EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/545605/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qutenza

International non-proprietary name: CAPSAICIN

Procedure No. EMEA/H/C/000909/II/0039

Note

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

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
AR	Autoregressive (structure used to model covariance)
BLOCF	Baseline or last observation carried forward
BOCF	Baseline observation carried forward
BPI-DN	Brief Pain Inventory – Diabetic Neuropathy
DM	Diabetes mellitus
ECG	Electrocardiogram
EMLA	Eutectic mixture of local anesthetic
EQ-5D	European Quality of Life Questionnaire in 5 Dimensions
EQ5D-VAS	European Quality of Life Questionnaire in 5 Dimensions Visual
Analogue Scale	HADS Hospital Anxiety and Depression Scale
HbA1c	Glycosylated hemoglobin
HIV-AN	Human immunodeficiency virus-associated neuropathy
ICH	International Conference on Harmonisation
ITT	Intention-to-Treat
MAA	Marketing Authorization Application
NPRS	Neuropathic Pain Rating Scale
NPSI	Neuropathic Pain Symptom Inventory
PDPN	Painful diabetic peripheral neuropathy
PGIC	Patient Global Impression of Change
PHN	Postherpetic neuralgia
PRAE	Postrandomization adverse event
PSUR	Periodic Safety Update Report
QOL-DN	Quality of Life Diabetic Neuropathy
RMP	Risk management plan
SAE	Serious adverse event
SAF	Safety Analysis Set
SmPC	Summary of Product Characteristics
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TRPV1	Transient receptor potential vanilloid 1
UENS	Utah Early Neuropathy Scale
UN	Unstructured (model of covariance)
VAS	Visual analogue scale
w/w	Weight/weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 4 December 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name:**
Qutenza	CAPSAICIN

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

The Marketing authorisation holder (MAH) applied for an extension of the indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE). Consequently, the MAH proposed the update of sections 4.1, 4.4 and 4.8 of the SmPC.

The Package Leaflet and Annex II (additional risk minimisation measures) were proposed to be updated in accordance.

In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and Package Leaflet.

An updated RMP (version 18) was provided as part of the application. The provision of studies STEP and PACE addresses MEA 001.4.

The variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Melinda Sobor

Timetable	Actual dates
Submission date	4 December 2014
Start of procedure:	26 December 2014
Rapporteur's preliminary assessment report circulated on:	20 February 2015
CoRapporteur's preliminary assessment report circulated on:	16 February 2015
PRAC Rapporteur's preliminary assessment report circulated on:	23 February 2015
PRAC Rapporteur's updated assessment report circulated on:	4 March 2015
Adoption of PRAC assessment report by the PRAC on:	12 March 2015
Joint Rapporteur's updated assessment report circulated on:	23 March 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2015
MAH's responses submitted to the CHMP on:	20 May 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 June 2015
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	29 June 2015
Joint Rapporteurs' assessment report on the MAH's responses circulated on:	30 June 2015
Adoption of PRAC assessment report on the MAH's responses by the PRAC on:	9 July 2015
CHMP opinion:	23 July 2015

2. Scientific discussion

2.1. Introduction

Qutenza is a capsaicin (8% w/w) cutaneous patch. Capsaicin is a selective agonist of the transient receptor potential vanilloid 1 receptor (TR PV1). The TR PV1 receptors, 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) promotes 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.

A Marketing Authorization (MA) has been granted by the European Commission in May 2009, for Qutenza cutaneous patch for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal pain products. The approved indication excluded patients with diabetes on the grounds that insufficient data for this population were included in the original MAA.

Accordingly, the MAH (Marketing Authorisation Holder) was asked to characterise efficacy and long-term safety in this population as a Follow-up Measure No. 001, witch consisted of the following 2 studies: E05-CL-3004: A phase III, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of QUTENZA in subjects with Painful Diabetic Peripheral Neuropathy (short title: STEP) and E05-CL-3002: A randomized, controlled, long-term safety study evaluating the effect of repeated applications of QUTENZA plus standard of care versus standard of care alone in subjects with Painful Diabetic Peripheral Neuropathy (short title: PACE).

Following the completion of the aforementioned studies, their results are submitted by the MAH in the type II variation application to extend the currently authorised indication to include patients with diabetes. The proposed indication is: “Qutenza is indicated for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain.”

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The Applicant did not submit an updated Environmental Risk Assessment. Taking into account, that the active substance of this medicinal product, capsaicin is a natural substance (found in chilli peppers), the CHMP agreed that an update to the environmental risk assessment is not necessary.

2.2.2. Conclusion on the non-clinical aspects

The CHMP concluded that capsaicin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2.7.3.1 Description of Clinical Efficacy and Safety Studies

Study ID No. of Centers Duration	Study Design	Study Drug & Control Dose	Study Objective	Number of Patients by Arm Entered/ Completed	Sex M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoints
E05-CL-3004	Multicenter, 2-arm, double-blind, placebo-controlled randomized study	Study drug: QUTENZA (Arm 1) Control: placebo (Arm 2)	To evaluate the efficacy of a single application of QUTENZA compared to that of placebo in reducing pain intensity in patients with PDPN	Arm 1 186/177 Arm 2 183/175	Arm 1 M: 114 F: 72 Mean Age: 63.9 Arm 2 M: 101 F: 82 Mean Age 62.0	Main inclusion criteria were: Diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy due to diabetes, for at least 1 year prior to screening visit Diagnosis of PDPN confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument Average baseline numeric pain rating scale (NPRS) score over the last 24 hours (question 5 in the brief pain inventory-diabetic neuropathy [BPI-DN]) ≥ 4 during the screening period Stable doses of pain medications for more than 4 weeks prior to the screening visit	Percent change in the average daily pain score (question 5 of the BPI-DN: "average pain for the past 24 hours" NPRS) from the average assessed during the baseline run-in period to the average daily pain score assessed between weeks 2 and 8 (i.e., average of daily pain scores during weeks 2 to 8, compared to the average of baseline scores) in the active arm compared to the placebo arm.
E05-CL-3002	Open label, multicenter, 3-arm randomized study	QUTENZA patch up to 7 applications removed after 30 minutes (Arm 1) or 60 minutes (Arm 2) plus SOC or SOC treatment only (Arm 3)	To assess the safety of repeat applications of QUTENZA administered over a period of 12 months in patients with PDPN	Arm 1 156/132 Arm 2 157/128 Arm 3 155/128	Arm 1 M: 74 F: 82 Mean Age: 60.9 Arm 2 M: 79 F: 78 Mean Age 61.0 Arm 3 M: 71 F: 84 Mean Age 59.1	Main inclusion criteria were: Diagnosis of painful, distal, symmetric, sensorimotor polyneuropathy, which was due to diabetes, for at least 1 year prior to screening visit Diagnosis of PDPN confirmed by a score of at least 3 on the MNSI Average Numeric Pain Rating Scale (NPRS) score over the last 24 hours of ≥ 4 at the screening and the baseline visit.	Study did not include a primary efficacy endpoint

2.3.2. Pharmacokinetics

No pharmacokinetic studies were submitted with this application.

2.3.3. Pharmacodynamics

No pharmacodynamic studies were submitted with this application.

2.3.4. Discussion on clinical pharmacology

Although no PD studies were submitted, CHMP considered particular safety concerns in the diabetic population related to symptoms called "diabetic foot" which may easily develop following skin lesions. Patients who have decreased sensory sensitivity towards sharp and thermal stimuli may be at increased risk of developing skin lesions. Therefore, the Applicant was requested to address the feasibility of a lower dose capsaicin patch and provide a literature overview of the efficacy and safety of lower concentration capsaicin in painful diabetic peripheral neuropathy. Furthermore, further discussion of pharmacodynamic effects in terms of epidermal nerve fibre density and function was requested in the target population. The MAH provided a detailed literature overview of the use of lower capsaicin products in peripheral painful diabetic neuropathy patients which showed that the results with lower dose local capsaicin are inconclusive. The MAH further argued that lower concentration capsaicin products have to be applied 3-5 times per day for longer periods which results in contamination of the patient's environment. This was agreed by the CHMP.

Regarding pharmacodynamic effects, some studies indicated that low-dose capsaicin may result in more pronounced epidermal denervation and slower regeneration in neuropathic patients with diabetes than in diabetic patients without neuropathy and in control patients. The rationale behind this observation may

be that tissue regeneration in general can be impaired in diabetic patients, particularly if they have complicated disease (e.g. with neuropathy, macro- or microangiopathy). However, clinical endpoints were not investigated in these studies and it was not entirely clear how these pharmacodynamic observations translate into clinical manifestations. Inconclusive results were also obtained for neurosensory changes in patients with symptomatic diabetic neuropathy following topical capsaicin application. While some studies found decreased warmth perception, others failed to demonstrate a decrease in sensory functions and neurovascular control. In summary, an increased risk of decreased regeneration of sensory functions cannot be excluded. However, based on the results of Qutenza STEP and PACE studies, the CHMP concluded that this risk can be managed with routine risk minimization measures.

2.3.5. Conclusions on clinical pharmacology

No pharmacokinetic or pharmacodynamic studies were submitted. This was acceptable to the CHMP. Regarding desensitisation of capsaicin sensitive nerve endings, which may be a particular concern in the diabetic population, the MAH provided adequate justification that the benefit/risk of lower concentration products are inconclusive and the risks of desensitisation may be sufficiently minimised with routine risk minimisation measures.

2.4. Clinical efficacy

The efficacy of Qutenza in Painful Diabetic Peripheral Neuropathy (PDPN)is primarily based on the data from the pivotal STEP study; a double-blind study to assess the efficacy of Qutenza compared with placebo in patients with PDPN. The primary objective of the supportive, open-label PACE study was to provide long-term safety data in patients with PDPN; long-term efficacy was a secondary objective.

2.4.1. Dose response study

Dose-response studies were not performed. Posology in STEP study was based on earlier studies conducted to support the neuropathic pain indication. The rationale for the 30 minutes application time in the PDPN studies was to keep the mode of administration of Qutenza in accordance with the approved Summary of Product Characteristics (SmPC).

