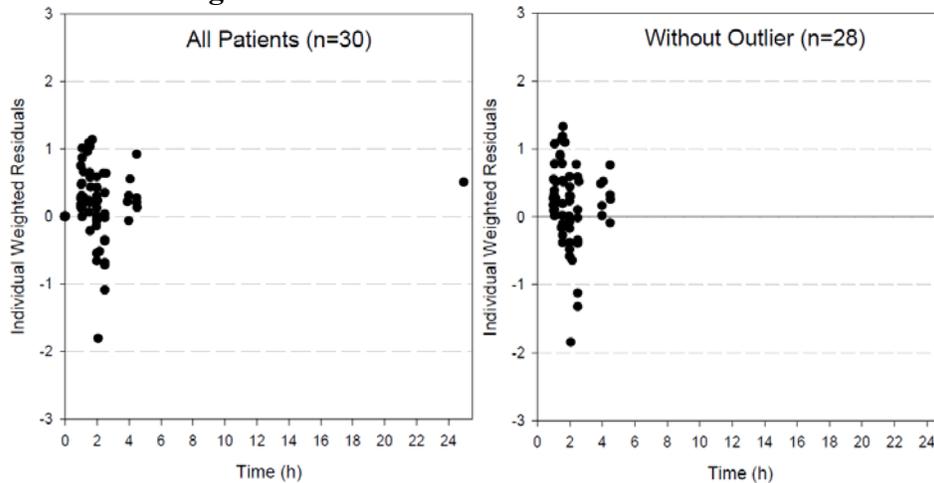
Observed and predicted plasma concentrations of capsaicin for all patients are presented below.

Observed vs. Predicted Plasma Concentrations of Capsaicin



Overall, individual plasma concentrations of capsaicin were fitted in the main dataset (n=30), with r^2 of 0.9755. Individual weighted residuals vs. time for the main and exploratory datasets are presented below.

Individual Weighted Residuals vs. Time



Individual weighted residuals were homogeneously distributed around zero for both datasets, suggesting no bias in the modeling of high and low concentration values of capsaicin.

Geometric mean population PK parameters of capsaicin along with inter-individual coefficient of variability (CV%) are presented below.

Overall Population PK Parameters of Capsaicin

Parameters	Combined Geometric Mean (CV%)	
	Main Dataset (n=30)	Exploratory Dataset (n=28)
Ka (1/h)	3.40 (18.6%)	3.40 (18.6%)
Vc/F (L)	138,000 (<1%)	136,000 (<1%)
Ke (1/h)	0.281 (287%)	0.444 (97.1%)
CL/F (L/h)*	32,440 (162%)	44,958 (111%)
T1/2 (h)*	2.18 (50.0%)	1.49 (18.8%)
AUCINF (ng.h/mL)*	6.99 (123%)	4.92 (75.2%)
Cmax (ng/mL)*	1.88 (104%)	1.74 (82.7%)
Tmax (h)*	1.30 (19.5%)	1.21 (15.1%)

Ka: rate constant of absorption, Lag: absorption lag time, Vc/F: apparent volume of distribution, Ke: rate constant of elimination, CL/F: apparent clearance, T1/2 : elimination half-life, AUCINF: area under the curve, Cmax: maximum plasma concentrations, Tmax: time to maximum plasma concentrations. * Bayesian (posthoc) estimates (Appendix 4); all other values are population derived parameters from NONMEM.

Summary of Bayesian PK Parameters Estimates for the 60 and 90-Minute Subpopulation of Capsaicin

Parameters	Geometric Mean (CV%)			
	Main Dataset (n=30)		Exploratory Dataset (n=28)	
	60-min	90-min	60-min	90-min
Ka (1/h)*	3.58 (9.0%)	3.66 (10.0%)	3.57 (10.1%)	3.66 (10.1%)
Vc/F (L)*	110183 (91.4%)	68226 (153%)	107380 (88.3%)	71424 (121%)
Ke (1/h)*	0.307 (46.0%)	0.378 (58.2%)	0.459 (19.9%)	0.489 (26.3%)
CL/F (L/h)*	36721 (137%)	25770 (218%)	51284 (101%)	34903 (128%)
T1/2 (h)*	2.26 (46.0%)	1.83 (58.2%)	1.51 (19.9%)	1.42 (26.3%)
AUCINF (ng.h/mL)*	5.71 (102%)	10.2 (148%)	3.94 (52.4)	7.57 (89.8%)
Cmax (ng/mL)*	1.48 (78.2%)	2.92 (128%)	1.38 (58.8%)	2.71 (99.6%)
Tmax (h)*	1.30 (17.1%)	1.22 (22.5%)	1.23 (16.5%)	1.14 (12.4%)

Ka: rate constant of absorption, Lag: absorption lag time, Vc/F: apparent volume of distribution, Ke: rate constant of elimination, CL/F: apparent clearance, T1/2 : elimination half-life, AUCINF: area under the curve, Cmax: maximum plasma concentrations, Tmax: time to maximum plasma concentrations. * Bayesian (post hoc) estimates

An apparent volume of distribution was very high (i.e., 138,000 L). A mean elimination half-life was approximately 2.18 hour.

