EMA/252892/2012
Committee for Medicinal Products for Human Use (CHMP)

2nd CHMP request for supplementary information to be addressed by the MAH in writing and in an oral explanation

Qutenza

capsaicin

Procedure No.: EMEA/H/C/000909/II/0020

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. RECOMMENDATION

Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/00909/II/020 for Qutenza (Capsaicin) 179 mg cutaneous patch, currently indicated in 'for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.' to extend the indication to include 'the treatment of peripheral neuropathic pain in adults excluding pain arising from diabetic neuropathy' is not approvable since major objections are identified, which precludes a recommendation for extending the indication of Qutenza. The details of the major objections are provided in the list of questions.

Proposal for Questions to be posed to additional Experts

N/A

Proposal for Inspection

N/A

2. Executive summary

2.1 Scope of the variation

In May 2009 the European Commission granted the marketing authorisation for Qutenza cutaneous patch (NGX-4010 patch) for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal pain products.

The currently approved indication as stated in the section 4.1 (Therapeutic indications) of the Summary of Product Characteristics is:

"Qutenza is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain."

The MAH proposed to change the indication as follows:

"Qutenza is indicated for the treatment of peripheral neuropathic pain in adults, excluding pain arising from diabetic neuropathy, either alone or in combination with other pain medications."

2.2 General comments on the submitted dossier

This extension of indication is based on a post-hoc analysis of the efficacy of the NGX-4010 patch, by diabetic status. No new studies have been submitted.

3. Scientific discussion

3.1. Introduction

About the product

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide; 6- onenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl] -8-methyl-, (6E)) is the active pharmaceutical ingredient of Qutenza patch. Qutenza is contains high concentration of purified drug in the patch (8% w/w).

Capsaicin is a selective agonist for the transient receptor potential vanilloid 1 receptor (TR PV1). The Transient Receptor Potential Vanilloid 1 receptors (TRPV1), which are located in the skin, are ligand-gated, non-selective cation channels preferentially expressed on small diameter sensory neurons, especially nociceptors that specialise in the detection of painful or noxious sensations. Qutenza (capsaicin) is a selective agonist for TRPV1 promoting the 'desensitisation' or 'defunctionalisation' of the cutaneous nociceptors that become less sensitive to a variety of stimuli, including further capsaicin exposure or thermal stimuli. Sensation from non TR PV1-expressing cutaneous nerves is expected to remain unaltered, including the ability to detect mechanical and vibratory stimuli. Capsaicin induced alterations in cutaneous nociceptors are reversible and it has been reported and observed that normal function (the detection of noxious sensations) returns within weeks in healthy volunteers.

Information on Paediatric requirements

With respect to the Regulation (EC) No 1901/2006, this application does not fall within the scope of Article 8 since Qutenza is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent.

3.2. Clinical aspects

3.2.1. Introduction

- Tabular overview of clinical studies

This extension of indication application is based on the re-analysis of the data originally submitted for the marketing authorisation application using 2 subsets of patients, namely those with and those without diabetes.

The aims of the application for extension of indication was to analyse the benefits and risks of using the NGX-4010 patch in the indicated population with co-morbid diabetes (excluding PDPN patients, that is patients in which the diabetic pain is caused by diabetic neuropathy) by means of a post-hoc analysis of the studies previously submitted to support the product Marketing Authorisation.

The subsets of patients with diabetes mellitus were identified as those that had the following words in their medical history: diabetes (diabitis, diabites, diabetis), diabetic (diabitec), IDDM, NIDDM, DM, DIAB, high blood sugar, high sugar, hyperglycemia (hyperglycaemia). Patients with the following terms in their medical history were excluded: PDPN, DN, or DPN.

In the initial MA application, the efficacy and safety of NGX-4010 in patients with peripheral neuropathic pain were determined from 12 clinical studies comprising controlled, open-label, and open-label extension studies in patients with PHN, HIV-AN, and PDPN. The current extension of indication

application considers data from only 6 of these 12 studies in the post-hoc efficacy analysis, while data from all 12 studies have been used in the abbreviated safety analysis.

Table 1. Studies in the NGX-4010 clinical development program.

Study No.	Study Phase	Study Design	Study Title	Indication	Abbreviated Analysis
Studies included in the Abbreviated Analysis Prepared for this Addendum					
C102	2	Controlled, with an open-label portion	A double-blind controlled pilot study of high-concentration capsaicin patches in the treatment of pain associated with postherpetic neuralgia	PHN	Safety
C108	2/3	Controlled, with an open-label extension	A randomized, double-blind, controlled dose-finding study of NGX-4010 the treatment of postherpetic neuralgia	PHN	Efficacy and Safety
C110	2/3	Controlled	A randomized, double-blind, controlled study of NGX-4010 the treatment of postherpetic neuralgia	PHN	Efficacy and Safety
C116	3	Controlled	A randomized, double-blind, controlled study of NGX-4010 the treatment of postherpetic neuralgia	PHN	Efficacy and Safety
C117	3	Controlled	A multicenter randomized, double-blind, controlled study of NGX-4010 the treatment of postherpetic neuralgia	PHN	Efficacy and Safety
C107	2/3	Controlled, with an open-label extension	A randomized, double-blind, controlled dose finding study of NGX-4010 for the treatment of painful HIV-associated distal symmetrical polyneuropathy	HIV-AN	Efficacy and Safety
C112	3	Controlled	A multicenter, randomized, double-blind, 12-week controlled study of NGX-4010 for the treatment of painful HIV-associated neuropathy.	HIV-AN	Safety
C119	3	Controlled	A multicenter, randomized, double-blind, controlled study of NGX-4010 for the treatment of painful HIV-associated neuropathy.	HIV-AN	Efficacy and Safety
C109	2	Open-label	An open-label pilot study of high-concentration capsaicin patches in the treatment of painful HIV-associated neuropathy	HIV-AN	Safety
C111	2	Open-label	A randomized, open-label study of the tolerability of three local anesthetic formulations in conjunction with NGX-4010 for the treatment of neuropathic pain	PHN HIV-AN PDPN	Safety
C106	2	Open-label extension (of C102)	An open-label, extension study of high-dose concentration capsaicin patches for the treatment of postherpetic neuralgia	PHN	Safety
C118	2	Open-label extension	A multicenter, open-label, phase 2 study of NGX-4010 for the treatment of neuropathic pain in patients with painful HIV-associated neuropathy (HIV-AN) or postherpetic neuralgia (PHN)	PHN HIV-AN	Safety

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

3.2.2. Clinical efficacy

Introduction

As no new studies were submitted with this application, for full details of the individual studies, reference is made to the EPAR of Qutenza. In this assessment report, the post-hoc analysis performed across these trials is discussed.

Analysis performed across trials

The efficacy analysis is based on the data from 6 double-blind, randomised controlled studies conducted in PHN and HIV-AN patients (Table 2). The data have been integrated into two sets based on the indication.

1. Integrated data from 4 studies in patients with PHN (C108, C110, C116, and C117).

2. Integrated data from 2 studies in patients with HIV-AN (C107 and C119).

All the controlled studies in this post-hoc efficacy analysis evaluated the effect of a single 30-, 60- or 90- minute treatment with NGX-4010 over a 12-week period.

Table 2. Patient populations included in the Post-hoc efficacy analysis.

	Number of Patients by Indication and Treatment							
	PHN				HIV-AN			
Populations used in the post-hoc analysis	C108, C110, C116, C117				C107 and C119			
	Diabetic		Non-diabetic		Diabetic		Non-diabetic	
	NGX	Control	NGX	Control	NGX	Control	NGX	Control
Pooled data	88	70	654	460	44	19	513	225
	N = 1272				N = 801			
60-minute data only	69	66	528	416	NA	NA	NA	NA
	N = 1079				-			
30-minute data only	NA	NA	NA	NA	23	6	216	94
	-				N = 339			

Methods

The overall designs of the controlled studies were similar: they were all randomised, double-blind, controlled, 12-week, multicenter studies, in which participating patients were aged 18 years or older and had a diagnosis of neuropathic pain associated with PHN or HIV-AN.

Randomisation ratio and duration of patch application differed by study. The different durations of patch application had implications on the integrated efficacy analysis. The implications of the length of the study assessment periods, the level of pain at baseline and the duration of pain at baseline are all fully explored in the original submission.

Six controlled studies were chosen for post-hoc efficacy analysis because, by nature of their design, they provided the most robust data. In addition, they were all similar in study methodology, shared the same efficacy endpoints and did not enrol PDPN patients. Thus, the 6 controlled studies are focused entirely on the indications of interest, namely PHN or HIV-AN patients who also have diabetes.

Study Participants and treatments

Overview of the 4 studies in PNH Patients

PHN was the therapeutic population in all 4 studies. A total of 1272 patients were enrolled in the 4 studies, of whom 742 (58%) received NGX-4010 (88 diabetic and 654 non-diabetic patients) (Table 2). In the post-hoc efficacy analysis, the 30-, 60- and 90-minute data were pooled in order to have a reasonably sized population.