2.4.2. Main studies

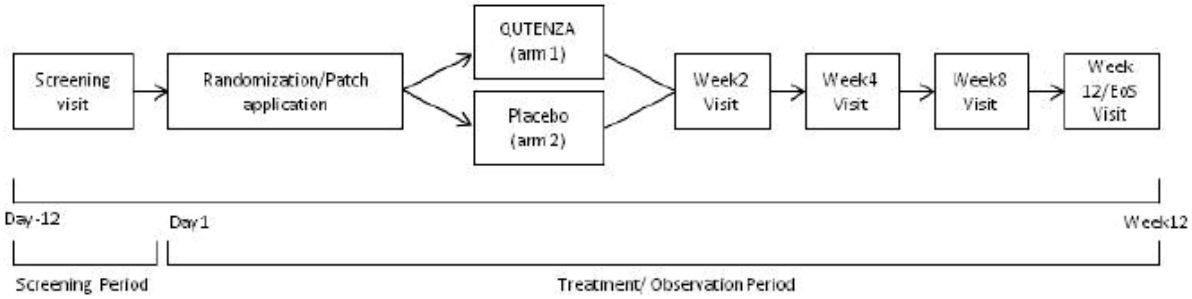
A Phase III, Double-blind, Randomized, Placebo-controlled, Multicenter Study Evaluating the Efficacy and Safety of Qutenza in Subjects with Painful Diabetic Peripheral Neuropathy (STEP). Study ID: E05-CL-3004.

Methods

Study design

It was a two-arm, double-blind, placebo-controlled study. Patients were randomized to receive a single Qutenza or placebo patch application to the feet for 30 minutes at the baseline visit. Patients were observed for 12 weeks following the patch application, involving visits at week 2, 4, 8 and 12.

Figure 1 Study Flow Chart



Study participants

Key Inclusion Criteria were as follows:

- Male or female >18 years of age
- Diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy which is due to diabetes, for at least 1 year prior to screening visit. Diagnosis of PDPN was confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI).
- At least one medical record of glycosylated hemoglobin (HbA1c) =< 11% at 3-6 months before screening visit; HbA1c =<11% at screening visit with variations of ≤1% point between the screening visit and the 3-6 month pre-screening value
- Average baseline NPRS score over the last 24 hours (Question 5 in the Brief Pain Inventory-Diabetic Neuropathy [BPI-DN]) >= 4 during the screening period
- A minimum of 6 consecutive pain recordings during the screening period
- Stable doses of pain medications for more than 4 weeks prior to the screening visit

Key exclusion criteria:

- Primary pain associated with PDPN in the ankles or above
- Pain that could not be clearly differentiated from, or conditions that might interfere with, the assessment of the PDPN, such as plantar fasciitis, heel spurs, tibial neuropathy, Morton's neuroma, bunions, metatarsalgia, arthritis in feet, peripheral vascular disease (ischemic pain), neurological disorders unrelated to diabetic neuropathy (e.g., phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation (e.g., plantar ulcer)
- Significant pain (moderate or above) of an etiology other than PDPN (e.g., compression-related neuropathies [e.g., spinal stenosis, fibromyalgia or arthritis]), that may interfere with assessment of PDPN-related pain
- Current or previous foot ulcer, skin areas to be treated with QUTENZA showing changes such as crusting or ulcers, any active signs of skin inflammation around onychomycosis sites
- Any amputation of lower extremity

- Depression or anxiety at baseline as assessed by the Hospital Anxiety and Depression Scale (HADS) (score ≥15 on either scale), active substance abuse or history of chronic substance abuse within 1 year prior to screening, poorly controlled major psychiatric disorder, at the investigator's discretion
- Impaired glucose tolerance (IGT) only – without DM
- Body mass index (BMI) ≥40 kg/m2
- Severe renal disease as defined by a creatinine clearance rate of <30 ml/min calculated according to the Cockcroft-Gault formula
- Clinically significant cardiovascular disease within 6 months prior to the screening,
- Significant peripheral vascular disease
- Clinically significant foot deformities
- Medications not permitted: Use of any topical pain medication or oral, transdermal or parenteral opioids, regardless of dose, within 7 days preceding the first patch application visit or use of transcutaneous nerve or spinal cord stimulators to relieve pain, regular use of antiemetics, antimanics, antimigraine medications, antipsychotics, chloral hydrate, guanethidine, MAOIs, psychostimulants, and oral and injectable steroids.

Treatments

Test:

Qutenza (8%) capsaicin patch. Up to 4 patches of Qutenza (1120 cm2 in total) were applied for 30 minutes to the painful areas of the feet (as identified by the study physician).

Reference:

The placebo patches contained no active ingredient but were visually and cosmetically indistinguishable from the active capsaicin patches.

Allowed concomitant medications:

Short-acting opioid or other short-acting analgesic could have been administered to relieve treatment-associated discomfort during treatment procedure and up to 5 consecutive days post-treatment with study drug.

Up to two analgesics from different drug classes, excluding opioids, at fixed doses, were allowed only if the patient has been on stable doses for more than 4 weeks prior to screening visit. Doses were to be maintained during the study.

Aspirin up to 325 mg/day for the prevention of ischemia

Antidiabetic medication (including insulin and oral hypoglycaemic agents).

Objectives

Primary objective:

To evaluate the efficacy of a single application of Qutenza compared to that of placebo in reducing pain intensity in subjects with Painful Diabetic Peripheral Neuropathy (PDPN)

Secondary objectives:

To evaluate the efficacy of a single application of Qutenza compared to that of placebo as measured by: responder rates, improvement in sleep interference, improvement in overall patient status, improvement in health-related quality of life (HRQOL), treatment satisfaction and safety and tolerability.

Outcomes/endpoints

Primary variable:

The percent change in the average daily pain score (question 5 of the Brief Pain Inventory-Diabetic Neuropathy (BPI-DN): "average pain for the past 24 hours": from the average assessed during the baseline run-in period to the average daily pain score assessed between weeks 2 and 8 in the active arm compared to the placebo arm.

Secondary efficacy variables:

- Percent change in the average daily pain score (question 5 of the BPI-DN) from the average assessed during the baseline run-in period to the average daily pain score assessed between weeks 2 and 12.
- Percent change of weekly average of "average pain for the past 24 hours" NPRS scores from baseline at every week after baseline.
- Weekly average of "average pain for the past 24 hours" NPRS scores at baseline and every week after baseline.
- Occurrence of 30% and 50% decrease in the average daily pain score (question 5 of the BPI-DN) from baseline to week 2 and 8 and from week 2 average to week 12
- Overall patient status using Patient Global Impression of Change (PGIC) questionnaire at weeks 2, 8 and 12
- Change in the European Quality of Life Questionnaire in 5 Dimensions (EQ-5D) total score and Depression and Anxiety scores on the HADS (Hospital Anxiety and Depression Scale) from baseline to weeks 2, 8 and 12
- Treatment satisfaction using the Self-Assessment of Treatment (SAT) questionnaire at baseline, weeks 8 and 12
- Percent change in the sleep interference NPRS score (question 9F of the BPI-DN) from baseline to between week 2 and 8 and week 2 and 12 (i.e., average of scores during weeks 2 to 8 and 2 to 12, compared to baseline).

The Patient Reported Outcome instruments used in the study (BPI-DN, EQ-5D, PGIC, SAT and HADS) were all validated questionnaires.

Neuropathic Pain Symptom Inventory (NPSI) was self-report questionnaire specifically designed to evaluate the different symptoms of neuropathic pain. The questionnaire comprised a list of 10 descriptors (plus 2 temporal items) reflecting spontaneous ongoing or paroxysmal pain, evoked pain and dysesthesia/paraesthesia. Each of these items is quantified on a (0 to 10) numerical scale. It can be used

to allow discrimination and quantification of 5 distinct clinically relevant dimensions of neuropathic pain syndromes. NPSI was used to characterize subgroups of neuropathic pain patients and to explore whether they respond differently to Qutenza and was performed at the baseline visit and at the End of Study (EoS) Visit.

Sample size

The sample size was calculated with a Student's t-test at the two-sided 0.05 significance level assuming a standard deviation (SD) of 33% to provide 90% power to detect a 12% difference in NPRS scores from baseline to week 2-8 between treatment arms. This required 160 subjects per group for a total of 320 subjects. As the expected drop-out rate was approx. 10%, 360 subjects were planned to be randomised.

Randomisation

Randomization ratio was 1:1. Randomisation was stratified by investigational site.

Blinding (masking)

Given that the application of the active capsaicin patch often, but not invariably, results in pain and erythema, the following measures were taken to maintain the study blind:

- The physician/ delegate conducting the clinical assessments and who had access to, and the responsibility to record subjects' efficacy and safety data was independent from the physician/ delegate or nurse who was responsible for the application of the patch(es).
- The physician/ delegate conducting the clinical assessments and who had access to, and the responsibility to record subjects' efficacy and safety data was independent from the physician/ delegate or nurse who was responsible for the dermal assessments at baseline (both before and after patch application).
- Results from the dermal assessments at baseline were recorded on paper and sealed in an envelope and therefore not be disclosed to any site staff apart from the physician/delegate who performed the dermal assessments
- The application site was covered using stretchable socks during patch application and for 24 hours subsequent to removal of the patch (to prevent the patient from identifying erythema)
- Instructions to the patient stressed that they may or may not experience pain during or after the application of the patch
- All subjects were pre-treated with EMLA containing lidocaine 2.5% and prilocaine 2.5% in order to limit the experience of pain and discomfort.

Statistical methods

The primary efficacy variable was the average daily pain score between Week 2-8. A repeated measures ANCOVA model was used for these inferential analyses. The model included treatment, week (set of [week 2,…, week 12]), treatment by week interaction, gender, pain score at baseline, HbA1c at screening and site as factors/covariates. A compound symmetry structure was used to model the covariance structure. Mean (±95% CI) of percent change from baseline in weekly averages of daily pain scores (including between weeks 2 and 8 and weeks 2 and 12) were presented graphically by treatment group.