Model validation

Models were validated using a nonparametric bootstrap re-sampling method. Approximately 2000 bootstrap runs were performed for the main dataset (n=30) and for the exploratory dataset (n=28). Median values with 95% confidence intervals are presented below.

Nonparametric PK Parameters of Capsaicin (Model Validation)

Parameters	Median (95% CI)	
	Main Dataset (n=30)	Exploratory Dataset (n=28)
Ka (1/h)	3.40	3.40
Vc/F (L)	134,000 (81,400 – 217,000)	131,000 (79,400 – 196,000)
Ke (1/h)	0.296 (0.0617 - 0.566)	0.457 (0.279 - 0.746)
CL/F (L/h)*	37,200 (9,830 – 75,276)	57,720 (36,270 – 96,841)
T1/2 (h)*	2.34 (1.22 - 11.23)	1.516 (0.929 - 2.484)

Ka: rate constant of absorption, Lag: absorption lag time, Vc/F: apparent volume of distribution, Ke: rate constant of elimination,

CL/F: apparent clearance, T1/2 : elimination half-life.

* Bayesian (post hoc) estimates

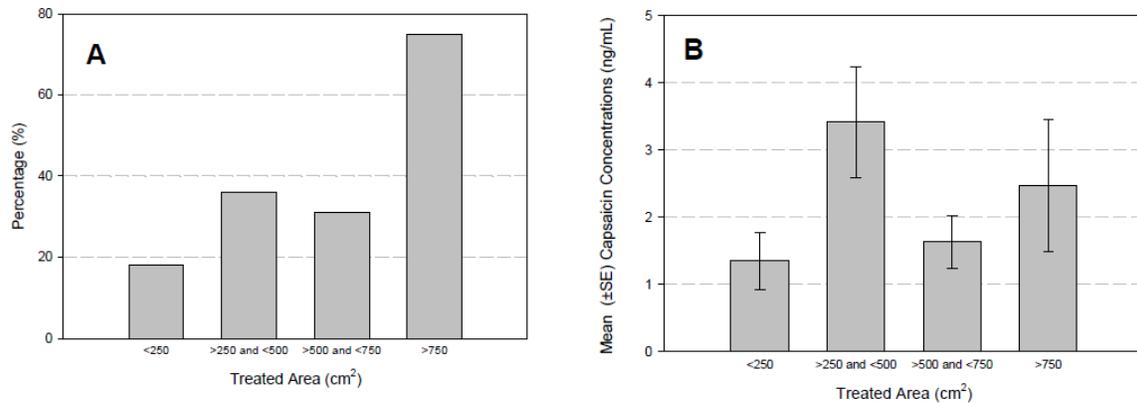
Overall, median values of PK parameters (Ka, Vc/F, and Ke) were in good agreement following the bootstrap re-sampling analysis with the population PK model.

Covariate Analysis

Preliminary Observations

The relationship between treated surface area and the percentage of patients displaying measurable plasma concentrations of capsaicin as well as mean concentrations values are presented below.

Treated Area and Capsaicin Measurable Concentration in PHN Patients



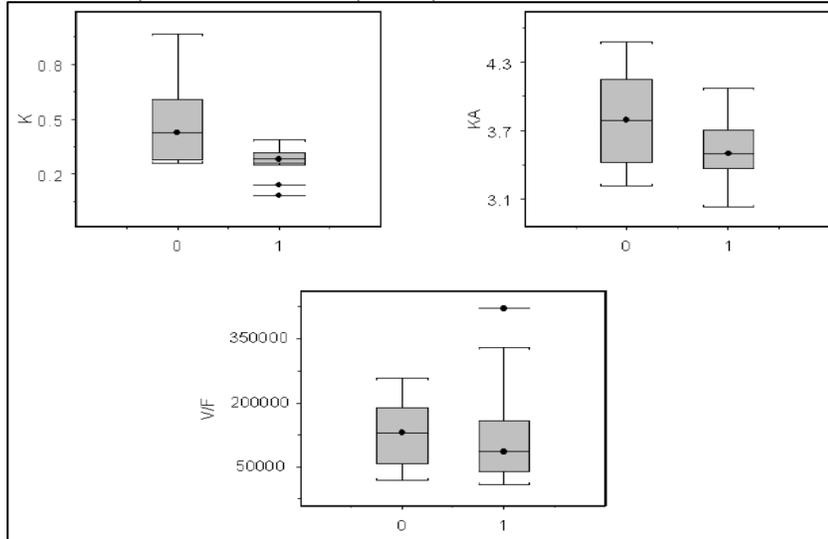
A higher percentage of PHN patients showed measurable capsaicin concentration values with increasing area of treatment (Panel A). On the other hand, larger areas of treatments were not associated to higher mean concentration values of capsaicin (Panel B).