However, as a 60-minute patch duration is the approved length of application in PHN patients (Qutenza Summary of Product Characteristics [SmPC]), a post-hoc analysis was performed on the 60-minute data only; in this subset of 1079 patients, 597 (55%) received NGX-4010 (69 diabetic and 528 non-diabetic patients).

Overview of the 2 Studies in HIV-AN Patients

HIV-AN was the therapeutic population evaluated in both studies. A total of 801 patients were enrolled, of whom 557 (70%) were treated with NGX-4010 (44 diabetics and 513 non-diabetics) (Table 2). In the post-hoc efficacy analysis, the 30-, 60- and 90-minute data were pooled in order to have a reasonably sized population.

However, as a 30-minute patch duration is the approved length of application in HIV-AN patients (SmPC), a post-hoc analysis was performed on the 30-minute data only; in this subset of 339 patients, 239 (71%) received NGX-4010 (23 diabetic and 216 non-diabetic patients).

A low-concentration capsaicin (3.2 mcg/cm^2; 0.04% w/w) patch was used as the control in the efficacy studies.

Baseline data

The demographics and baseline characteristics were not analysed separately for the 6 studies included in this abbreviated efficacy analysis. However, in the 8 Controlled studies (i.e., data from C102 and C112 were also included), there were no differences between the diabetic and non-diabetic populations or between them and their respective controls for most demographic and baseline characteristics.

Mean Baseline NPRS scores were similar regardless of indication, diabetic status or treatment received. They ranged from 5.6 to 6.2, reflective of a population with moderate pain.

Although the duration of pain was similar between diabetics and non-diabetics and between active and Control group status, it did differ by indication. Thus, while the duration of pain in PHN patients ranged from 3.1 and 3.6 years, it was longer and ranged from 5.6 to 6.9 years in HIV-AN.

Outcomes/endpoints

The primary efficacy endpoint used throughout the NGX-4010 clinical development program was the percent change from Baseline to weeks 2 to 8 (PHN studies) and weeks 2 to 12 (HIV AN studies) in "average pain for the last 24 hours" Numeric Pain Rating Scale (NPRS) scores. The NPRS is a uni-dimensional, 11-point scale (0 to 10), with 0 indicating no pain and 10 indicating worst possible pain. Patients used this scale to rate "pain now", "worst pain", and/or "average pain for the past 24 hours" for their painful area(s).

The secondary endpoints used in the NGX-4010 clinical development program and included in this post-hoc efficacy analysis were:

● Changes from Baseline to weeks 2 to 8 (PHN studies) and weeks 2 to 12 (HIV AN studies) in NPRS scores at multiple time points;

● The percentage of subjects who met the "responder" definition (a mean percent decrease of ≥ 30% from Baseline to weeks 2 to 8 [PHN studies] and weeks 2 to 12 [HIV AN studies] NPRS scores);

● Cumulative distribution of the percent change in NPRS scores from Baseline to weeks 2 to 8 [PHN studies] and weeks 2 to 12 [PHN and HIV AN studies] NPRS scores);

● The Patient Global Impression of Change (PGIC) at week 8 (PHN studies only) and week 12 (PHN and HIV-AN studies).

Statistical methods

All analyses were based on the ITT population. The ITT population included all randomised patients who received any study patch application and had at least 3 days of non-missing, "average pain for the past 24 hours" NPRS scores for the calculation of baseline average score. For all the efficacy analyses, for both the PHN and the HIV-AN populations, the patient data were summarised under the randomised treatment.

Data have been presented for the "pooled" treatment groups, (i.e., 30-, 60- and 90-minute data) for NGX-4010 and Control groups. In addition, the 60-minute (PHN studies) and 30-minute (HIV-AN studies) application data were analysed separately, as these are the approved application times for NGX-4010 in PHN and HIV-AN patients, respectively.

Results (comparison of results in subpopulations)

Participants flow

In the studies, a very low percentage of patients received repeated exposure. This is discussed more in depth in the safety section.

Outcomes and estimation

Studies in PHN patients

Primary efficacy endpoint: change in NPRS from baseline to week 2 to 8 (see Table 3)

Table 3. Integrated efficacy analysis of change in the NPRS scores from baseline to Weeks 2 to 8 in the diabetic and non-diabetic patients (PHN).

	Diabetic Patients		Non-diabetic Patients	
	NGX-4010	Control	NGX-4010	Control
	n=88	n=70	n=654	n=460
n	88	70	654	460
Baseline mean (SE)	6.2 (0.2)	6.1 (0.2)	5.6 (0.1)	5.6 (0.1)
Change LS mean (SE)	-1.6 (0.2)	-1.4 (0.2)	-1.6 (0.1)	-1.2 (0.1)
95% CI	-2.0, -1.2	-1.9, -1.0	-1.8, -1.5	-1.4, -1.1
% Change LS mean (SE)	-28.3 (3.3)	-22.4 (3.7)	-30.6 (1.2)	-22.3 (1.5)
95% CI	-34.8, -21.8	-29.7, -15.1	-33.0, -28.2	-25.2, -19.5

LS=least squares; NPRS=Numeric Pain Rating Scale

NOTES:

1. 30-, 60- and 90-minute NGX-4010 and Control groups are used in this analysis
2. Control = capsaicin 3.2 mcg/m^2; NGX-4010 = capsaicin 640 mcg/m^2. Patients are summarized under randomized treatment.
3. For studies C108 and C110 Baseline pain level is defined as the mean of all available nonbiased screening NPRS scores in that category. For C116 and C117, Baseline pain level is defined as the mean of all available Screening NPRS scores from day -14 to day -1.
4. If NPRS scores are missing on any of days 0 to 8 and $\geq$ 1 consecutive day, or if all posttreatment NPRS scores are missing, then Baseline score is used for imputation. If NPRS score is missing after day 8, the previous non-missing score is used for imputation.

The data were combined from diabetic patients in 4 studies (108, 110, 116 and 117). In the pooled data analysis a single treatment with NGX-4010 resulted in a 28.3% and a 30.6% decrease in NPRS scores from baseline to weeks 2 to 8 in diabetic and non-diabetic patients respectively. The decreases in NPRS scores in diabetic and non-diabetic control groups were 22.4% and 22.3% respectively (table 3). NGX-4010 was equally efficacious in diabetic patients and in non-diabetic patients in respect of reducing peripheral neuropathic pain.

Similar results to those obtained for primary endpoints were also seen for secondary efficacy endpoints in PNH patients:

• Changes in NPRS from Baseline to week 2 to week 12: a single treatment with NGX-4010 resulted in a 28.1% and 30.3% decrease in NPRS scores (i.e., average pain in the past 24 hours) from Baseline to weeks 2 to 12, for the diabetic and non-diabetic patients, respectively. For both populations, the changes in the control groups were 23.9% and 22.4%, for diabetic and non-diabetic patients, respectively.

• Analysing the combined data from the 60 min treatment group only a single 60 min treatment with the product resulted in 28.6% (n=69) and 31.7% (n=528) decrease in NPRS scores from baseline to weeks 2 to 8 in diabetic and non-diabetic patients, respectively. The change in the score of control groups were 24.4% (n=66) and 23.9% (n=416) for diabetic and non-diabetic control groups respectively.

• NPRS responders: among the diabetic population, the proportion of NGX-4010-treated patients considered responders to treatment, during weeks 2 to 8 and during weeks 2 to 12, was 39% at both endpoints. Among the non-diabetic patients, 43% and 44% of NGX-4010-treated patients were considered responders, respectively. In both populations, the proportions of responders during weeks 2 to 12 were slightly improved to those during weeks 2 to 8, indicating that the treatment response was maintained through the 12 weeks of the studies. For both populations, the proportion of responders in the control treated groups during weeks 2 to 8 and during weeks 2 to 12 was 34% and 36%, respectively in the diabetic group, and 34% and 35%, respectively, in the non-diabetic control groups

• Cumulative response: the proportion of patients reporting decrease in pain was similar in the diabetic and non-diabetic patients treated with NGX-4010 at most levels of cumulative response.

• Patient's Global Impression of Change: in the diabetic and non-diabetic populations treated with the NGX-4010 patch, 69% and 59% patients, respectively at week 8, and 64% and 58%, respectively at week 12, felt improved (very much, much, or slightly).

Studies in HIV-AN patients

Primary efficacy endpoint – change in NPRS from baseline to week to 12 (see Table 4).

A single treatment with NGX-4010 (90, 60 or 30 min duration of treatment) resulted in 34.7% and 26.1% decrease in NPRS scores from baseline to weeks 2 to 12 in diabetics and non-diabetics respectively. The decrease in control groups were 21.8% and 19.8% for diabetic and non-diabetic control groups, respectively.

Table 4: Integrated efficacy analysis of change in NPRS scores from baseline to weeks 2 to 12, in the diabetic and non-diabetic populations (HIV-AN patients).