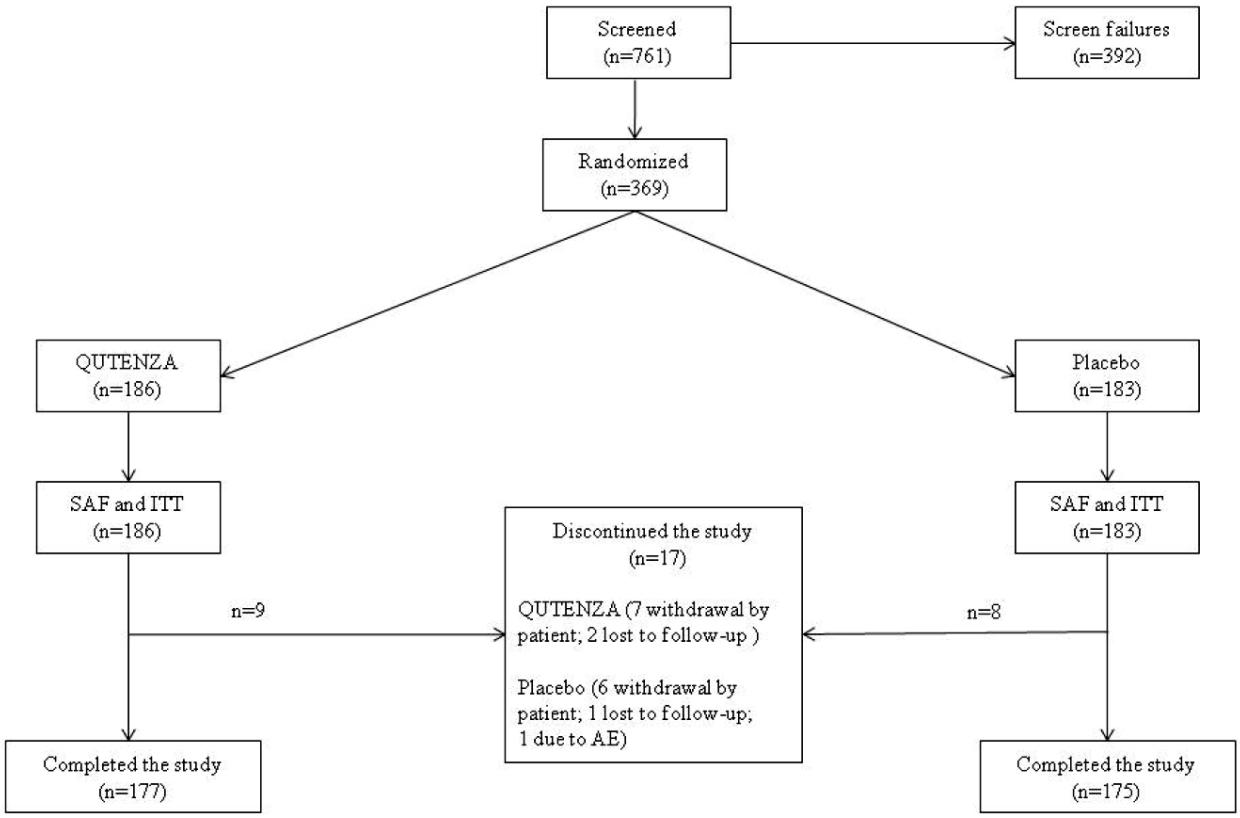
Patients achieving a 30% decrease in the average daily pain score between weeks 2 and 8 were analysed as:

- The number and percentage of patients achieving this reduction [SEV]
- A p-value, an LS mean estimate and a CI, reported for the odds ratio (OR) of QUTENZA and placebo for patients achieving reduction [SEV].
- A logistic regression model was used for these inferential analyses. The model included treatment, gender, pain score at baseline, HbA1c at screening and site as factors/covariates.

To explore the effect of 2 important covariates on the primary endpoint, 2 additional ANCOVA analyses were performed: An ANCOVA model with treatment, gender, pain score at baseline and PDPN duration as factors/covariates and ANCOVA model with treatment, gender, pain score at baseline and NPSI total score at baseline as factors/covariates.

Results

Participant flow



Recruitment

Study Initiation Date: 06 Feb 2012

Study Completion Date: 13 Feb 2014

Conduct of the study

This study was conducted in the United States. The study protocol was reviewed and endorsed by the CHMP.

Protocol deviations occurred in 106 patients, the majority of them were due to receiving excluded concomitant treatment and procedures inadvertently not (or incorrectly) performed. In both treatment arms, a comparable number of patients deviated from the study protocol for at least 1 reason and a comparable number of deviations was observed.

Baseline data

Demographics and baseline data are presented in Table 1 below.

Table 1 Demography and baseline characteristics, safety analysis set

Parameter Category/Statistics	QUTENZA (N = 186) n (%)	Placebo (N = 183) n (%)	Total (N = 369) n (%)
Sex, n (%)			
Male	114 (61.3)	101 (55.2)	215 (58.3)
Female	72 (38.7)	82 (44.8)	154 (41.7)
Race, n (%)			
White	132 (71.0)	131 (71.6)	263 (71.3)
Black or African American	36 (19.4)	38 (20.8)	74 (20.1)
Asian	4 (2.2)	4 (2.2)	8 (2.2)
American Indian or Alaskan Native	2 (1.1)	1 (0.5)	3 (0.8)
Native Hawaiian or Other Pacific Islander	1 (0.5)	2 (1.1)	3 (0.8)
Other	11 (5.9)	7 (3.8)	18 (4.9)
Age, years			
Mean (SD)	63.90 (10.64)	62.00 (10.81)	63.00 (10.75)
Median	64.00	61.00	62.00
Min - Max	36.0 - 89.0	33.0 - 89.0	33.0 - 89.0
Weight (kg)			
Mean (SD)	94.36 (16.16)	92.46 (17.07)	93.42 (16.62)
Median	94.15	92.30	93.30
Min - Max	49.8 - 150.9	45.5 - 135.9	45.5 - 150.9
Height (cm)			
Mean (SD)	171 (9.94)	171 (10.17)	171 (10.04)
Median	172.00	170.18	171.00
Min - Max	147.30 - 200.66	149.90 - 201.00	147.30 - 201.00
BMI (kg/m^2)			
Mean (SD)	32.23 (4.50)	31.59 (5.03)	31.91 (4.78)
Median	32.90	31.50	32.20
Min - Max	18.3 - 39.8	18.3 - 39.9	18.3 - 39.9
Duration of PDPN (years)			
Mean (SD)	5.83 (4.01)	5.72 (3.98)	5.78 (3.99)
Median	4.84	4.55	4.62
Min - Max	1.2 - 22.7	1.0 - 22.7	1.0 - 22.7

The treatment arms were similar with respect to all baseline characteristics with the exception of gender; more males were enrolled in to the study overall (58.3%) and there was a higher proportion in the Qutenza arm (61.3%) than in the placebo arm (55.2%).

Numbers analysed

The overview of numbers analysed is presented in Table 2 below. The safety analysis set included all randomized patients who received study patch application (grouped by actual treatment received). The intention to treat set included all randomized patients who received study patch application (grouped by

randomization assignment). The per protocol set was defined as a subset of the intention to treat set selected to increase the likelihood of exhibiting a treatment effect.

Table 2 Patient disposition and analysis sets

Analysis Set	QUTENZA (N = 186) n (%)	Placebo (N = 183) n (%)	Total (N = 369) n (%)
Randomized	186 (100)	183 (100)	369 (100)
Safety Analysis Set (SAF)†	186 (100)	183 (100)	369 (100)
Intention to Treat Set (ITT)‡	186 (100)	183 (100)	369 (100)
Per Protocol Set (PPS)§	172 (92.5)	166 (90.7)	338 (91.6)
Study discontinuation	9 (4.8)	8 (4.4)	17 (4.6)
Withdrawal by patient	7 (3.8)	6 (3.3)	13 (3.5)
Lost to follow up	2 (1.1)	1 (0.5)	3 (0.8)
Discontinuation due to AE	0	1 (0.5)	1 (0.3)

Outcomes and estimation

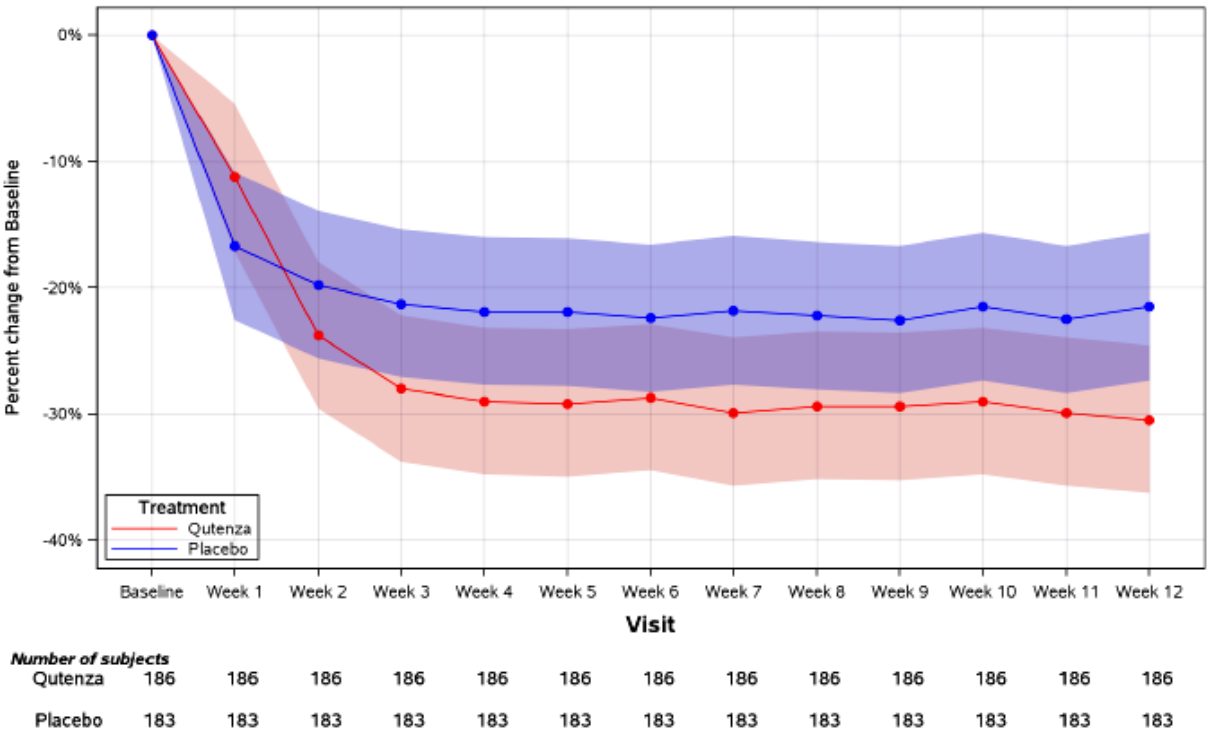
Primary Efficacy Analysis, Average Daily Pain NPRS Score (Question 5 of the BPI-DN) Week 2 to 8

The results of the primary endpoint analysis are presented in Table 3 and Figure 2 below.