Relationship between PK Parameters and Covariates

Overall, no relationship between pharmacokinetic parameters, rate constant of absorption (KA), apparent volume of distribution (Vc/F), and rate constant of elimination (Ke) of capsaicin and covariates were observed.

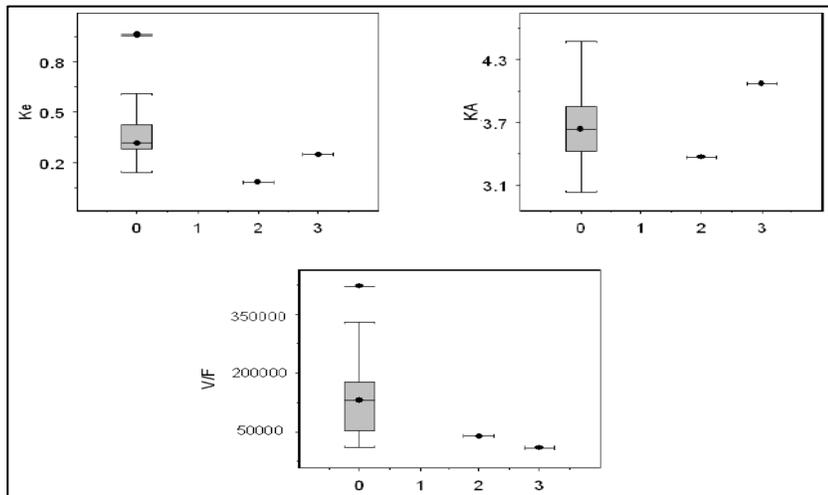
Gender:

Relationship Between PK Parameters of Capsaicin and Sex (0=Male; 1=Female) Main Dataset (N=30)



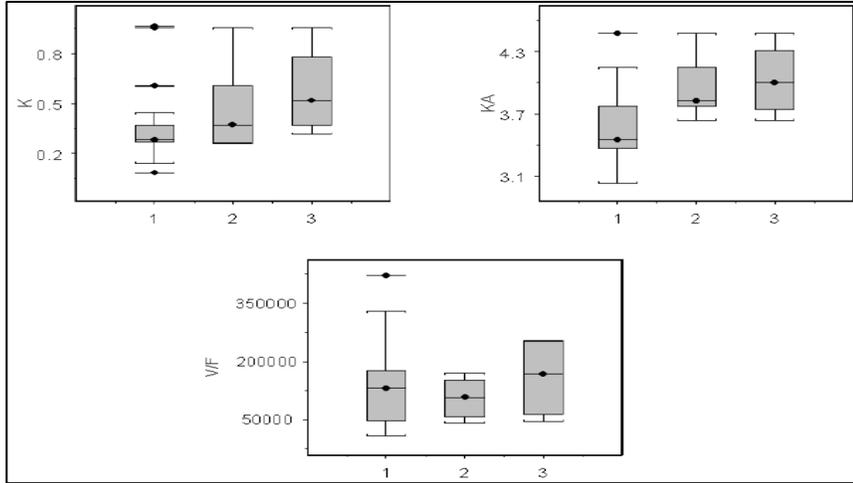
Race:

Relationship Between PK Parameters of Capsaicin and Race (0=White; 1=African American; 2=Asian; 3=Other) Main Dataset (N=30)



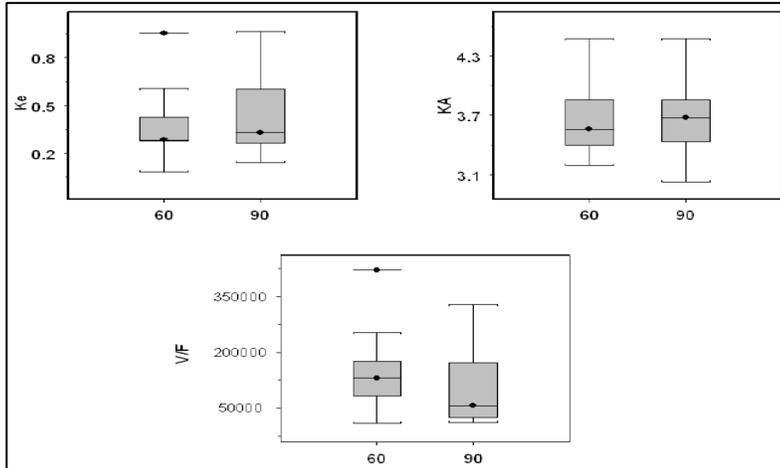
Re-application:

Relationship between PK Parameters of Capsaicin and Re-application (1=1st, 2=2nd, and 3=3rd re-application) Main Dataset (N=30)



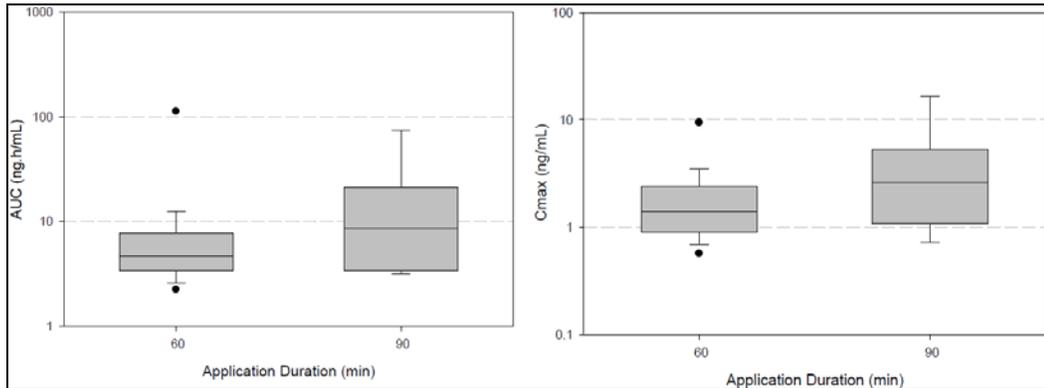
Patch application duration:

Relationship between PK Parameters of Capsaicin and Application Time (60=60 minutes; 90=90 minutes) for Main Dataset (N=30)



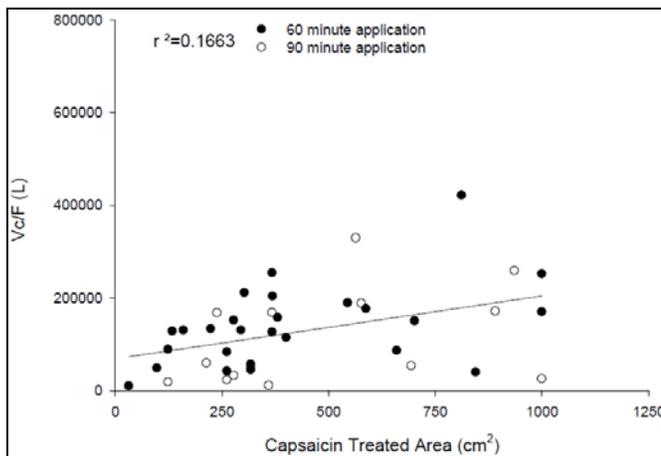
The relationship between the 60 and 90 minutes application periods and the resulting AUCINF and Cmax values of capsaicin are shown below. Geometric mean (CV%) AUCINF values of capsaicin for 60 and 90 minutes application were 5.71(102%) and 10.2 (148%) ng.h/mL, respectively. Geometric mean (CV%) Cmax values of capsaicin for 60 and 90 minutes application were 1.48 (78.2%) and 2.92 (128%) ng/mL, respectively. Overall, these results suggest that 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, respectively. Considering the variability and the relatively small number of subjects receiving the 60 and 90 minutes applications (22 and 14, respectively), the increase in AUCINF was not statistically significant at the 5% level when compared using an ANOVA (assuming homogeneity of variance). A statistical trend was observed for the increase in Cmax value (i.e., p-value < 0.001).



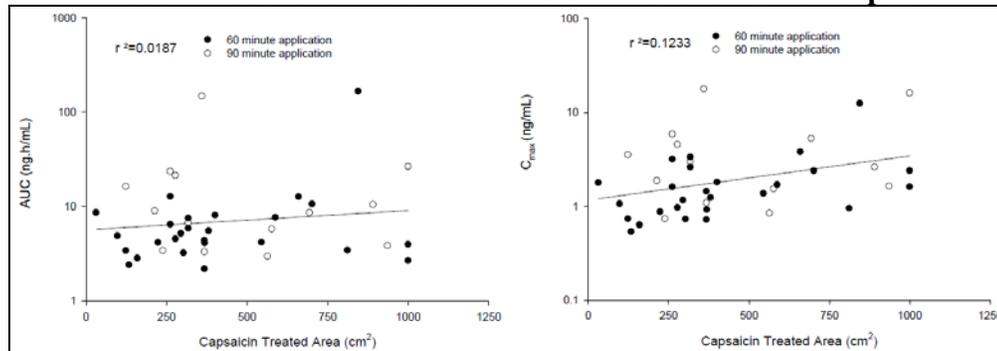
The Effect of Size of Treatment Area

The analysis showed that there was a small trend between the size of treatment area and the predicted Vc/F of capsaicin. The relationship between the size of treatment area and the Vc/F of capsaicin is shown below.