	Diabetic Patients					Non-diabetic Patients				
	NGX-4010				Control	NGX-4010				CONTROL
	Total	90 mins	60 mins	30 mins	Total	Total	90 mins	60 mins	30 mins	Total
	n=44	n=1	n=20	n=23	n=19	n=513	n=74	n=223	n=216	n=225
Baseline mean (SE)	6.2 (0.2)	9.6 (N/A)	6.3 (0.3)	5.9 (0.3)	5.8 (0.4)	6.0 (0.1)	6.0 (0.2)	6.0 (0.1)	6.0 (0.1)	5.9 (0.1)
Change LS mean (SE)	-2.1 (0.3)	-0.5 (2.4)	-2.3 (0.5)	-2.0 (0.5)	-1.4 (0.5)	-1.5 (0.1)	-1.3 (0.2)	-1.6 (0.1)	-1.5 (0.1)	-1.2 (0.1)
95% CI	-2.8, -1.4	-5.2, 4.3	-3.4, -1.3	-2.9, -1.0	-2.5, -0.4	-1.7, -1.4	-1.8, -0.9	-1.8, -1.3	-1.7, -1.3	-1.4, -0.9
Treatment difference	-0.7	1.1	-0.8	-0.8	-	-0.4	-0.2	-0.2	-0.6	-
95% CI treatment difference	-1.9, 0.6	-4.2, 6.3	-2.6, 1.0	-2.9, 1.3	-	-0.6, -0.1	-1.0, 0.7	-0.6, 0.2	-1.1, -0.2	-
% Change LS mean (SE)	-34.7 (5.2)	-13.7 (37.0)	-37.3 (7.9)	-33.3 (7.6)	-21.8 (8.0)	-26.1 (1.3)	-24.5 (3.6)	-26.6 (2.0)	-25.9 (2.1)	-19.8 (2.0)
95% CI	-45.1, -24.2	-88.0, 60.6	-53.1, -21.4	-48.5, -18.1	-37.9, -5.7	-28.7, -23.5	-31.6, -17.4	-30.5, -22.6	-29.9, -21.8	-23.8, -15.9
Treatment difference	-12.9	3.9	-14.3	-10.6	-	-6.3	-4.5	-2.6	-10.7	-
95% CI treatment difference	-32.4, 6.6	-79.2, 86.9	-42.6, 14.1	-43.8, 22.6	-	-11.0, -1.5	-18.4, 9.4	-9.6, 4.4	-18.1, -3.4	-

LS=least squares; NPRS=Numeric Pain Rating Scale

NOTES:

1. 30-, 60- and 90-minute data for NGX-4010 and Control Total are pooled in this analysis
2. For C107, Baseline Pain Level is defined as the mean of all available non-biased screening NPRS scores in the category. For C119, Baseline NPRS score was the average of all NPRS scores from day -14 through to day -1.
3. Control = capsaicin 3.2 mcg/m^2; NGX-4010 = capsaicin 640 mcg/m^2. Patients are summarized under randomized treatment.
4. If NPRS scores are missing on any of days 0 to 8, or on day 8 and $\geq$ 1 consecutive day, or if all posttreatment NPRS scores are missing, then Baseline score is used for imputation. If NPRS score is missing after day 8, the previous non-missing score is used for imputation.
5. Treatment difference is the difference of the LS mean between NGX-4010 and respective Control groups using ANCOVA with Baseline pain, pre-LMX4 pain, and % change in pain during LMX4application as covariates. For 90-minute comparisons, gender is not included in the ANCOVA model.

The results obtained for the secondary endpoints were as follows:

• The NPRS responder's rate was 48% and 39% in diabetic and non-diabetic population, respectively. In the control groups the rate of responders was 42% and 29%, respectively.

• When the analysis was performed only the combined data from 30 min treatment groups the rate of responders in diabetic population (n=23) was similar to in non-diabetic population (n=216) reaching 39% and 40%, respectively. The rate of responders in the respective controls was 42% (n=19) and 29% respectively (n=225).

• In the cumulative response it was found that the proportion of patients reporting decrease in pain was higher in the diabetic than in non-diabetic patients at all levels of response. Patients who experienced worsening of their pain represented 7.0% and 18% respectively of diabetic and non-diabetic patients. Analysing the data obtained after 30 min treatment similar results were seen. The proportion of patients reporting decrease in pain was higher in diabetic than in non-diabetic patients.

Nine percent of diabetic and 19% of non-diabetic NGX-4010 treated patients experienced worsening of their pain.

● A Global Impression of Change: 76% of patients in diabetic population and 66% in the non-diabetic population felt improved. In both populations these rates were higher than seen in control patients (61% and 46% respectively). Similar results were seen when data obtained from the 30 min treatment groups only were analysed (74% in the diabetic population versus 64% in the non-diabetic population).

Discussion of clinical efficacy

Currently, Qutenza is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain. The new indication has been proposed to extend the treatment to adult patients with peripheral neuropathic pain with exclusion of patients with painful diabetic neuropathy. In support of this variation the MAH provided the post-hoc analysis of existing data from studies in PHN and HIV-AN using 2 subsets of patients, i.e. those with and without diabetes.

Combined data from the diabetic patients in PHN Studies C108, C110, C116 and C117, demonstrated that treatment with NGX-4010 was efficacious in diabetic patients and in non-diabetic patients in reducing peripheral neuropathic pain as assessed by mean change (-1.6 for both groups) and mean percent change (-28.3 for diabetic patients and -30.6 for non-diabetic patients) in NPRS scores from baseline to endpoint at 8 weeks. The 60 minute treatment with NGX-410 resulted in 28.4 % and 31.6 % decrease in NPRS scores from baseline to week 2 to week 8 in diabetic patients and in non-diabetic patients with PHN, respectively. Consistent results were observed in both primary and secondary end-points as compared with placebo.

Combined data from HIV-AN Studies C107 and C119 demonstrated that treatment with NGX-4010 was efficacious in diabetic patients and in non-diabetic patients in reducing peripheral neuropathic pain (as assessed by mean change and mean percent change in NPRS scores from baseline to endpoint at 12 weeks). Single 30 minute treatment resulted in a 33.8 % (n=23) decrease in NPRS score in diabetic patients and 26.3 % (n=216) in non-diabetic patients. Consistent results were observed in both primary and secondary end-points as compared with placebo.

The methods for evaluation of the effects used in these 4 studies were similar and the post-hoc analysis was accomplished on the 60 minute data only. In the subset of 1079 patients 597 (55 %) received NGX-4010 (69 diabetic and 528 non-diabetic patients). Due to the small number of diabetic patients versus non-diabetic patients included in the individual PHN studies no results were presented for the individual studies. The same methodology was used for the re-analysis of the HIV-AN studies.

With respect to the demographic characteristics there were no differences in diabetic and non-diabetic population.

The CHMP expressed concern that this extension of indication is not supported by any formal statistical hypothesis test. Rather the previously submitted clinical trial data were tabulated again and summary data were presented for diabetic and non-diabetic groups. In addition least-squares (LS) means, LS mean standard errors, along with 95 % confidence intervals (CI-s) were provided for each of the four treatment groups (diabetic treated, diabetic control, non-diabetic treated, non-diabetic control). The treatment groups were split further by disease modality (PNH or HIV) and trial design (controlled studies, open label extension). Finally an integrated efficacy and analysis are presented. Nevertheless,

as there is no formal hypothesis test, the argumentation accompanying the data is only narrative. This might be misleading because the efficacy results were compared only between groups based on the co-morbidity status and between control and treated groups were not considered.

The applicant argued that similar results to those seen with primary endpoints were also seen with the secondary efficacy endpoints in patients PHN patients (e.g. changes in NP RS from baseline to week 2 to week 12, percent of responders, cumulative response, Patients Global Impression of Change). However the secondary endpoint analysis yields the same controversial conclusion which is mentioned above. It is considered that the post-hoc analysis of data on efficacy of NGX-4010 (Qutenza) in patients with PNH or HIV-AN with diabetes co-morbidity compared with those obtained in non-diabetic patients may have many uncertainties even unintended biases.

The number of patients with diabetes involved in the clinical development program of NGX-4010 was very small in each group, as compared to non-diabetic patients. This situation questions the reliability of comparing such unbalanced data from both practical and statistical point of view. This analysis can only be regarded as exploratory in nature.