Table 3 Percent Change from Baseline to Between Weeks 2 and 8 (BLOCF) for Average Daily Pain Score; Question 5 of the BPI-DN (ITT and PPS).

Primary endpoint	Analysis set, ITT		Analysis set, PPS	
	QUTENZA (N = 186)	Placebo (N = 183)	QUTENZA (N = 172)	Placebo (N = 166)
Mean (SD) % Change from Baseline	-27.44 (26.79)	-20.85 (28.92)	-27.55 (26.86)	-21.40 (29.31)
LS Mean Difference (QTZ – Placebo)†	-6.6		-6.3	
95% CI for Difference	[-12.3, -0.8]		[-12.4, -0.2]	
p-value	0.025		0.042	

Figure 2 Percent Change from Baseline to Between Weeks 2 and 8 in "Average Pain for the Past 24 Hours" (Question 5 of the BPI-DN)



Sensitivity analyses for the primary endpoint

The robustness of the primary endpoint results was demonstrated using either BOCF imputation or repeated measures mixed model analysis with either AutoRegressive 1 (AR 1) or unstructured UN covariance structures. Missing values were considered missing at random in the repeated measures mixed model; therefore, no active imputation was needed for this model analysis.

As shown in Table 4 below, the results were consistent with those for the primary analysis.

Table 4 Impact of Sensitivity Analyses on Estimates of Percent Change from Baseline to Between Weeks 2 and 8 (BOCF and Mixed Model Analyses) for Average Daily Pain Score; (ITT).

Sensitivity Analysis	Analysis set, ITT	
	QUTENZA (N = 186)	Placebo (N = 183)
BOCF		
Mean (SD) % Change from Baseline	-22.93 (24.03)	-18.41 (26.06)
LS Mean Difference (QTZ – Placebo)†	-4.7	
95% CI for Difference	[-9.7, 0.4]	
p-value	0.072	
Mixed Model – UN		
Mean (SD) % Change from Baseline	-27.43 (26.47)	-20.73 (28.89)
LS Mean Difference (QTZ – Placebo)‡	-6.6	
95% CI for Difference	[-12.3, -0.8]	
p-value	0.026	
Mixed Model – AR		
Mean (SD) % Change from Baseline	-27.43 (26.47)	-20.73 (28.89)
LS Mean Difference (QTZ – Placebo)‡	-6.5	
95% CI for Difference	[-12.1, -1.0]	
p-value	0.022	

Secondary efficacy endpoints

Percent Change in the Average Daily Pain Score (Question 5 of the BPI-DN) (between weeks 2 and 12)

Patients treated with Qutenza had a greater reduction in pain from baseline to between weeks 2 and 12 (BLOCF) compared with placebo (p = 0.018).

Percent Change of Average Pain Score by Week (Question 5 of the BPI-DN)

Clear separation could be observed between the Qutenza and placebo, starting at week 3 to the end of the study (week 12). Estimated differences per week varied between 6.3% (week 6) to 9% (week 12) with supporting p-values varying between 0.051 (week 6) and 0.005 (week 12). The week by week comparison showed that the primary analysis result was based on a consistent improvement over time till the end of the study.

30% Reduction in Average Pain Score (Question 5 of the BPI-DN)

More patients treated with Qutenza achieved at least a 30% reduction in average daily pain score from baseline to between weeks 2 and 8 (39.8%) compared with placebo (32.8%) (p=0.108).

In addition, more patients treated with Qutenza achieved at least a 30% reduction in average daily pain score from baseline to between weeks 2 and 12 (40.9%) compared with placebo (31.7%; p=0.050)

50% Reduction in Average Pain Score (Question 5 of the BPI-DN)

The 50% responder rate was achieved for 21% of patients in the Qutenza arm compared with 18.0%) in the placebo arm (either for weeks 2 to 8 or weeks 2 to 12 (p = 0.403 and p = 0.446 respectively).

Time to Treatment Effect

Time to treatment effect was defined as the time taken for patients to first experience a 30% reduction in pain for 3 consecutive days. The median time to pain relief for the ITT data set was numerically shorter for

the Qutenza arm; 19 days (95% CI: 12.0, 37.0) versus 72 days (95% CI: 19.0, not reached) for the placebo arm.

Sleep Interference (Question 9F of the BPI-DN)

Patients treated with Qutenza had a greater mean percent (SD) reduction in sleep interference score from baseline to between weeks 2 and 8 (-33.12 [33.68]) compared with patients treated with placebo (-24.15 [45.02]; p = 0.030)

Patient Global Impression of Change

for the overall status of patients (PGIC self-assessment), from week 8 onwards, a greater proportion of patients reported they were either very much improved or much improved in the Qutenza arm compared to the placebo arm (week 8: 39.4% versus 30.2%; and week 12: 40.5% vs 29.7%, respectively)

European Quality of Life Questionnaire in 5 Dimensions

The increases in the EQ-5D scores have shown a small numerical difference in favour of QUTENZA compared to placebo.

Hospital Anxiety and Depression Scale

For the ITT and PPS analysis sets, the mean change from baseline in HADS were similar in both treatment groups for the anxiety and depression subscale total scores at all timepoints.

Self-Assessment of Treatment (SAT)

At week 8 there were no statistically significant differences observed between treatment groups based on the rating of any of the self-assessment questions.

At week 12, for the following questions, there was evidence of an association between treatment and outcome favouring QUTENZA:

- Over the past 7 days, how much has the study treatment improved your pain level? – a greater proportion of patients in the Qutenza arm (17.5%) compared with (8.2%) in the placebo arm reported their pain level was “quite a bit better” and a greater proportion of patients in the Qutenza arm (13.9%) compared with (7.0%) in the placebo arm reported their pain level was “moderately better”.
- Over the past 7 days, how much has the study treatment improved the following aspects of your life; emotional wellbeing, such as mood, temperament or outlook on life? – a lower proportion of patients reported “not at all” in the Qutenza arm (41.6%) compared with the placebo arm (59.1%) and a larger proportion of patients reported they were “slightly better”, “moderately better” and “quite a bit better” in the Qutenza arm (20.5%, 16.3% and 12.0%) than in the placebo arm (14.0%, 9.9% and 8.8%).

The association between treatment and outcome favouring Qutenza as decribed above for the 12-week analysis was also observed for the end of study (BLOCF, ITT) analysis.

Ancillary analyses

Subgroup analysis

Patients were allocated to 1 of 5 dimensions of the NPSI according to their highest subscale/dimension score. The following order (the order in which the items appear in the calculation manual) were used for

allocation: 1) evoked pain; 2) pressing (deep) spontaneous pain; 3) paroxysmal pain; 4) paresthesia/dysesthesia; and 5) burning (superficial) spontaneous pain.

Subgroup analyses were conducted to assess the potential impact of maximum NPSI dimension/subscale, age, gender, race, site, baseline average daily pain score category, duration of PDPN and screening HbA1c value on the mean percent change in average daily pain score from baseline to the primary analysis period (weeks 2 to 8). In general, subgroups were only analysed descriptively, with the exception of gender and site which were added to the primary ANCOVA model as covariates.

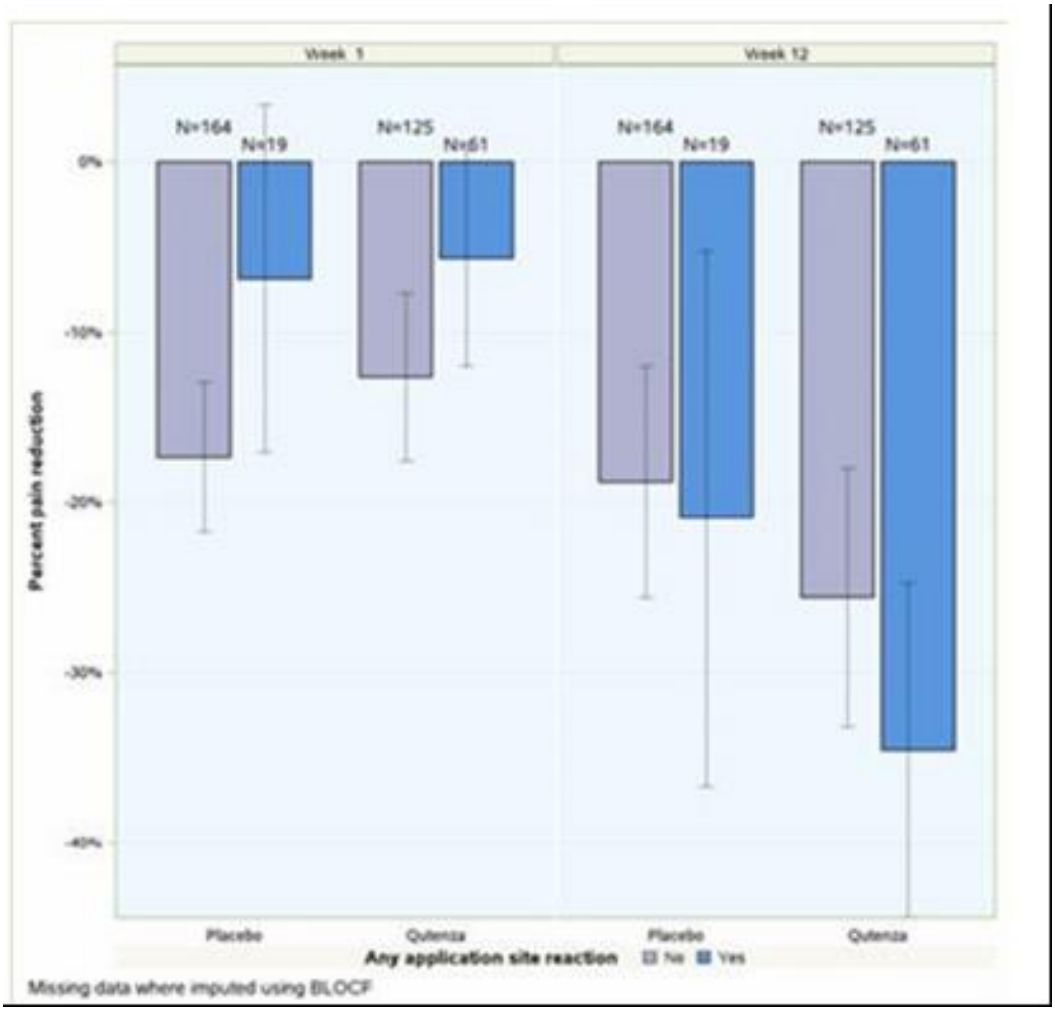
There were no subgroup differences for age, gender, race, site, baseline average daily pain category, duration of PDPN or screening HbA1c value. Subgroup differences were identified for the NPSI dimension/subscale.