No relationship was observed between the size of the treatment area and the predicted AUCINF values of capsaicin. A small trend between the size of treatment area and the predicted Cmax values of capsaicin was observed. The relationship between size of treatment area and the resulting AUCINF and Cmax of capsaicin is shown below.

The Effect of Treatment Area on the AUCINF and Cmax of Capsaicin



Considering the relatively small number of patients with limited capsaicin observed systemic levels making the utility of these findings questionable.

2.3.3 What pregnancy and lactation use information is there in the application?

No clinical data on exposed pregnancies are available from the Qutenza clinical development program, except for one 32-year-old HIV-AN (Study C107) subject, who became pregnant 60 days after the study patch application. This patient 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.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

No formal drug interaction studies have been performed. The in vitro data indicated that capsaicin does not inhibit or induce enzymes. Additionally, there is minimal to no capsaicin skin metabolism. Finally, low levels of systemic capsaicin concentrations were observed. Therefore, drug-drug interaction is not expected with capsaicin.

Interestingly, as previously stated, the patch application area was pretreated with a topical anesthetic (4% lidocaine non-U.S. approved products) for 60-minutes, due to the pain associated with capsaicin. After 60-minutes, the applied topical anesthetic was wiped clean with a dry cloth prior to Qutenza patch application. It is expected that the used of non-U.S. topical anesthetic will have minimal to no impact on the systemic capsaicin exposure findings due to the fact that the topical anesthetic is wiped clean prior to Qutenza patch application and interaction between lidocaine and capsaicin is not likely to occur.

With the exception of the use of topical anesthetic products, e.g., lidocaine, the use of other topical analgesic products was prohibited in the clinical studies. Therefore, it is recommended and should be reflected in the Product Insert that patients do not apply

topical analgesic products immediately prior to treatment, such as NSAIDs, methyl salicylate, corticosteroids, or other capsaicin-containing products to the treatment areas.

2.4.1.1 Is the drug a substrate of CYP enzymes?

Human CYP enzymes identification

Summary: CYP2C9 was identified as the primary enzyme responsible for converting ¹⁴C-capsaicin to 16-hydroxy-capsaicin and 16, 17-dehydro-capsaicin. The results also suggested that CYP2C19 may be involved in the formation of 16-hydroxy-capsaicin. For the formation of the third metabolite, 17-hydroxy-capsaicin, which was thought to be nicotinamide adenine dinucleotide phosphate (NADPH) dependent, the CYP enzyme(s) responsible for its formation was not identified.

[¹⁴C] *trans*-Capsaicin (2 and 20 μM), when incubated with recombinant human CYP enzymes (rCYP1A1, rCYP1A2, rCYP2A6, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C18, rCYP2C19, rCYP2D6, rCYP2E1, rCYP3A4, rCYP3A5 and rCYP4A11), at 25 pmol P450 per incubation, was converted to 16-hydroxy- and 16, 17-dehydro- predominantly by rCYP2C9 and rCYP2C19. The greatest formation of 17-hydroxy- was observed in incubations with rCYP3A4, but was below the limit of quantification.

[¹⁴C] *trans*-Capsaicin (2 μM) was incubated with a bank of 16 samples of human liver microsomes and formation of each metabolite was correlated with the sample-to-sample variation in various CYP enzyme activities. Formation of 16-hydroxy moderately correlated with CYP2C9 (diclofenac 4'-hydroxylase) and CYP2C19 (*S*-mephenytoin 4'-hydroxylase) activity with correlation coefficients (r) of 0.680 and 0.504, respectively. Multiple linear regression of 16-hydroxy, CYP2C9 and CYP2C19 activity gave a correlation coefficient of 0.863. Formation of 16,17-dehydro-capsaicin strongly correlated with CYP2C9 activity with a correlation coefficient (r) of 0.856. 17-hydroxy-capsaicin formation correlated with both CYP2D6 (dextromethorphan *O*-demethylase) and CYP2E1 (chlorzoxazone 6-hydroxylase) activity, with correlation coefficients of 0.698 and 0.704, respectively.