In the original submission diabetic status had not been identified as a covariate factor of concern that would have an impact on the efficacy of the product. This subpopulation was identified only post-hoc. Many important data are missing in the submitted dossier, e.g. the most important being the characteristics of the diabetic patients and how the patients with diabetes were identified. The applicant identified the diabetic patients based on the presence of a number of terms in the medical history: diabetes, IDDM, NIDDM, DM, high blood sugar, high sugar, and hyperglycaemia. However, aethiopathology, the diabetes treatment or state of the disease and severity of complications (CV, neurological) were not mentioned in the provided documentation. It has to be noted that the cause of hyperglycaemia, or even diabetes could also be iatrogenic, e.g. due to the use of protease inhibitors for treatment of the patients with HIV. Therefore, the CHMP requested the Applicant to explain the methodology used for the identification of diabetic patients for the post-hoc analysis, including the following points: how the diagnosis was confirmed, what type of diabetes and complications patients presented with, and which treatment was introduced. The MAH clarified that for the purpose of patients identification medical histories were reviewed for each patient. Out of 235 patients originally identified as being diabetic, 16 (6.8%) had a diagnosis of diabetes that was not adequately supported by the available data. Of those patients for whom the type of diabetes was identified the majority were characterized by type 2 diabetes. 60.3% of all diabetic patients were being treated with anti-diabetic medication on entry to the study and 5% presented with diabetic complications such as diabetic retinopathy. The CHMP considered that the MAH's response did not address the major objection satisfactorily. In particular, the Committee noted that in 16 patients the diagnosis was not confirmed, and that the type of diabetes was not specified in more that 50% of patients. Moreover, 60.3% of patients had no medication however the reasons for absence of anti-diabetic treatment were not provided.

Additionally, the Committee noted that extending the indication for Qutenza to include diabetic patients without painful diabetic neuropathy would require specific diagnostic tools allowing for differentiation between neuropathic pain of different origin. The MAH was requested to comment on feasibility of performing a differential diagnoses in the real-life setting to exclude patients with diabetic neuropathy from the treatment. In their responses the MAH acknowledged that for patients with peripheral polyneuropathy (classic stocking-glove symptom distribution, e.g. alcoholic, HIV-related, B-12 deficiency and chemotherapy) who had diabetes, there was no objective diagnostic test for determining whether the peripheral polyneuropathy was due to the diabetes or to the other disorder. In particular, the diagnostic differentiation would be difficult for HIV-AN, which like PDPN, is also a

length dependant neuropathy predominantly afflicting the feet. The situation might be slightly different for patients with focal peripheral neuropathy (e.g. PHN, post-traumatic neuropathy, carpal tunnel syndrome, etc.) and diabetes. In PHN or other peripheral neuropathic pains in regions of the body other than the feet, albeit there are no specific diagnostic tools the distinction might be easier as it would be based on anatomical grounds.. Therefore, the MAH proposed the inclusion of the warning in the SmPC section 4.4: 'Patients with diabetes should only be treated where their peripheral neuropathic pain is judged to be attributable to an aetiology other than diabetes'. The CHMP acknowledged the Applicant's responses, however difficulties in reliable differential diagnosis remain and would leave it entirely dependent on the clinical judgment.

Conclusion on the clinical efficacy

In conclusion, the CHMP believes that currently there are too many uncertainties regarding the efficacy of Qutenza in diabetic patients to approve this extension of indication, including:

- Feasiblity to perform a differential diagnoses in the real-life setting to exclude patients with diabetic neuropathy from treatment.
- whether the patients, identified as diabetic in the clinical trials indeed had diabetes (type I or type II);
- what were the characteristics of their diabetes co-morbidity.

3.2.3. Clinical safety

In support of the proposed change in the indication, the MAH has re-analysed the original safety data from the 12 clinical studies using 2 subsets of patients, namely those with and those without diabetes.

Patient exposure

A total of 2357 patients were enrolled in the 12 clinical studies comprising the "All Studies" grouping within the NGX-4010 clinical development program. Of the 2357 patients, 1696 (248 diabetics and 1448 non-diabetics) received the NGX-4010 patch and 661 the Control patch (Table 5).

Table 5: Summary of diabetic and non-diabetic study populations, number of patients by indication and treatment.

Study Grouping	Diabetic Population							
	NGX-4010				Control			
	PHN	HIV-AN	PDPN	Total	PHN	HIV-AN	PDPN	Total
All studies	107	50	91	248	66	16	0	82†
Controlled studies	90	44	0	134	72	19	0	91
Open-label extension studies	39	16	0	55	0	0	0	0
	Non-diabetic Population							
All studies	813	635	0	1448	409	170	0	579†
Controlled studies	677	516	0	1193	471	227	0	698
Open-label extension studies	331	321	0	652	0	0	0	0

HIV-AN=Human Immunodeficiency Virus-Associated Neuropathy; PDPN=painful diabetic peripheral neuropathy; PHN=postherpetic neuralgia.

The studies included in each of the 4 study groupings were as follows:
All Studies: C102, C106, C107, C108, C109, C110, C111, C112, C116, C117, C118, and C119
Controlled Studies: C102 (double-blind portion), C107 (double-blind portion), C108 (double-blind portion), C110, C112, C116, C117, and C119
Open-label extension studies: C106, C107 (open-label portion), C108 (open-label portion) and C118

† Patients in extension studies (C106, C107, C108) who first received control and subsequently received active treatment are counted under NGX-4010. The control group only contains patients that never received NGX-4010; this explains why the number of patients in the PHN, HIV-AN and Total groupings in the 'All studies" Control category are smaller than their totals in the Control 'Controlled' studies categories.

The extent of exposure for patients with and without diabetes participating in the 12 studies is summarised by indication, treatment duration and number of treatments in Table 6 and Table 7, respectively.

Table 6. Exposure by indication and treatment duration, diabetic population.

Patients, n (%)	PHN (n=107)	HIV-AN (n=50)	PDPN (n=91)	Total (n=248)
NGX-4010				
Duration (of the first active treatment) †				
90 minutes	14 (13)	2 (4)	47 (52)	63 (25)
60 minutes	85 (79)	25 (50)	44 (48)	154 (62)
30 minutes	8 (8)	23 (46)	0	31 (13)
Area (cm^2)				
Area ≤ 250 cm^2	33 (31)	0	0	33 (13)
Area > 250 cm^2 and ≤ 500 cm^2	38 (36)	5 (10)	1 (1)	44 (18)
Area > 500 cm^2 and ≤ 750 cm^2	25 (23)	10 (20)	11 (12)	46 (19)
Area > 750 cm^2	11 (10)	35 (70)	79 (87)	125 (50)
Number of Treatments				
One treatment	88 (82)	42 (84)	91 (100)	221 (89)
Two treatments	6 (6)	4 (8)	0	10 (4)
Three treatments	8 (8)	1 (2)	0	9 (4)
Four treatments	5 (5)	3 (6)	0	8 (3)
Total Number of Patients	107	50	91	248
Total Number of Treatments ‡	144	65	91	300

DB=double-blind; OL=open-label.

NOTES:

1. Patients in extension studies (C106, C107, C108) who first received Control and subsequently received active are counted under NGX-4010.
2. PHN data were derived from Studies C102, C106, C108 (DB and OL portions), C110, C111 (PHN patients), C116, C117, and C118 (PHN patients). For Study C106, the number of exposures in previous trials is included.
3. HIV-AN data were derived from Studies C107 (DB and OL portions), C109, C111 (HIV-AN patients), C112, C118 (HIV-AN patients), and C119.
4. PDPN data were derived from Study C111 (PDPN patients).

† Treatment durations are for the first active treatment.

‡ The number of NGX-4010 treatments were calculated by adding the number of patients multiplied by the number of treatments received (e.g., [221 x 1] + [10 x 2] + [9 x 3] + [8 x 4] for the total number of treatments).

Table 7. Exposure by indication and treatment duration, non-diabetic population.

Patients, n (%)	PHN (n=813)†	HIV-AN (n=635)	PDPN (n=0)	Total (n=1448)‡
NGX-4010				
Duration (of the first active treatment) §				
90 minutes	71 (9)	105 (17)	0	176 (12)
60 minutes	678 (83)	314 (49)	0	992 (69)
30 minutes	64 (8)	216 (34)	0	280 (19)
Area (cm^2) †				
Area ≤ 250 cm^2	349 (43)	7 (1)	0	356 (25)
Area > 250 cm^2 and ≤ 500 cm^2	281 (35)	37 (6)	0	318 (22)
Area > 500 cm^2 and ≤ 750 cm^2	126 (16)	92 (15)	0	218 (15)
Area > 750 cm^2	56 (7)	499 (79)	0	555 (38)
Number of Treatments				
One treatment	603 (74)	443 (70)	0	1046 (72)
Two treatments	94 (12)	72 (11)	0	166 (12)
Three treatments	77 (10)	74 (12)	0	151 (10)
Four treatments	39 (5)	46 (7)	0	85 (6)
Total Number of Patients	812	635	0	1447‡
Total Number of Treatments ¶	1178	993	0	2171

DB=double-blind; OL=open-label.

NOTES:

1. Patients in extension studies (C106, C107, C108) who first received Control and subsequently received active are counted under NGX-4010.
2. PHN data were derived from Studies C102, C106, C108 (DB and OL portions), C110, C111 (PHN patients), C116, C117, and C118 (PHN patients). For Study C106, the number of exposures in previous trials is included.
3. HIV-AN data were derived from Studies C107 (DB and OL portions), C109, C111 (HIV-AN patients), C112, C118 (HIV-AN patients), and C119.
4. PDPN data were derived from Study C111 (PDPN patients).

† PHN patients: n = 812 for Treatment area of first active treatment in PHN population, as 1 patient had missing baseline treatment area data.