The results of the subgroup analysis of the maximum NPSI dimension/subscale showed the mean (SD) percent change from baseline to between weeks 2 and 8 (BLOCF) daily pain score for patients with paroxysmal pain was -32.49 (30.86) in the Qutenza arm compared with -17.32 (25.28) in the placebo arm. The mean (SD) percent change from baseline to between weeks 2 and 8 (BLOCF) daily pain score for patients with paresthesia/dysesthesia was -30.37 (28.41) in the active arm compared with -23.29 (31.05) in the placebo arm. In both treatment groups the absolute mean percent change from baseline to between weeks 2 and 8 was greater than seen for the ITT population. The mean percent change from baseline to between weeks 2 and 8 (BLOCF) daily pain score for patients with burning (superficial) spontaneous pain was similar to that seen for the ITT population. For the evoked pain and pressing (deep) spontaneous pain subgroups there was notably no difference between the Qutenza and placebo arms and improvement in pain was not as pronounced as in the ITT population particularly in the pressing (deep) spontaneous pain subgroup where overall mean (SD) percent change was -17.47 (23.99) compared with -24.17 (28.02) for the ITT population. The numbers of patients in each subgroup based on maximum NPSI pain with the exception of paresthesia/dysesthesia were low (< 50 patients) and therefore results should be interpreted with caution.

“Functional unblinding”

To investigate the potential for unblinding in patients who experienced a local reaction and whether the evidence of efficacy was compromised by unblinding of treatment allocation that may affect the patient’s perception and reporting of pain, additional analyses were performed. Figure 3 below is based on numeric pain rating score (NPRS) scores in patients with and without application site reactions in STEP.

Figure 3 Treatment Effect of Qutenza in STEP by patients who had and had not application site reaction (pain in extremity, application site pain or burning sensation)



At week 12, patients on Qutenza experienced a greater percentage reduction in NPRS scores, compared to patients on placebo, regardless of the application site reaction. This observation was in contrast to what was observed at week 1, where the percentage reduction in the NPRS score was numerically greater for patients on placebo.

Concomitant medications

Pain medications taken at or after baseline

74.0% of patients took pain medications at or after baseline; a similar proportion of patients received them in each treatment arm. Rescue pain medications (for pain caused by patch application) were taken by 12.2% of patients overall with more patients in the Qutenza arm taking them than in the placebo arm. 8.4% of patients took opioids at or after baseline . The proportion of patients using opioid medications for pain at or after baseline was larger in the Qutenza arm compared with the placebo arm; opioids were taken both as rescue medication and for other reasons later in the study.

Pain medications taken at or after baseline were comparable between the treatment arms; 76.3% patients in the Qutenza and 71.6% of patients in the placebo arm. The most commonly used were within

the chemical subgroup “other analgesics and antipyretics” (72 patients [38.7%] in the Qutenza arm and 82 patients [44.8%] in the placebo arm), “other antiepileptics” (72 patients [38.7%] in the Qutenza arm and 82 patients [44.8%] in the placebo arm) and “propionic acid derivatives” (49 patients [26.3%] in the Qutenza arm and 38 patients [20.8%] in the placebo arm).

Rescue medication:

Rescue pain medication was defined as all pain medication that a patient was taking between day 1 and day 5 after patch application treatment. Overall, a larger proportion of rescue pain medications for pain caused by patch application were taken by patients in the Qutenza arm (35 patients [18.8%]), compared with the placebo arm (10 patients [5.5%]). Within 7 days preceding the patch application visit the subject should not have used any oral, transdermal or parenteral opioids, regardless of dose. Overall, the proportion of patients using opioid medications for pain at or after baseline was larger in the Qutenza arm (20 patients [10.8%]) compared with the placebo arm (11 patients [6.0%]).

Additional analysis was performed to investigate analgesic use in patients experiencing application site reactions. The pattern od use is presented in Table 5 below.

Table 5 Analgesic Use in STEP by Adverse Event Experiencing Application Site Reactions

Description of Planned Arm=Placebo Patch (30 minutes)			
Analgesics	Application Site Reaction		
Frequency	No	Yes	Total
No	165 (90.16%)	6 (3.28%)	171 (93.44%)
Yes	2 (1.09%)	10 (5.46%)	12 (6.56%)
Total	167 (91.26%)	16 (8.74%)	183 (100.00%)
Description of Planned Arm = Qutenza Patch (30 minutes)			
Analgesics	Application Site Reaction		
Frequency	No	Yes	Total
No	123 (66.13%)	28 (15.05%)	151 (81.18%)
Yes	3 (1.61%)	32 (17.20%)	35 (18.82%)
Total	126 (67.74%)	60 (32.26%)	186 (100.00%)

Source: Study E05-CL-3004, ad-hoc analysis

To investigate the impact of any bias on the estimated treatment effect due to analgesics use, a sensitivity analysis was performed. The sensitivity analysis was a variation of the primary analysis, excluding any pain scores that might have been influenced by the use of analgesics from week 2 onwards. The results are summarised in Table 6 below.

Table 6 Impact on concomitant analgesic use: Percent Change form Baseline to Between Weeks 2 and 8 (BLOCF) for Average Daily Pain.

Primary Model [E05-CL-3004, Table 12]	Qutenza (n = 186)		Placebo (n = 183)	
Mean % change from baseline	-27.4%		-20.9%	
LS mean difference (Qutenza-placebo)†	-6.6%			
95% CI for difference	[-12.3%, -0.8%]			
P value	0.025			
Primary Model, Censoring Patients' Data When They Started Using Analgesics				
LS mean % change from baseline	-28.7%		-21.4%	
LS mean difference (Qutenza-placebo)†	-7.2%			
95% CI for difference	[-12.9%, -1.5%]			
P value	0.013			
	Analgesics used week 2 onwards		Analgesics used week 2 onwards	
	Yes n = 7	No n = 179	Yes n = 10	No n = 173

Intent to treat sets.

BLOCF: baseline and last observation carried forward

† The difference between Qutenza and placebo for percent change from baseline was compared using an analysis of covariance model including treatment, gender, pain score at baseline, HbA1c at screening and site as factors/covariates.

Source: E05-CL-3004, Attachments 3, Additional Analysis 4

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 Summary of efficacy for trial STEP

Title: A Phase III, Double-blind, Randomized, Placebo-controlled, Multicenter Study Evaluating the Efficacy and Safety of Qutenza in Subjects with Painful Diabetic Peripheral Neuropathy (STEP)		
Study identifier	E05-CL-3004.	
Design	two-arm, double-blind, placebo-controlled, multicentre (US)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable not applicable

Hypothesis	Superiority		
Treatments groups	Qutenza		Qutenza 8% capsaicin patch, 12 weeks, N=186 (randomised)
	placebo		inert (“real”) placebo, 12 weeks, N=183 (randomised)
Endpoints and definitions	Primary endpoint	NPRS score	percent change in the average daily pain score (question 5 of the BPI-DN: “average pain for the past 24 hours” NPRS): average of scores during weeks 2 to 8, compared to the average of baseline scores in the active arm compared to the placebo arm
	Secondary endpoint	NPRS score	percent change in the average daily pain score (question 5 of the BPI-DN: “average pain for the past 24 hours” NPRS): average of scores during weeks 2 to 12, compared to the average of baseline scores in the active arm compared to the placebo arm
	Secondary endpoint	NPRS score	Percent change of weekly average of “average pain for the past 24 hours” NPRS scores from baseline at every week after baseline Weekly average of “average pain for the past 24 hours” NPRS scores at baseline and every week after baseline
	Secondary endpoint	responder analysis (NPRS)	Occurrence of 30% and 50% decrease in the average daily pain score (question 5 of the BPI-DN) from baseline to week 2 and 8 and from week 2 average to week 12
	Secondary endpoint	time to effect	median time to pain relief (where 50% of patients had a 30% reduction in the average daily pain score)

	Secondary endpoint	PGIC	Overall patient status using Patient Global Impression of Change (PGIC) questionnaire at weeks 2, 8 and 12
	Secondary endpoint	HADS	
	Secondary endpoint	EQ-5D	Change in the European Quality of Life Questionnaire in 5 Dimensions (EQ-5D) total score and Depression and Anxiety scores on the HADS from baseline to weeks 2, 8 and 12
	Secondary endpoint	SAT	Treatment satisfaction using the Self-Assessment of Treatment (SAT) questionnaire at baseline, weeks 8 and 12
	Secondary endpoint	sleep interference	Percent change in the sleep interference NPRS score (question 9F of the BPI-DN) from baseline to between week 2 and 8 and week 2 and 12 (i.e., average of scores during weeks 2 to 8 and 2 to 12, compared to baseline)
Database lock	the date of database lock was not reported Study completion (date last subject completed the last visit): 13 Feb 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (*per protocol*)		
Descriptive statistics and estimate	Treatment group	Qutenza	placebo

variability	Number of subject	186 (*172*)	183 (*166*)
	Percent Change from Baseline to Between Weeks 2 and 8 in Average Pain for the Past 24 Hours mean	-27.44 % *(-27.55%)*	-20.85% *(-21.40%)*
	SD	26.79 (*26.86)*	28.98 (*29.31)*
	Percent Change in the Average Daily Pain Score between weeks 2 and 12 mean	-27.96	-21.00
	SD	27.25	29.42