Confirmation by CYP specific inhibitor

Summary: Sulfaphenazole, a directacting inhibitor against CYP2C9, strongly inhibited both 16-hydroxy and 16,17-dehydro-capsaicin formation by as much as 100%. Orphenadrine, an inhibitor of CYP2B6, and ketoconazole, an inhibitor of CYP3A4, completely inhibited 17-hydroxy formation. No metabolism-dependant inhibition of metabolites by the compounds evaluated (furafylline, 8-methoxypsoralen, ticlopidine and troleandomycin) was observed.

Inhibitory monoclonal and polyclonal antibodies against CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) were incubated with a pool of human liver microsomes to examine their effects on the formation of metabolites. Various chemical inhibitors against CYP enzymes were incubated with a pool of human liver

microsomes to examine their effects on the metabolism of [¹⁴C] *trans*-capsaicin (2 μM). Sulfaphenazole, a directacting inhibitor against CYP2C9, strongly inhibited both 16-hydroxy- and 16,17-dehydro- formation by as much as 100%. Orphenadrine, an inhibitor of CYP2B6, and ketoconazole, an inhibitor of CYP3A4, completely inhibited 17-hydroxy- formation.

2.4.1.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Inhibition

The ability of *trans*-capsaicin to inhibit *in vitro* the major CYP enzymes in human liver microsomes (namely CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 [using two different substrates]) were examine. The target concentrations of *trans*-capsaicin ranged from 0.01 to 10 μM in the clinical settings. The results from these experiments indicate that *trans*-capsaicin likely will not inhibit the clearance of concomitantly administered drugs metabolized by any of the CYP enzymes evaluated. For each of the enzymes studied, the [I]/K_i ratio is less than 0.1.

Enzyme	CYP Activity	IC ₅₀ (μM)	Estimated K _i ^a (μM)	Estimated degree of inhibition <i>in vivo</i>	
				$\frac{[I]}{K_i}$ ^b	Risk of drug- drug interaction
CYP1A2	Phenacetin <i>O</i> -deethylation	2.1	1.1	0.06	low
CYP2B6	Bupropion hydroxylation	24	12	0.01	low
CYP2C9	Diclofenac 4'-hydroxylation	2.0	1.0	0.07	low
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylation	3.2	1.6	0.04	low
CYP2D6	Dextromethorphan <i>O</i> -demethylation	18	9.0	0.01	low
CYP2E1	Chlorzoxazone 6-hydroxylation	> 10	NA	NA	low
CYP3A4/5	Midazolam 1'-hydroxylation	38	19	0.00	low
CYP3A4/5	Nifedipine oxidation	12	6.0	0.01	low

a Assuming competitive inhibition where K_i ≈ IC₅₀/2.

b $\frac{[I]}{K_i} < 1$; indicates a low potential for clinically significant drug interactions. [I] is the C_{max} of *trans*-capsaicin (0.065 μM), and K_i is the inhibitory constant for competitive inhibition.

NA Insufficient inhibition was observed to determine an accurate IC₅₀ value.

Induction

The ability of *trans*-Capsaicin to induce CYP enzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 and CYP3A4/5 were examined, in primary cultures of human hepatocytes. Individual preparations of cultured human hepatocytes from three separate human livers were treated with various drugs:

Enzyme	Marker Probe	Inducer drug
Solvent Control	dimethyl sulfoxide (DMSO; 0.1 %, v/v) or saline (0.1%, w/v)	-
CYP1A2	7-ethoxyresorufin <i>O</i> -dealkylation (EROD)	omeprazole (100 µM)
CYP2B6	bupropion hydroxylation	phenobarbital (750 µM)
CYP2C9	diclofenac 4'-hydroxylation	rifampin (10 µM)
CYP2C19	<i>S</i> -mephenytoin 4'-hydroxylation	rifampin (10 µM)
CYP2E1	chlorzoxazone 6-hydroxylation	isoniazid (100 µM)
CYP3A4/5	testosterone 6β-hydroxylation	rifampin (10 µM)

The results indicated that *trans*-Capsaicin did not cause an increase in the activity of any of the enzymes examined.

2.4.1.3 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The patch application area was pretreated with a topical anesthetic (4% lidocaine non-U.S. approved products) for 60-minutes, due to the pain associated with capsaicin. After 60-minutes, the applied topical anesthetic was wiped clean with a dry cloth prior to Qutenza patch application. Since the topical anesthetic was non-U.S. approved products, an internal meeting was conducted on 4/16/09 to discuss the Applicant's use of an unapproved local anesthetic product in the clinical trials. The clinical team concluded that the Applicant needs to examine the topical anesthetic pre-treatment stage using an U.S. approved local anesthetic agent to verify that the pain associated with capsaicin is adequately blocked. A teleconference was held on 5/9/09 to convey the message to the Applicant. With respect to clinical pharmacology concerns regarding this issue, it is expected that the used of non-U.S. topical anesthetic will have minimal to no impact on the systemic capsaicin exposure findings due to the fact that the topical anesthetic is wiped clean prior to Qutenza patch application and interaction between lidocaine and capsaicin is not likely to occur.