‡ One non-diabetic PHN subject had missing baseline treatment area data. Thus, whilst some of the exposure tables that deal with treatment area data give the non-diabetic population as 1447, all the other summary tables show the non-diabetic population as 1448.

§ Treatment durations are for the first active treatment

¶ The number of NGX-4010 treatments were calculated by adding the number of patients multiplied by the number of treatments received (e.g., [221 x 1] + [10 x 2] + [9 x 3] + [8 x 4] for the total number of treatments).

Of the 248 study patients with diabetes who received NGX-4010 treatment, the safety analyses have focused on the 157 patients that had either PHN (n = 107) or HIV-AN (n = 50) (i.e., the 91 patients with PDPN have been excluded). Of these, 134 received NGX-4010 treatment in controlled studies (90 PHN patients; 44 HIV-AN patients) and 55 received NGX-4010 treatment in open-label extension studies (39 PHN patients; 16 HIV-AN patients), 27 of whom received more than one NGX-4010 treatment.

All the patients exposed to NGX-4010 in the clinical trials were exposed to the patch at the recommended dose (640 mcg/cm^2). In almost all studies, the patch application was for the recommended length of time as stated in the SmPC. The exceptions were C108 (30- and 90-minute durations were used in PHN patients, in addition to 60 minutes), C119 (60-minute duration was used in HIV-AN patients, in addition to 30-minutes) and C111 (60- and 90-minute applications were used in PHN, HIV-AN and PDPN patients). Overall, exposure to NGX-4010 was comparable between the 2 populations of interest. In the open-label extension studies, re-treatments were at least 12 weeks apart, as recommended in the SmPC.

Patient population

With respect to age, male/female ratio, race, ethnicity, and duration of pain and use of concomitant medication, there were no fundamental differences between the diabetic and non-diabetic populations or between them and their respective controls. In both populations the majority of patients (65%) were male, mostly due to a predominance of males in the HIV-AN population.

The mean age of diabetic patients treated with NGX-4010 was 63 years (range, 33 to 89) and of non-diabetic patients was 61 years (range, 21 to 94). In the diabetic population treated with NGX-4010, 111/248 (45%) patients were aged 65 years or over and 49/248 (20%) were aged 75 years or over. The corresponding numbers in the non-diabetic population were 636/1448 (44%) and 348/1448 (24%), respectively.

Adverse events

The analysis of the AE's focuses on two "study groupings":

- Controlled Studies: Studies C102 (double blind portion only), C107 (double blind portion only), C108 (double blind portion only), C110, C112, C116, C117 and C119.
- Open-label Extension Studies: Studies C106, C107, C108 and C118.

Data from the open-label studies were not integrated for the analyses of AEs.

Frequently Reported Adverse Events

In the diabetic and non-diabetic populations NGX-4010 treatment was frequently associated with transient, capsaicin-related application site AEs including erythema, pain, pruritus, oedema, dryness and papules. The SmPC lists application site pain and application site erythema as 'very common' (i.e., occurring in ≥ 1/10 patients), and application site pruritus, application site papules, application site vesicles, application site edema, application site swelling, application site dryness as common (i.e., occurring in ≥ 1/100 and < 1/10 patients).

For all comparisons, there were no apparent differences between the diabetic and non-diabetic patients.

Controlled studies

In the controlled studies, the overall incidence of treatment-emergent AEs reported across all indications in the total NGX-4010 group was similar in the diabetic and non-diabetic populations (83% and 84% patients, respectively). The incidence in both cases was slightly higher compared with the respective total Control group (75% and 78%, respectively), primarily due to the higher incidence of application site AEs among patients in the NGX-4010 groups (69% in both populations) compared with the Control group (58% in both populations). The most frequently reported application site AEs, in both the diabetic and non-diabetic populations, were application site pain and application site erythema. The incidence of application site pain was higher in the NGX-4010 groups (diabetic and non-diabetic, 41% and 46%, respectively) compared with the Control groups (19% and 23%, respectively) and the incidence of application site erythema was similar between the NGX-4010 groups (46% and 43%) and the Control groups (47% and 41%, respectively).

Open-label extension studies

Patients who received multiple treatments were more likely to be in a study longer than patients who received only 1 treatment and, thus, had more opportunity to experience AEs. Therefore, an analysis

of most frequently reported treatment-emergent AEs (>3% patients in any group) with an onset date within 12 weeks of treatment was performed in the open-label extension studies. In the diabetic population, the overall incidences of treatment-emergent AEs following a second, third, and fourth exposures did not increase relative to the first exposure with NGX-4010 (first [56%], second [63%], third [53%], fourth [63%] NGX-4010 treatment). Similar findings were reported for the non-diabetic population in the open-label extension studies. Thus, the overall incidences of treatment-emergent AEs following a second, third, and fourth exposures did not increase relative to the first exposure with NGX-4010 (first [67%], second [54%], third [61%], fourth [61%] NGX-4010 treatment for diabetic and non-diabetic patients, respectively.

The incidence of treatment related AE's present in more than 1% of patients in any group following 4th exposure increased slightly relative to the 1st, 2nd and 3rd exposure to the NGX-4010 in the diabetic patients (1st 27%, 2nd 30%, 3rd 30%, 4th 38%). The same slight increase could be seen in the non-diabetic population in the open label extension study.

The MAH argued that it should be noted that this apparent increase was related to the change in how information on pain and erythema was collected over time and the relative shift in proportion of subjects from early to later studies with increasing number of treatments and treatment related application site AEs.

With respect to the treatment-related AEs in the open-label studies, the incidence was similar in the diabetic and non-diabetic populations. Furthermore, in both populations, the most frequently reported treatment-related AEs across all indications were application site pain and application site erythema.

Serious adverse events and deaths

Deaths

In the clinical development program for NGX-4010, 9 patients died while in the study. One patient was a diabetic patient. All 9 patients were enrolled in the Controlled studies, as follows: 6 HIV-AN patients from Study C107, 1 HIV-AN patient from Study C119, 1 PHN patient from Study C108 and 1 PHN patient from Study C117. None of these deaths was considered by the investigator to be related to the study medication.

Other serious AEs

Controlled studies

In the diabetic and non-diabetic populations the overall incidence of SAEs was low in both the total NGX-4010 groups (11/134 patients, 8% and 67/1193 patients, 6%, respectively) and the Control groups (4/91 patients and 30/698 patients, respectively; 4% of both populations).

Within the diabetic NGX-4010 group, only myocardial infarction was reported in at least 1% of patients (3 patients, 2.2%). In the Control group, non-cardiac chest pain, medical device complication, asthma and chronic obstructive pulmonary disease were all reported in at least 1% of patients (each 1 patient, 1%). No event was reported in more than 1 patient in the Control group.

In the non-diabetic population no SAE was reported in ≥ 1% patients in either the NGX-4010 or the Control groups. In the non-diabetic population, myocardial infarction was reported in 2/1193 (0.2%) NGX-4010-treated patients and 2/698 (0.3%) Control patients. One non-diabetic PHN patient enrolled in C117 and treated with NGX-4010, experienced 2 cardiac SAEs, myocardial infarction and atrial fibrillation. The Investigator judged both events as unrelated to study medication.

All SAEs (including 7 myocardial infarction events) were considered to be unrelated to study medication with one exception. This was an SAE of increased blood pressure in a non-diabetic PHN patient in Study C116 that was considered probably related to the study medication by the Investigator.

Open-label extension studies

The incidence of other SAEs in the open-label extension studies was not reanalysed by diabetic status. However, the MAH reported that the overall incidence was low and not affected by the number of NGX-4010 treatments received. In the open-label extension studies 3 patients with myocardial infarction in the diabetic population were reported in the 1st treatment cycle (3/55.6 %). There were no episodes of myocardial infarction in the non-diabetic population in the open label studies. According to the applicant these three episodes were all considered to be serious but unrelated to the study medication. None of the myocardial infarction occurred within 7 days of treatment.

All other events, except for 1, were considered to be of remote or with no relationship to the study medication. The only exception was an SAE of moderate application site pain that occurred on the day of the first retreatment in a non-diabetic, HIV-AN patient in Study C107, which was considered probably related to medication drug by the Investigator.

Safety Topics of Special Interest

AEs associated with cardiac disease including change in blood pressure

Incidence of events which occurred within 7 days of treatment, a time frame during which most of the transient treatment associated effects of NGX-4010 would be expected to occur, was compared between the diabetic and non-diabetic populations. Small percentage of patients experienced a cardiac event and there was a small difference in the incidence of cardiac AEs between the diabetic and non-diabetic groups treated with NGX-4010 (1.5% and 0.7%, respectively). This difference in incidence may be a reflection of the fact that patients with diabetes are at a higher risk of developing cardiac disorders.