	Weekly Average Daily Pain NPRS Scores		
	week 2 (mean (SD))	-22.97 (26.24)	-19.00 (27.99)
	week 3 (mean (SD))	-27.17 (27.28)	-20.51 (29.96)
	week 6 (mean (SD))	-27.87 (30.02)	-21.66 (31.45)
	week 7 (mean (SD))	-29.03 (29.98)	-21.02 (32.50)
	week 8 (mean (SD))	-28.53 (31.92)	-21.46 (31.29)
	week 12 (mean (SD)	-29.64 (31.20)	-20.76 (33.33)
	responder rates (30% reduction in NPRS score) (number of patients)		
	week 2-8	74 (N=39.8)	60 (N=32.8)
	week 2-12	76 (N=40.9)	58 (N=31.7)

	responder rates (50% reduction in NPRS score) (number of patients) week 2-8 week 2-12	 39 (N=21.0) 41 (N=22.0)	 33 (N=18.0) 35 (N=19.1)
	median time to pain relief (where 50% of patients had a 30% reduction in the average daily pain score) median time (95%CI)	 19 (12.0, 37.0)	 72 (19.0, not reported
	PGIC proportion of patients who reported they were “very much improved + much improved”(week 8)	39.4%	30.2%
	HADS mean (SD)	 -0.7 (2.72)	 -0.6(3.11)
	EQ-5D mean (SD)	 4 (19.09)	 3.5 (18.36)
	SAT	please see in the text	

	percent reduction in sleep interference score from baseline to between week 2-8 mean [SD]	-33.12% [33.68]	-24.15 %[45.02]
Effect estimate per comparison	Primary endpoint	Comparison groups	Qutenza - placebo ITT *(PP)*
	Percent Change from Baseline to Between Weeks 2 and 8 (BLOCF) for Average Daily Pain Score	LS mean difference	ITT:-6.6% *(PP: -6.3%)*
		95% CI for difference	ITT:-12.3, -0.8 *(PP:-12.4; -0.2)*
		P-value	ITT:0.025 *(PP:0.042)*
Effect estimate per comparison	Secondary endpoints	Comparison groups	Qutenza - placebo
Notes	% change in average NPRS between week 2-12	LS mean difference	-7.1
		95% CI	[-12.9, -1.2]
		P-value	0.018
	% change in average NPRS between week 2-12 Weekly Average		

	Daily Pain NPRS Scores LS mean difference [95% CI], P-value	week 2	-4.1 [-10.4, 2.3] p-value 0.208
		week 3	-6.7 [-13.1, -0.4] p-value 0.036
		week 6	-6.3 [-12.6, 0.0] p-value 0.051
		week 7	-8.1 [-14.4, -1.8] p-value 0.012
		week 8	-7.2 [-13.5, -0.8] p-value 0.026
		week 12	-9.0 [-15.3, -2.7] p-value 0.005
	responders, 30% reduction in NPRS week 2-8 *(week 2-12)*	odds ratio	1.4 *(1.5)*
		95% CI for difference	[0.9, 2.2] *[1.0, 2.4]*
		P value	0.108 *(0.05)*
	responders, 50% reduction in NPRS week 2-8 *(week 2-12)*	odds ratio	1.2 *(1.2)*
		95% CI for difference	[0.7, 2.1] *[0.7, 2.0]*

		P value	0.403 *(0.0446)*
	PGIC proportion of patients who reported they were “very much improved + much improved” (week 8)	P value	0.075
	HADS	difference	0.1
		P value	0.034
	EQ-5D	difference	0.5
		P value	n.s.
	percent reduction in sleep interference score from baseline to between week 2-8 mean [SD]	difference	-9
		95% CI for difference	-17.2, -0.9
		P value	0.030

Analysis performed across trials (pooled analyses and meta-analysis)

The effects of Qutenza in PDPN versus PHN and HIV-AN were compared across a range of approaches that included the percentage change from baseline in the average of daily pain scores between weeks 2 and 8, the percentage change from baseline to end of study (week 12), responder analysis (patients with either = 30% or = 50% [average] reduction on Numeric Pain Rating Scale [NPRS]) over 2 to 8 weeks or at end of study (week 12). End of study (week 12) was the only common endpoint across studies and was chosen for the comparison of efficacy between the populations studied. The main results summarized in Table 8 and 9 show that the magnitude of effect of Qutenza in PDPN versus PHN and HIV-AN across these parameters was consistent.

Table 8 Percent Change from Baseline for the primary endpoint at week 12 of Qutenza studies in different populations.

Indication	Study	Percent change from baseline to end of study on average pain for the past 24 hours †			
		Qutenza (n)	Placebo ‡ (n)	Delta §	P-value
PDPN	STEP (E05-CL-3004)	29.6% (n = 186)	20.8% (n = 183)	9.0%	0.005
PHN	C116	31.4% (n = 185)	21.6% (n = 172)	9.8%	0.010
	C117	33.7% (n = 187)	25.9% (n = 176)	7.8%	0.023
HIV-AN	C107	19.5% (n = 129)	6.9% (n = 69)	12.6%	0.016
	C119	31.3% (n = 294)	28.1% (n = 144)	3.2%	0.272

HIV-AN: human immunodeficiency virus-associated neuropathy; PDPN: painful diabetic peripheral neuropathy; PHN: postherpetic neuralgia.

† Mean over the past 7 days.

‡ Placebo patch in STEP, low dose capsaicin patch in the other studies.

§ For E05-CL-3004, the difference between Qutenza and placebo for percent change from baseline was compared using an analysis of covariance model including treatment, gender, pain score at baseline, HbA1c at screening and site as factors/covariates. For the other studies, delta is the difference between the percent change from baseline to end of study on average pain for the past 24 hours in the Qutenza and placebo groups.

Source: E05-CL-3004, Table 12.3.1.1.1; C107, Table 14.2.5.1; C116, Table 14.2.7; C117, Table 14.2.6C; C119, Table 14.2.4

Table 9 30% responder rates in Qutenza Phase 3 studies using Week 12 endpoint in different patient populations.

Indication	Study	Percentage of patients with ≥ 30% reduction in average daily pain score from baseline to week 12 †			
		Qutenza	Placebo ‡	Delta	P-value
PDPN	STEP (E05-CL-3004)	41%	33%	8%	0.049
PHN	C116	46%	37%	9%	0.060
	C117	46%	39%	7%	0.193
HIV-AN	C107 (week 2-12) §	36%	19%	17%	0.010
	C119	46%	45%	1%	0.613

HIV-AN: human immunodeficiency virus-associated neuropathy; PDPN: painful diabetic peripheral neuropathy; PHN: postherpetic neuralgia.

† Average pain score over the past week was used.

‡ Placebo patch in STEP, low dose capsaicin patch in the other studies.

§ Average of week 2 to 12 was used.

Source: E05-CL-3004, Table 12.3.1.1.1, C107, Table 14.2.5.1; C116, Table 14.2.7; C117, Table 14.2.6A; C119, Table 14.2.5A

The clinical relevance of the observed effect of Qutenza was also evaluated in comparison with other agents indicated for the treatment of PDPN. To this end, a network meta-analysis (NMA) was conducted to assess the treatment effect of Qutenza in PDPN compared with other treatment options (pregabalin, gabapentin, duloxetine and amitriptyline). The point estimates of the absolute treatment effects from the random effects model are presented in Figure 4 and the results of the fixed effects model are presented in Figure 5.

Figure 4 Results of the Random Effects Model for Pain Score Reduction; Change from Baseline; Scenario Analysis Including PACE Trial Data

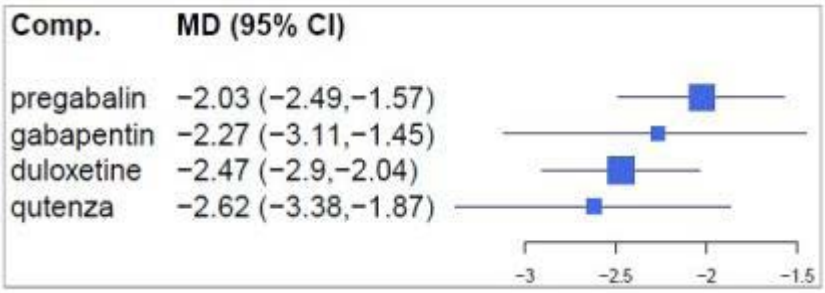
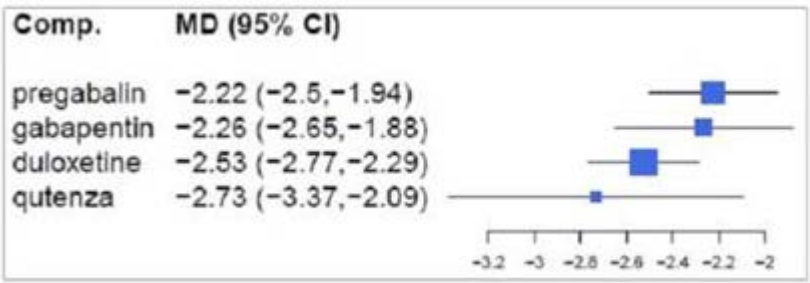


Figure 5 Results of the Fixed Effects Model for Pain Score Reduction; Change from Baseline



Only 9 PDPN-studies reported the number of patients with at least 30% pain reduction. Eight of them and the Qutenza STEP trial were included in the base case analysis; one trial was of too short duration (5 weeks) compared to the other studies and was excluded. A significant difference of Qutenza compared to placebo, numerical advantages of Qutenza compared to pregabalin and gabapentin, and parity of Qutenza to duloxetine have been shown. Pregabalin and gabapentin were performing better than placebo with corresponding 95% credibility intervals indicating no significant differences. (Table 10)

Table 10. Results of the Fixed Effects Model for Number of Patients Reporting at Least 30% Pain Reduction

Drug	Probability†	95% CrI (%)	Probability best	Probability worst	Rank¥
placebo	42.6%	(39.3-45.8)	0%	92.2%	5
pregabalin	48.3%	(43.3-53.3)	0%	2.9%	4
gabapentin	51.1%	(41.7-60.4)	0.7%	4.4%	3
duloxetine	63.2%	(59.3-67)	57.5%	0%	1
Qutenza®	61.4%	(47.3-74.6)	41.9%	0.5%	2

†estimated by applying OR against placebo to the weighted average placebo probability in the network

¥These ranks are based on the probability of being best, i.e. demonstrating higher proportion of patients reporting at least 30% pain reduction.