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The pivotal Phase 3 studies were conducted with the final formulation or to-be-marketed formulation.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations? Which metabolites have been selected for analysis?

Capsaicin and metabolites, 16-hydroxy-capsaicin, 16,17-dehydro-capsaicin and 17-hydroxy-capsaicin, in human plasma with K3EDTA by HPLC System with subsequent analysis using tandem mass spectrometric detection (MS/MS). The internal standard used was (b) (4) Study C102, an early Phase 2 study, employed HPLC with fluorescence detection with a lower limit of quantitation (LLOQ) of 2.5 ng/mL. Only capsaicin levels were determined in this study. For other studies, capsaicin and its metabolites were assayed. Both capsaicin and metabolites LLOQs were 0.5 ng/mL.

2.6.2 What is the range of the standard curve? What curve fitting techniques are used?

Results were calculated using peak area ratios and calibration curves were generated using a weighted (1/x) linear least-squares regression.

2.6.3 What are the lower and upper limits of quantification? What is the accuracy, precision and selectivity at these limits? What is the QC sample plan? What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

The lower limit of quantitation (LLOQ) for Capsaicin, M1, M2, and M3 in human plasma was 0.500 ng/mL, with linearity up to 50.0 ng/mL (upper limit of quantitation, ULOQ), using a sample volume of 0.100 mL. The results from the quality control samples were acceptable. Typical assay information is presented below.

Analysis Group	Theoretical Concentration (ng/mL)							
	0.500	1.00	2.50	5.00	10.0	25.0	40.0	50.0
001	0.437	0.994	2.52	5.49	10.5	24.7	40.9	48.5
002	0.472	1.02	2.42	5.24	10.3	25.0	39.8	49.8
005	0.425	1.01	2.55	5.32	10.6	25.8	40.5	47.8
n	3	3	3	3	3	3	3	3
Mean	0.445	1.01	2.50	5.35	10.5	25.2	40.4	48.7
SD	0.0244	0.0131	0.0681	0.128	0.153	0.569	0.557	1.01
RSD (%)	5.5	1.3	2.7	2.4	1.5	2.3	1.4	2.1
Accuracy (%)	89.0	101.0	100.0	107.0	105.0	100.8	101.0	97.4

Quality Control Sample Data for Capsaicin in Human Plasma						
Analysis Group	Theoretical Concentration (ng/mL)					
	2.00	DEV (%)	20.0	DEV (%)	35.0	DEV (%)
001	2.12	6.0	19.7	-1.5	35.5	1.4
	2.05	2.5	19.9	-0.5	34.7	-0.9
	2.08	4.0	20.2	1.0	34.8	-0.6
	2.05	2.5	20.0	0.0	34.6	-1.1
	1.99	-0.5	19.9	-0.5	35.4	1.1
	2.12	6.0	20.1	0.5	35.2	0.6
n	6		6		6	
Within-Group Mean	2.07		20.0		35.0	
SD	0.0496		0.175		0.383	
RSD (%)	2.4		0.9		1.1	
Accuracy (%)	103.5		100.0		100.0	
002	2.05	2.5	19.5	-2.5	35.0	0.0
	2.10	5.0	19.5	-2.5	34.9	-0.3
	2.20	10.0	19.9	-0.5	34.9	-0.3
	2.05	2.5	20.2	1.0	33.5	-4.3
	2.04	2.0	20.1	0.5	35.6	1.7
	2.05	2.5	19.3	-3.5	34.7	-0.9
n	6		6		6	
Within-Group Mean	2.08		19.8		34.8	
SD	0.0618		0.367		0.692	
RSD (%)	3.0		1.9		2.0	
Accuracy (%)	104.0		99.0		99.4	
005	1.95	-2.5	20.2	1.0	34.7	-0.9
	1.97	-1.5	19.2	-4.0	35.5	1.4
	2.00	0.0	20.1	0.5	36.7	4.9
	2.11	5.5	21.0	5.0	36.4	4.0
	2.06	3.0	20.9	4.5	36.1	3.1
	2.10	5.0	20.8	4.0	36.1	3.1
n	6		6		6	
Within-Group Mean	2.03		20.4		35.9	
SD	0.0679		0.683		0.717	
RSD (%)	3.3		3.3		2.0	
Accuracy (%)	101.5		102.0		102.6	
n	18		18		18	
Overall Mean	2.06		20.0		35.2	
SD	0.0606		0.505		0.769	
RSD (%)	2.9		2.5		2.2	
Accuracy (%)	103.0		100.0		100.6	