In the diabetic and non-diabetic populations, the overall incidence of cardiovascular AEs was similar in NGX-4010 patients with an increase in SBP of ≥ 30 mmHg compared with patients with an increase in SBP of < 30 mmHg. In the diabetic population in 20/90 (22 %) PHN patients treated with NGX-4010 the change in SBP was 30 mmHg or more compared to only 3/44 (7 %) HIV-AN patients. In general, the incidence of the treatment-emergent AE in PHN patients with greater increases in BP was higher compared to patients with smaller changes in BP. In contrast, for HIV-AN patients treated with NGX-4010, the incidence of most frequent treatment-emergent AE tended to be lower in patients with great increases in SBP. In the non-diabetic population in 158/519 (23 %) PHN patients treated with NGX-4010 the change in SBP was 30 mmHg or more compared to only 42/474 (8 %) HIV-AN patients. In diabetic population and non-diabetic population in the control groups very few patients had a change in SBP of 30 mmHg or more 6/72 (8 %) PHN patients 1/19 (5 %) HIV-AN patients, in the diabetic population and 59/471 (13 %) PHN patients and 10/227 (4 %) HIV-AN patients in the non-diabetic population.

Within 7 days of treatment the incidence of AEs associated with BP changes was very low in both the diabetic and the non-diabetic populations (0.7 % of both diabetic and non-diabetic patients treated with NGX-4010; controls 0 % and 0.3 %), respectively.

Six (5%) diabetic patients treated with NGX-4010 had an SAE coded to the Cardiac disorder SOC, including 3 (2%) patients who reported a myocardial infarction; no Control diabetic patients had an

SAE in this SOC. In the non-diabetic population, 10 (0.8%) NGX-4010 patients and 4 (0.6%) Controls had an SAE coded to the Cardiac disorder SOC including myocardial infarction (see above). Atrial fibrillation was reported in 2/1193 (0.2%) NGX-4010 treated patients and no Control patients. Only one cardiovascular-related SAE (blood pressure increased in a non-diabetic NGX-4010 patient) was considered treatment-related.

Adverse Events associated with Maximum change in pain score

In the diabetic and non-diabetic populations, the incidences of the most frequent treatment-emergent AEs in patients with a maximum change in NPRS score of > 2 points was similar to patients with a maximum change in NPRS score of ≤ 2 points in patients treated with NGX-4010.

Adverse Events associated with loss of neurosensory function

After the prolonged exposure to capsaicin the small diameter sensory axons become less sensitive to variety of stimuli, resulting in a reduced pain response. The reduction of protective sensory function and detection of noxious stimuli could potentially cause injury or delay wound healing in the affected area.

However, the Applicant argues that there was no indication of increased dermal injury following patch application, and no evidence of AEs associated with loss of neurosensory function in the controlled studies. According to the results of neurosensory testing (deep tendon reflexes, vibration, warm sensation and sharp sensation), no significant changes could be observed at week 12 in the neurosensory assessment following treatment with NGX-4010. In the open-label extension studies there was also no evidence that the repeated treatments could result in a permanent impairment of neurological function.

Dermal assessment on the day of treatment

Dermal assessments using an 8-point scale were performed prior to the application of topical anaesthetic and study medication and at selected time after removal of the patch. The dermal irritation observed in controlled studies was comparable in diabetic and non-diabetic populations. No patient in any group had a score of 6 (vesicular eruption) or 7 (strong reaction spreading beyond test site).

Tolerability

Overall, NGX-4010 patients had a greater maximum change in NPRS scores compared with Control patients during and after patch application (2.4 vs. 0.3 [diabetics]; 2.7 vs. 0.3 [non-diabetics]). In addition, in the diabetic population, a higher proportion of NGX-4010 patients (46%) had an increased NPRS score of > 2 points compared with Control patients (15%) on the day of treatment. Similar results were seen in the non-diabetic (53% vs. 17%, for NGX-4010 and Control patients, respectively).

The increases in NPRS score observed in NGX-4010 patients during and after patch application were transient in both the diabetic and non-diabetic patients. There was a trend toward slightly smaller maximum increases in NPRS score with increasing numbers of treatment.

Laboratory findings

N/A

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

N/A

Post marketing experience

The current indication does not include diabetic patients and therefore, in Europe, treatment of diabetics with NGX-4010 would be off-label. As too few diabetic patients have been exposed to NGX-4010, a comment cannot be made on the postmarketing safety information of NGX-4010 with respect to diabetic status.

Additional analyses provided by the MAH in response to the request for supplementary information

Following the request from the CHMP the MAH provided the breakdown of reasons for withdrawal from the open-label extensions of studies C102 (open label = C106), C107, C108 and C118. Majority of the withdrawal reasons for diabetic patients were "other", followed by "unsatisfactory therapeutic responses", "lost to follow up" and "adverse events".

Table 8. Withdrawals of diabetic patients by study and reason.

	Study ID			
Reasons for Discontinuation	C107	C108	C118	Total
Lost To Follow-Up		2	1	3
Unsatisfactory Therapeutic Response	1	5		6
Other	1	7		8
Adverse event	1	1		2
Total	3	15	1	19

Note: Reasons for discontinuations are presented for patients who received at least one re-treatment

In C106, 24 subjects were enrolled (3 diabetics); of these, 2 (8.3%) withdrew due to "Unsatisfactory therapeutic response"; no diabetics withdrew from the study.

In study C107, of the 307 patients randomized and treated in the controlled phase of the study (12 weeks), 272 (201 NGX and 71 control) patients (89%) completed the 12-week study and enrolled in the open-label phase. In the open-label phase, 81 (6 diabetics), 90 (4 diabetics), 55 (2 diabetic), and 46 (2 diabetics) patients received 0, 1, 2, and 3 re-treatments, respectively. A total of 84 (31%) patients withdrew from the open-label phase of the study prematurely, of these 4 were diabetics. Reasons for premature termination included "lost to follow-up" (n = 20, 7%, of these 1 diabetic patient) and "unsatisfactory therapeutic response" (n = 18, 7%, of these 1 diabetic patient), as assessed qualitatively using the patients' case report forms. Seven (3%, of these 1 diabetic) patients withdrew due to an AE, including 2 (1%) patients who withdrew due to treatment-related application site pain. Twenty-nine patients (11%, of these 1 diabetic) withdrew prematurely for "other reasons"; the most common of these were withdrawal of consent (n = 11, 4%, of these 1 diabetic patient), patient relocation (n = 9, 3%), and finding the treatment too painful (n=1, < 1%). Three (1%) patients died during the open-label phase; none of the deaths were considered to be related to study treatment.

In study C108, a total of 273 (91%) subjects completed the double-blind phase: 200 (90%) subjects in the total NGX-4010 group and 73 (95%) subjects in the pooled Control group. A total of 93 subjects

(14 diabetic) received no re-treatment in open label phase. The number of subjects receiving 1 or more open-label treatments was 206 (69%; of these 16 diabetics). 105 subjects (10 diabetics) received 1 open-label treatment, 75 (5 diabetics) received 2 open-label treatments and 26 (1 diabetic) received three open-label treatments. During the open-label period, 160 subjects (of these 15 diabetics) discontinued from the study, 94, 57 and 9 subjects after the first, second and third open-label treatment, respectively (9, 5 and 1 diabetics, respectively). The most frequent reason for withdrawal during the open-label period was "Other" (100 subjects or 48.5% of subjects entering the open-label phase, of these 7 diabetics). The majority of these withdrawals were due to the study being terminated early. The second most frequent reason for discontinuation during the open-label period was "Unsatisfactory therapeutic response" (46 subjects, or 22.3% of subjects entering the open-label phase; 5 of these subjects were diabetics).

In C118 106 subjects entered the open-label treatment period (54 PHN subjects and 52 HIV-AN). Of these, 27 withdrew from the study (11 PHN and 16 HIV-AN); amongst the subjects to withdraw from the study, only one was diabetic. The most common reasons for withdrawal were "Loss to follow-up" (10 subjects, of these 1 diabetic), "Adverse event" (5 subjects, of these 1 diabetic), "Unsatisfactory therapeutic response", and other (both 5 subjects).

Reasons for discontinuation of open label re-treatment phase for diabetic population are presented in the table below.

Table 9. Reasons for discontinuation for diabetic patients in the open label extension studies.