Clinical studies in special populations

NA

Supportive study

Study title: A Randomized, Controlled, Long-term Safety Study Evaluating the Effect of Repeated Applications of QUTENZA plus Standard of Care versus Standard of Care alone in Patients with Painful Diabetic Peripheral Neuropathy (PACE).

Methods

The PACE study was an open label, long-term safety study (52-week) assessing the safety of repeated Qutenza treatment for 30 minutes plus standard of care (SOC) medication, versus Qutenza treatment for 60 minutes plus SOC medication versus SOC medication alone. Patients and investigators were not blinded to treatment but physicians assessing neurological function were.

Figure 6 Study Flow Chart

Study period	Screening visit	Base line visit	Treatment period											
Total Study Period: Arms I and II: Patients will receive up to 7 patch applications with the last patch application administered no later than week 52. Arm III: Patients will receive SOC treatment for 52 weeks														
Duration relative to Baseline	Day-7 +/- 3	Day 1	Approximately 12 Months											
Month #				M2[a]		M4[a]		M6[a]		M8[a]		M10[a]		M12[a]
Bi-monthly visit	V1	V2		V3		V4		V5		V6		V7		V8
Permissible range relative to Baseline (weeks)	Wk -1 +/- 3 days	Randomization = Arm I: 1st Patch application (30 minutes) + SOC or Arm II: 1st Patch application (60 minutes) + SOC versus arm III: SOC only	Telephone contact M1	Wk 8 +/- 3 days	Telephone contact M3	Wk 17 +/- 3 days	Telephone contact M5	Wk 26 +/- 3 days	Telephone contact M7	Wk 34 +/- 3 days	Telephone contact M9	Wk 43 +/- 3 days	Telephone contacts M11	Wk 52 +/- 3 days

EoS visit [b,c]
V9
[b] Wk 60-64 +/- 3 days if patch applied at V8 [c] Wk 52-56 +/- 3 days

a = QUTENZA patch re-application (arm I and II) may take place at scheduled bi-monthly visits or unscheduled visit at intervals of at least 8 weeks. Additional visits for all arms between the scheduled bi-monthly visits may take place immediately following one of the bi-monthly scheduled telephone contacts.
b = End of Study visit for arms I and II will take place between 8 and 12 weeks after last patch application if patch is applied at V8/M12 and between week 52-56 for subjects who do not have a patch application at V8/M12
c = End Of Study visit for the Standard of Care (SOC) arm (arm III) will take place between week 52 and week 56

Adult, male or female patients with painful, distal, symmetric, sensorimotor polyneuropathy due to diabetes, for at least 1 year prior to the screening visit were eligible for enrolment in this study. Diagnosis of PDPN had to be confirmed by a score of at least 3 on the MNSI and the average Numeric Pain Rating

Scale (NPRS) score over the last 24 hours should have been ≥ 4 at the screening and the baseline visit. Patients should have stable glycemic control for at least 6 months prior to the screening visit, i.e., on antidiabetic drugs (including insulin and/or oral hypoglycemic agents). At least 1 medical record of glycosylated hemoglobin (HbA1c) of ≤ 9% at 3 to 6 months before screening visit and an HbA1c of ≤ 9% at screening visit was required. Similar exclusion criteria were applied as in the STEP study.

The following concomitant medications were permitted during the study:

- Patients received a topical anaesthetic, EMLA prior to placement of Qutenza patches.
- A short-acting analgesic (including short-acting opioid if required) could be administered to relieve treatment-associated discomfort during the treatment procedure and for up to 5 consecutive days post-treatment.
- Any pain medications used as SOC in PDPN as per the investigator's discretion.
- Aspirin up to 325 mg/day for the prevention of ischemia.
- Anti-diabetic medication (including insulin and oral antidiabetics)
- Other medical therapy not specifically prohibited (e.g., statins, fibric acid derivatives, etc.).
- Patients could receive oral and transdermal opioid medication if it did not exceed a total oral daily dose of morphine of 80 mg or the equivalent, which was to be calculated using the Opioid Dose Worksheet. Any changes, additions or discontinuations to medications were assessed and recorded at every study visit.
- Cooling measures, such as cool packs, a light wrapping of gauze misted with cool water or a fan were permitted only after patch removal.

There was no primary efficacy endpoint in this long term safety study. The secondary efficacy endpoints included:

- Change from baseline to end of study in average pain (Question 5 of the BPI-DN), Pain Severity Index, and Pain Interference Index;
- Change from baseline to end of study in Questions 3, 4, 6, 8, and 9a to g of the BPI-DN;
- Time to effect of BPI-DN Question 5 (average pain);
- PGIC,
- HRQOL by assessing the change from baseline to end of study in the EQ-5D;
- Change from baseline to end of study in SAT;
- Change in use of concomitant medications from screening visit to planned or early termination.

Results

Demographics and baseline data are presented in the Table 10 below.

Table 10 Summary of demographics and baseline characteristics (Safety Analysis Set)

Parameter category/statistics	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
Sex, n (%)			
Male	74 (47.4)	79 (50.3)	71 (45.8)
Female	82 (52.6)	78 (49.7)	84 (54.2)
Race, n (%)			
White	154 (98.7)	155 (98.7)	154 (99.4)
Other	2 (1.3)	2 (1.3)	1 (0.6)
Age, years			
Mean (SD)	60.9 (10.88)	61.0 (10.30)	59.1 (10.32)
Median	62.0	62.0	59.0
Min - max	26 - 82	28 - 84	21 - 81
Weight (kg)			
Mean (SD)	86.57 (14.477)	86.71 (16.353)	89.62 (17.641)
Median	86.00	86.00	86.55
Min - max	52.0 - 131.0	50.0 - 124.0	46.0 - 160.0
Height (cm)			
Mean (SD)	169.67 (8.890)	169.70 (9.048)	169.32 (10.912)
Median	170.00	169.00	168.00
Min - max	145.0 - 196.0	143.0 - 196.0	146.0 - 195.0
BMI (kg/m^2)			
Mean (SD)	30.07 (4.562)	30.07 (4.972)	31.19 (4.909)
Median	30.05	30.00	30.90
Min - max	20.1 - 39.6	20.0 - 41.0	19.1 - 42.1
Duration of PDPN (years)			
Mean (SD)	4.1 (3.68)	4.4 (3.86)	4.4 (3.61)
Median	3.3	2.8	3.3
Min - max	1 - 32	1 - 21	1 - 22

All randomized patients who received study patch application (grouped by actual treatment received).

BMI: Body mass index (weight [kg]/height^2 [m^2]); Max: Maximum; Min: Minimum; N: Number of patients in the intention to treat set; n: Number of patients in the sample; PDPN: Painful diabetic peripheral neuropathy; SOC: Standard of care

Source: Table 12.1.2.1.1 and Table 12.1.2.2.1

The demographic and baseline characteristics were similar across treatment arms. All patients used medication prior to baseline. The use of prior treatment, including pain medications and SOC for PDPN, was balanced between treatment groups.

A total of 468 patients were randomized into the study, comprising the Safety Analysis Set (SAF). All randomized patients in the Qutenza arms received treatment. Most patients completed the study; a total of 17.1% of patients discontinued the study post baseline, the most common reason for study discontinuation was withdrawal of consent.

Efficacy outcomes

Percent Change in Average Pain Score (Question 5 of the BPI-DN)

A reduction in average pain, based on the BPI-DN scores, was observed from baseline to the end of the study in the Qutenza (30 minutes; -2.0), Qutenza (60 minutes; -2.3), and SOC (-1.1) arms. Patients treated with Qutenza had a greater reduction in average pain compared to the SOC alone arm, as shown in Figures 7 and 8 and Table 11 below.

Figure 7 Percent Change from Baseline to the End of the Study in "Average Pain for the Past 24 Hours" (Question 5 of the BPI-DN)

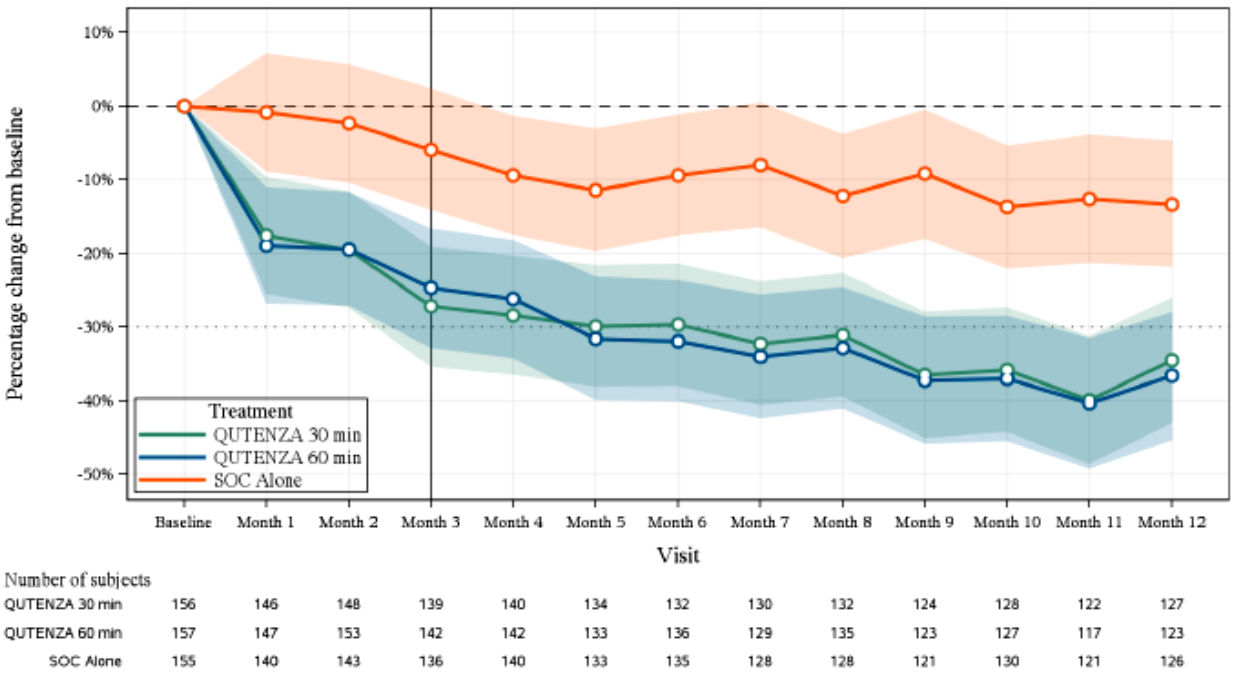


Figure 8 Mean (SD) BPI-DN indices for average pain (Safety analysis set)