Short-Term Matrix Stability Data for Capsaicin in Human Plasma				
Analysis Group	Theoretical Concentration (ng/mL)			
	2.00	DEV (%)	35.0	DEV (%)
<u>Three Freeze/Thaw Cycles</u>				
005	1.97	-1.5	33.6	-4.0
	2.01	0.5	35.9	2.6
	2.08	4.0	36.3	3.7
	2.05	2.5	36.4	4.0
	2.11	5.5	35.3	0.9
	2.10	5.0	36.3	3.7
n	6		6	
Mean	2.05		35.6	
SD	0.0547		1.08	
RSD (%)	2.7		3.0	
Accuracy (%)	102.5		101.7	
<u>24 Hours at Room Temperature</u>				
005	2.00	0.0	34.2	-2.3
	1.90	-5.0	34.9	-0.3
	2.08	4.0	36.1	3.1
	2.04	2.0	34.3	-2.0
	2.05	2.5	35.1	0.3
	2.06	3.0	35.6	1.7
n	6		6	
Mean	2.02		35.0	
SD	0.0652		0.737	
RSD (%)	3.2		2.1	
Accuracy (%)	101.0		100.0	

Processed-Sample Viability Data for Capsaicin in Human Plasma Stored Refrigerated (2 to 8°C) for 72 Hours		
Theoretical Concentration (ng/mL)	Calculated Concentration (ng/mL)	DEV (%)
<u>Calibration Standards</u>		
0.500	0.456	-8.8
1.00	1.03	3.0
2.50	2.42	-3.2
5.00	5.20	4.0
10.0	10.2	2.0
25.0	26.7	6.8
40.0	40.3	0.7
50.0	47.6	-4.8
<u>Quality Control Samples</u>		
2.00	2.08	4.0
	2.07	3.5
	2.08	4.0
	2.07	3.5
	2.04	2.0
	2.09	4.5
Mean Accuracy (%)	2.07 103.5	
20.0	19.2	-4.0
	20.0	0.0
	19.6	-2.0
	20.5	2.5
	19.4	-3.0
	20.5	2.5
Mean Accuracy (%)	19.9 99.5	
35.0	36.7	4.9
	36.2	3.4
	36.1	3.1
	32.6	-6.9
	33.4	-4.6
	34.7	-0.9
Mean Accuracy (%)	35.0 100.0	
Extraction Date:	14-Jun-05	
Analysis Date:	17-Jun-05	
Slope:	5.69E-02	
y-Intercept:	1.78E-03	
Correlation Coefficient:	0.9989	

3 Detailed Labeling Recommendations

Delete the following paragraphs. The main reason for this recommendation is that the sampling time-points are not optimal.

12.1 Pharmacokinetics

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 Qutenza. The highest plasma concentration of capsaicin detected was 4.64 ng/mL and occurred immediately after Qutenza removal. Most quantifiable levels were observed at the time of Qutenza removal and were below the limit of quantitation 3 to 6 hours after Qutenza removal. No detectable levels of metabolites were observed in any subject.

15 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

4.3 Consult Review (including Pharmacometric Reviews)

Not applicable.

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-395	Brand Name	Qutenza
OCPB Division (I, II, III)	II	Generic Name	Capsaicin 8%
Medical Division	HFD-170	Drug Class	-
OCPB Reviewer	David Lee	Indication(s)	Pain
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Patch

		Dosing Regimen	Single dose
Date of Submission	10/13/08	Route of Administration	Topical
Estimated Due Date of OCPB Review	-	Sponsor	
Medical Division Due Date		Priority Classification	7S
PDUFA Due Date	8/16/09		
Clin. Pharm. and Biopharm. Information			
	“X” included if at filing	Number of studies submitted	Number of studies reviewed
STUDY TYPE			Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
I. Clinical Pharmacology			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:	x		
Plasma protein binding:	x		
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:	x	5	5
multiple dose:			
Patients-			
single dose:			
multiple dose:			
Dose proportionality -			
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:			
Drug-drug interaction studies -			
In-vivo effects on primary drug:			
In-vivo effects of primary drug:			
In-vitro:			
Subpopulation studies -			
ethnicity:			
gender:			
pediatrics:			Deferral
geriatrics:			
renal impairment:			
hepatic impairment:			
PD:			
Phase 1:			
Phase 2/3:			
PK/PD:			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
Population Analyses -	x	1	1

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		

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/s/

David Lee
7/7/2009 01:53:54 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/7/2009 03:06:16 PM
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