Study ID	Patient ID	Treatment cycle *	Reasons for Discontinuation
C107	C107-804	1	Unsatisfactory Therapeutic Response
C107	C107-819	1	Other: WITHDREW CONSENT
C107	C107-823	0	Lost To Follow-Up
C107	C107-5203	0	Noncompliance
C107	C107-9302	2	Adverse Event: HIV VIRAL LOAD INCREASE, PT.C/O MORE S/S POSSIBLY ASSOCIATED WITH HIS HIV STATUS. HIV MEDICATION NEEDED TO BE CHANGED.
C108	C108-204	0	Adverse Event: MYOCARDIAL INFARCTION WITH SUBSEQUENT CABG
C108	C108-813	0	Other: PATCH TREATMENTS TOO FAR APART
C108	C108-818	1	Unsatisfactory Therapeutic Response
C108	C108-917	2	Unsatisfactory Therapeutic Response
C108	C108-928	0	Other: MOVED OUT OF STATE
C108	C108-1701	1	Adverse Event: HERNIA (L) FLANK - WORSENING INTERCURRENT ILLNESS
C108	C108-1813	3	Other: SPONSOR DECISION
C108	C108-1818	2	Unsatisfactory Therapeutic Response
C108	C108-1822	0	Unsatisfactory Therapeutic Response
C108	C108-1826	0	Other: SPONSOR DECISION
C108	C108-1834	1	Unsatisfactory Therapeutic Response
C108	C108-1835	1	Other: SPONSOR DECISION
C108	C108-1836	0	Other: TREATMENT TOO PAINFUL
C108	C108-1837	2	Lost To Follow-Up
C108	C108-1910	0	Other: PATIENT OUT OF COUNTRY - WILL NOT RETURN TO US UNTIL 2005
C108	C108-1912	2	Other: SPONSOR TERMINATED STUDY
C108	C108-1913	1	Lost To Follow-Up
C108	C108-2101	1	Unsatisfactory Therapeutic Response
C108	C108-2402	1	Other: WITHDREW CONSENT/CERTIFIED LETTER SENT 020904
C108	C108-2409	0	Lost To Follow-Up
C108	C108-2705	1	Other SPONSOR TERMINATED OPEN-LABEL EXTENSION
C108	C108-3402	2	Other: PATIENT WITHDREW CONSENT, DECIDED PROTOCOL WAS TOO INCONVENIENT.
C108	C108-3502	0	Adverse Event: ALZHEIMER'S DISEASE WORSEN
C108	C108-3709	0	Lost To Follow-Up
C108	C108-3835	0	Other: STUDY TERMINATION BY SPONSOR
C108	C108-3839	1	Other: STUDY TERMINATION BY SPONSOR
C118	C118-42099	2	Lost To Follow-Up

* Note: Number of re-treatments in open label phase. Patients with 0 treatment cycle either withdrawn during 12 week treatment phase (before open label extension phase) or did not receive re-treatment during open label extension phase.

Discussion of clinical safety

The risk associated with NGX-4010 treatment are well characterised and the post-hoc analysis of data from double-blind randomised studies conducted in PHN and HIV-AN patients demonstrated – as argues the MAH – that the all observed AEs connected with the use of MGX-4010 are similar in diabetic and non-diabetic patients with PHN or HIV-AN. A slightly higher incidence of cardiovascular adverse events was observed in the diabetic patients. The systemic effect of the locally applied capsaicin was judged to be minimal or none. However, it cannot be excluded that patients with diabetic coronary arteries atherosclerosis were more susceptible for any coronary events due to the stress of the treatment.

The current indication of Qutenza as specified in the SmPC is as follows:

"Qutenza is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults, either alone or in combination with other medicinal product for pain."

At the time of the initial marketing authorisation the Committee was of the opinion that after local exposure of capsaicin the small diameter sensory axons would become less sensitive to a variety of stimuli resulting in the reduced pain response, and in the loss of other neurosensory defensive signals, which were already impaired in diabetic patients. Even if the desensitisation caused by capsaicin exposure lasts only a few weeks, during this period non detected noxious stimuli may cause rapid deterioration of the very thin and sensitive skin and the subcutaneous tissues with insufficient microcirculation of the feet of diabetic patients. Moreover, capsaicin itself has a very strong local irritative effect. It cannot be excluded that the use of NGX-4010 may increase the risk of the development of ulcer and the very serious complication of the diabetic neuropathy: the development of the diabetic foot. Thus the CHMP maintains its initial opinion.

According to the proposed indication only diabetic patients with neuropathy caused by the diabetes itself (PDPN) are excluded from the treatment with Qutenza. However, the differentiation between different neuropathies is difficult namely between HIV-AN and diabetic neuropathy. There are probably no reliable clinical or electrophysiological diagnostic tools available today that would allow a clear distinction in patients with both conditions. The incidence of HIV-AN is gradually decreasing due to the early diagnosis and treatment of the disease. On the contrary, the incidence of diabetes among HIV infected patients is increasing as the life expectancy of these patients is much longer today due to the available antiretroviral treatments. The situation in diabetic patients with PHN is somewhat less unfavourable, because the neuropathic pain typically is confined to dermatomes of the skin in line with the herpetic vesicles. Consequently, in typical cases, the chance of misdiagnosing the origin of PHN is probably less than in case of HIV-AN in diabetic patients.

In almost all studies, the patch application was for the recommended length of time as stated in the SmPC. Therefore, the data are sufficient to demonstrate that the safety profile is known for the doses at the current treatment schedule. However, in the diabetic population, it should be pointed out that these analyses were limited due to the low number of patients and the rather "liberal" identification of diabetic. The experience with the treatment of Qutenza in PDPN patients is limited. The use of the product in these patients would only be 'off label' today. Accordingly, the MAH does not have any postmarketing experience with this product in PDPN.

It was noted that less and less patients participated in the open label extensions of clinical trials in the course of time. The number of patients with diabetes in the first cycle was 157, in the second 10, in the third 9 and in the fourth only 8 patients. 1447 non-diabetic patients participated in the first cycle, 166in the second, 151 in the third and only 85 patients in the fourth cycle. Accordingly, the tolerability of repeated use of NGX-4010 can not be justified by the small percent of the treated patients. The treatment with NGX-4010 is a symptomatic treatment. It was not clear what happened with the

patients receiving the capsaicin treatment who dropped out from the studies. Therefore, the CHMP requested the MAH to clarify whether these patients had been treated successfully, discontinued the treatment due to the lack of efficacy or adverse events. In response the MAH presented the breakdown of withdrawals by study and the reasons for withdrawal. Majority of the withdrawal reasons for diabetic patients were "other", followed by "unsatisfactory therapeutic responses", "lost to follow up" and "adverse events". The CHMP acknowledged the response provided by the Applicant, however requested further clarification as it was considered that reasons for the reduced number of patients submitted to 4 cycles of treatments remained unclear. In particular, the Committee noted that the most frequent reason for withdrawal was classified as "other" which could not preclude that discontinuations were due to intolerability or unsatisfactory efficacy of the treatment.

It can be said that only a small percentage of patients in both diabetic and non-diabetic groups received 4 cycles of treatment (n=8, 5% and n=85, 5.9%, respectively). These patients very probably experienced none or mild adverse reactions during the 1st, 2nd and 3rd cycle. It seems very likely that these small groups of patients with or without diabetes were the most tolerant patients to the treatment with NGX-4010 for whom the AEs were more tolerable than for the other patients who discontinued the therapy.

It has also to be highlighted, that accepting the modified indication of Qutenza as proposed by the MAH may widely open the 'off label' use of the product. Consequently, the Applicant was requested to revise the pharmacovigilance plan and risk minimisation measures to address this issue.

Conclusion on clinical safety

The specific risks associated with NGX-4010 treatment of diabetic patients are the reduction or loss of protective neurosensoric function which may increase the risk of injury, especially of the skin of those patients whose neurosensory perception had already been impaired, e.g. diabetic patients. Moreover, the integrated analysis had been performed only on a very low number of diabetic patients, and their identification was very uncertain; therefore the safe use of NGX-4010 in these patients based on the presented data can not be considered as justified.

Risk Management Plan

The currently approved therapeutic indication of Qutenza "treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain" is proposed to change to "the treatment of peripheral neuropathic pain in adults, excluding pain arising from diabetic neuropathy, either alone or in combination with other pain medications". The Applicant submitted updated version of Risk Management Plan (version 11 with DLP 01-04-2011).

The extension of indication has been proposed based on a post-hoc analysis and no new study data have been submitted. However the indication has been extended by including a new patient group (diabetic patients without diabetic neuropathy) while the list of safety concerns has not been changed.

Important Identified Risks	Application site reactions.
	Unintentional contact with patch or other materials that have come in contact with treated area resulting in transient erythema and burning sensation or coughing or sneezing in case of inhalation of airborne capsaicin.

	Transient small increase in blood pressure during patch application.
	Lack of response to oral analgesics in those subjects with a high opioid tolerance when treated for acute pain during and following the procedure.
	Minor, temporary decrease in the ability to detect heat stimuli and sharp sensations at the application site in healthy volunteers.
Important Potential Risks	Loss of neurosensory function after repeated treatments
Important Missing Information	None

The proposed RMP is not acceptable as the new proposed indication (and the method of confirmation of enlarged target population) suggests new identified and potential risks and missing information as follows:

Additional Identified Risk:

Off label use

Qutenza is indicated for PHN and HIV-AN, but not for peripheral neuropathy due to diabetes mellitus. Since the listed types of peripheral neuropathies can be generally considered predominantly axonal the differentiation between indicated and not indicated neuropathic pains is questionable therefore a high amount of 'off label' use is probable.

Additional Potential Risk:

Danger of skin lesion / formation of diabetic skin ulcer.

The Applicant states in section 4.4 of the proposed SmPC that "When treating painful areas involving the lower limbs in diabetic patients, the patient's risk profile for foot ulceration should be assessed. High risk patients should be appropriately followed and, if required, proper preventive measures and treatment should be implemented". However one of the best "preventive measures" is to avoid any local irritative effect on the endangered area. This additional warning also calls attention to potential skin ulcer if the patch is not used properly in diabetic patients.

Foot ulceration can occur not only due to local effect of highly concentrated capsaicin on skin of poor microcirculation but also the danger of undetected injury is also increased due to loss of neurosensory function after repeated treatment.

Missing information

Data in diabetic patients are very limited.

Throughout the clinical development program for Qutenza, 1639 individuals received 2495 Qutenza treatments: 914 subjects with PHN, 634 subjects with HIV-AN, and 91 subjects with diabetes. Since patients have been identified by post-hoc analysis the lack of appropriate characterisation of diabetic patient population can be supposed (e.g. confirmed or not-confirmed diabetes; type of diabetes – IDDM or NIDDM).

Long-term use and safety

The MAH plans two studies on safety of repeated application of Qutenza patch administered over a 12 months. Until results are available long-term safety of Qutenza Cutaneous Patch, 179 mg can be regarded as missing information.

The MAH was requested to analyse the above risks and missing information and provide appropriate pharmacovigilance plan to gain further information and data, as well as effective risk minimisation measures. In response the MAH provided revised Risk Management Plan version 12. Potential risk of foot ulceration in diabetic patients has been introduced in the RMP and thoroughly discussed. The pharmacovigilance plan (including routine ADR collection, signal detection and analysis in PSURs, as well as an additional long-term safety study on repeated use in diabetic patients) and risk minimisation measures proposed were considered adequate providing the warnings in the SmPC would be amended as proposed by the CHMP and additional information on safety studies submitted.

During the revision of the RMP, off-label use has not been included in the potential risks section of the RMP. The CHMP considered that Pharmacovigilance Plan and Risk Minimisation measures for off-label use should be proposed and discussed as for all other identified and potential risks, and details of the proposed routine pharmacovigilance activities to estimate the extent of off-label use should be provided. The CHMP expressed concerns whether off-label use can be captured via a routine collection of ADRs and recommended an active follow-up in each case when indication is not reported. Furthermore, a drug utilisation study was proposed to quantify possible off-label use with Qutenza. Risk minimisation measures including clear formulation of the therapeutic indication, introducing proper warnings in the product information as well as emphasising proper use in educational materials were encouraged.

Similarly, the lack of long-term safety data for Qutenza in patients with diabetes has not been addressed in the revised RMP. The CHMP acknowledged the two long-term safety studies on repeated use; however, requested that protocols be provided in the RMP.

Furthermore, the CHMP requested the Applicant to consider the use of the requested drug utilisation study to verify the success of the educational program.

4. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

There was no evidence to suggest that NGX-4010 was less efficacious in diabetic than in non-diabetic PHN and HIV-AN patients. In spite of some weaknesses of the statistical analysis the post-hoc analysis of the data seems to suggest that NGX-4010 is equally efficacious in diabetic and non-diabetic patients. Thus, patients in the diabetic subset who were treated with NGX-4010 showed similar reductions in pain, as measured by change in NPRS from Baseline to week 2 to 8 and week to 12, to the non-diabetic patients.

When the post-hoc analysis was confined to the combined data from the 60–minute (PHN studies) and 30-minute (HIV-AN) treatment groups only, similar results were seen for most of the efficacy endpoints in both PHN and HIV-AN subpopulations.

Uncertainty in the knowledge about the beneficial effects

The number of the patients in the diabetic subset was very low, the identification of patients with diabetes was too "liberal", happened post-hoc and the analysis of the results was not supported by any formal statistical hypothesis testing. This kind of narrative argumentation may be misleading because it compares numerically the results only between the diabetic and non-diabetic groups and the efficacy differences between the control and treated groups individually were not considered.

Risks

Unfavourable effects

The risk associated with NGX-4010 treatment are well characterised and the present new integrated analysis of safety data suggests that the safety profile of the product in diabetic patients with PHN and HIV-AN does not differ from that which has already been established in previous studies. The most frequently reported treatment-emergent AEs of NGX-4010 in both the diabetic and non-diabetic population were application site AEs.

Most diabetic patients were able to complete at least 90% of the planned application periods. The most frequent AEs, as expected, were transient application site pain, erythema and pruritus.

A specific risk for diabetic patients is the reduction or loss of protective neurosensoric function following NGX-4010 treatment. The loss of noticing any harmful noxious stimuli – should it be only transient, confined only to a few days of weeks – may potentially increase the risk of injury in diabetic patients whose neurosensory function had already been impaired. Loss of neurotrophic impulse may delay wound healing in the treatment area and could lead to development of diabetic foot and finally amputation. What should also be taken into account is that the patch of high capsaicin concentration (8%) has strong irritative effect on the painful area which effect could be extremely perilous on the very thin and atrophied skin of the feet of many diabetic patients with already impaired micro-macro circulation, and as a consequence with already present trophic disturbances in the affected area.

Uncertainty in the knowledge about the unfavourable effects

The analysis of the safety of NGX-4010 in the diabetic versus non-diabetic patients with peripheral neuropathic pain is based exclusively on the data of the clinical trials. The number of diabetic patients involved in these trials was extremely low in each group and the identification of diabetic patients was too "liberal". The criteria of the diagnosis were not standardised, no information was provided about the type and medical control of the disease and about its complications when the patients entered the clinical trial. The current indication of NGX-4010 does not include diabetic patients, thus post-marketing safety experience with the product in respect to diabetes status is not available at present.

Benefit-risk balance

There are several options for control of neuropathic pain. At present the systematic medical treatment usually alleviates pain and may control some associated symptoms but the process can be progressive (depending on the origin of the neuropathy) and to achieve a successful pain control a local treatment on the painful area, at least as an adjuvant treatment, may be needed.

The local treatment of the painful area with NGX-4010 seems to provide a significant decrease in neuropathic pain (decrease in NPRS ~30%). Its use in patients with PHN and HIV-AN proved to be efficacious and relatively safe.

However, the safe use of a patch with a very high capsaicin concentration (8%) which itself is very painful and irritative on the application area in diabetic patients, is very questionable and not devoid of risks.

For safety reason the CHMP does not recommend the use of Qutenza for diabetic neuropathy. Accordingly the treatment with Qutenza would only be indicated for diabetic patients with PHN or HIV-AN in case if the origin of the pain is not the diabetes itself.

The main problem is that there are no clinical and electrophysiological diagnostic tools suitable for making a correct differential diagnosis between neuropathies of different origin today, at least not in every day clinical practice. Any diagnostic mistake which may promote the development of ulcer and diabetic foot in given case could be fatal for diabetic patients.

Discussion on the benefit-risk assessment

The post hoc analysis of the data from clinical trials with NGX-4010 on diabetic and non-diabetic patients with PHN and HIV-AN seems to justify that the 8% capsaicin patch is equally efficacious in both populations. However the safe use of NGX-4010 in diabetic patients needs to be confirmed with more clinical experience. To exclude patients with DPNP from the indication seems to be unrealistic in the clinical practice at present.

Accordingly the CHMP is of the opinion that the proposed extension of indication is not approvable, unless the major objections and other concerns are satisfactorily addressed.

5. CHMP Request for supplementary information

5.1. Clinical aspects

Major objections (to be addressed in writing and in an oral explanation)

1. The benefit risk of Qutenza in the applied indication is negative due to the difficulties in reliable differential diagnosis between neuropathies of different origin and safety concerns related to the use of capsaicin in patients with increased risk of skin ulcerations.

Other concerns (to be addressed in writing, and in an oral explanation as appropriate)

2. Diabetic patients included in the post-hoc analysis are not properly characterised hampering the evaluation of the efficacy and safety of Qutenza in this population. The MAH should provide more detailed information on the standardisation of the diagnosis, type of diabetes (type 1 / 2, iatrogenic – due to specific diabetogenic effects of some anti-HIV agents), complications of the disease at the time of inclusion, antidiabetic treatment, and metabolic control of the patients.

3. The reasons for the reduced number of patients submitted to 4 treatments were not adequately addressed. Please provide further information on the cause of the high percentage of discontinuations, focusing especially on the cause of discontinuation of diabetic patients.

4. The concern that the revised indication, as proposed by MAH "Qutenza is indicated for the treatment of peripheral neuropathic pain in adults, excluding pain arising from diabetic neuropathy, either alone or in combination with other pain medication" very probably would increase the 'off label' use of the product still remains. A reinforced risk management plan to prevent the widespread off label use of Qutenza in the future is needed:

- The RMP should address off-label use as a potential risk and a specific plan to minimisze it should be provided in RMP. A specific plan to collect safety data on diabetes off label use should be provided.

- Please detail pharmacovigilance activities planned to catch ADRs from off-label indications and comment on the feasibility of a drug utilisation study, to quantify off-label use. The Applicant is invited to amend the RMP accordingly and to attach the protocol synopsis of such a study in Annex 5.

5. The RMP should address the missing information on safety in diabetic patients and on long-term repeated use. Please provide all documents in the RMP that have been referenced, in particular, a clear summary on the protocols of the two long-term safety studies.