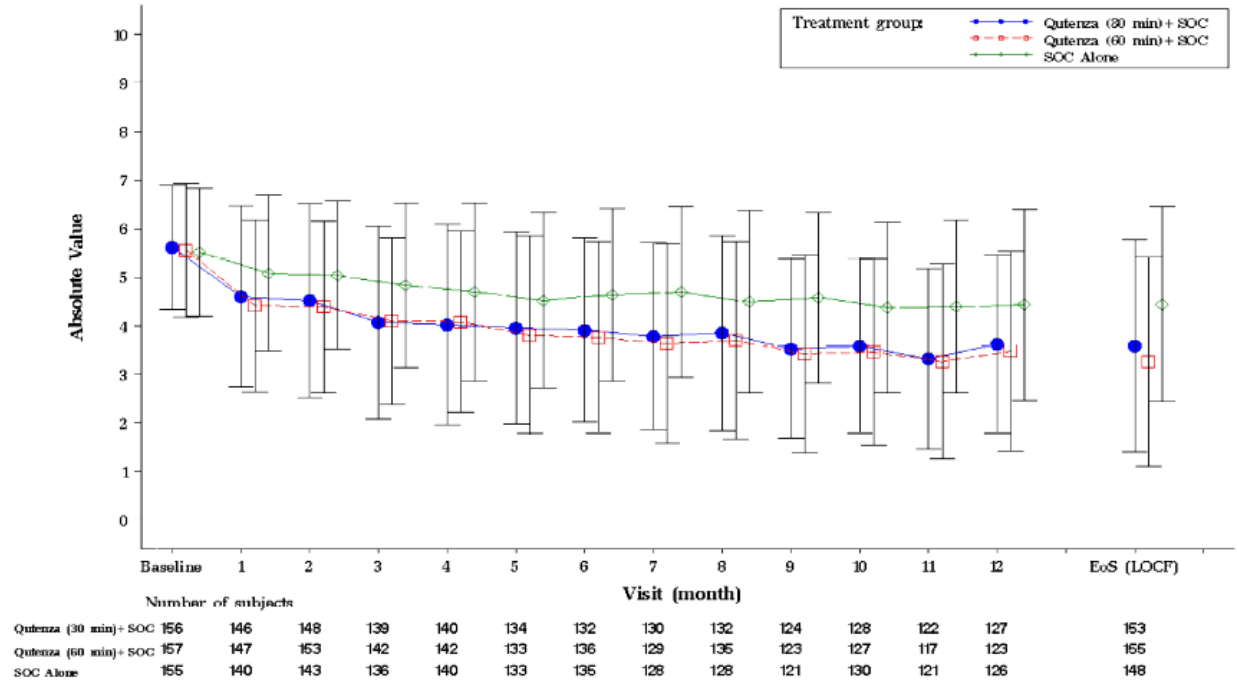


Table 11 Mean change from baseline to end of study in average pain (safety set)

	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
EoS (LOCF)			
n	153	155	148
Mean (SD)	-2.0 (1.82)	-2.3 (2.11)	-1.1 (2.01)
LS mean difference (QUTENZA – SOC alone)	-1.0	-1.2	-
90% CI for difference (QUTENZA – SOC alone)	-1.4, -0.6	-1.6, -0.9	-

EoS: End of study; LOCF: Last observation carried forward; N: Number of patients; n: Number of patients in the sample; SOC: Standard of care.

Source: Table 12.3.1.2.1

30% Reduction in Average Pain Score (Question 5 of the BPI-DN)

67.3% of patients in the Qutenza 30 minutes arm and 67.5% patients in the Qutenza 60 minutes arm had at least a 30% reduction in average pain compared with the SOC alone arm (40.6%). Of those patients, a greater proportion showed a 30% reduction in average pain at month 1 in the Qutenza 30 minutes arm (28.6%) and Qutenza 60 minutes arm (22.6%) compared with the SOC alone arm (14.3%)

50% Reduction in Average Pain Score (Question 5 of the BPI-DN)

44.8% of patients in the Qutenza 30 minutes arm and 48.4% of patients in Qutenza 60 minutes arm had at least a 50% reduction in average pain compared with the SOC alone arm (23.8%). Of those patients, 20% in the Qutenza 30 minutes arm, and 21.1% in the Qutenza 60 minutes arm showed a 50% reduction in average pain at month 1 while no patients demonstrated this effect in the SOC alone arm.

Time to loss of effect

During the study, loss of treatment effect (time to treatment failure) was observed in a comparable proportion of patients in the Qutenza 30 minutes arm (15.4%), Qutenza 60 minutes arm (12.1%) and the SOC alone arm (12.9%). Loss of treatment effect was first observed at month 3 in the Qutenza 60 minutes arm (26.3%) and the SOC alone arm (5.0%) and at month 4 in the Qutenza 30 minutes arm (16.7%). However, loss of treatment effect occurred in no more than 5 patients in each month from month 3 to month 13.

Time to treatment effect and loss of treatment effect pain were analyzed by whether SOC medication was used or not in combination with Qutenza at baseline, and stable or not stable SOC medication in combination with Qutenza throughout the first 2 months. There were no relevant differences between the analysis groups, and the results were consistent with the main analysis.

Percent Change in Pain Severity Index

A reduction in pain severity, based on the BPI-DN scores, was observed from baseline to up to 12 months in the Qutenza 30 minutes (-1.9), Qutenza 60 minutes (-2.2), and SOC alone (-0.9) arms. Patients treated with Qutenza had a greater reduction in pain severity compared with SOC alone. Patients in the Qutenza arms showed sustained improvement in pain severity from baseline to month 1 and up to 12 months, and greater improvements compared with the SOC alone arm.

Change in Pain Scores

A greater improvement in BPI-DN pain scores, assessing daily pain, pain right now, and pain interference, were observed from baseline to up to 12 months in the Qutenza arms compared with the SOC alone arm, as shown in Table 12 below.

Table 12 Mean Change from Baseline to End of Study for Questions 3, 4, 6, 8 and 9a to g

EoS (LOCF)	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
	n = 153	n = 155	n = 148
Pain at its worst in last 24 hours (Question 3)			
Mean (SD)	-2.3 (2.22)	-2.6 (2.40)	-1.2 (2.05)
LS mean difference (QUTENZA – SOC alone)	-1.1	-1.4	-
90% CI for difference (QUTENZA – SOC alone)	-1.5, -0.7	-1.8, -0.9	-
Pain at its least in last 24 hours (Question 4)			
Mean (SD)	-1.5 (2.05)	-1.8 (2.15)	-0.7 (1.95)
LS mean difference (QUTENZA – SOC alone)	-0.8	-1.1	-
90% CI for difference (QUTENZA – SOC alone)	-1.2, -0.4	-1.5, -0.7	-
Pain right now (Question 6)			
Mean (SD)	-1.7 (2.28)	-2.0 (2.19)	-0.8 (1.98)
LS mean difference (QUTENZA – SOC alone)	-0.9	-1.3	-
90% CI for difference (QUTENZA – SOC alone)	-1.3, -0.5	-1.7, -0.9	-
Relief pain treatments provided (Question 8)			
Mean (SD)	12.5 (33.7)	18.6 (36.14)	6.9 (33.53)
LS mean difference (QUTENZA – SOC alone)	5.6	11.7	-
90% CI for difference (QUTENZA – SOC alone)	-0.9, 12.2	5.2, 18.2	-
Pain interfered with general activity (Question 9a)			
Mean (SD)	-1.7 (2.32)	-1.9 (2.63)	-0.9 (1.94)
LS mean difference (QUTENZA – SOC alone)	-0.8	-1.1	-
90% CI for difference (QUTENZA – SOC alone)	-1.2, -0.4	-1.5, -0.7	-
Pain interfered with mood (Question 9b)			
Mean (SD)	-1.9 (2.63)	-2.3 (2.89)	-0.9 (2.24)
LS mean difference (QUTENZA – SOC alone)	-1.0	-1.4	-
90% CI for difference (QUTENZA – SOC alone)	-1.5, -0.5	-1.9, -0.9	-
Pain interfered with walking ability (Question 9c)			
Mean (SD)	-1.8 (2.41)	-1.9 (2.58)	-1.0 (2.03)
LS mean difference (QUTENZA – SOC alone)	-0.8	-1.0	-
90% CI for difference (QUTENZA – SOC alone)	-1.2, -0.3	-1.4, -0.5	-
Pain interfered with normal work (Question 9d)			
Mean (SD)	-1.9 (2.44)	-2.0 (2.74)	-1.0 (2.18)
LS mean difference (QUTENZA – SOC alone)	-1.0	-1.0	-
90% CI for difference (QUTENZA – SOC alone)	-1.4, -0.5	-1.5, -0.5	-
Pain interfered with relations (Question 9e)			
Mean (SD)	-1.5 (2.47)	-1.4 (2.45)	-0.3 (2.31)
LS mean difference (QUTENZA – SOC alone)	-1.1	-1.0	-
90% CI for difference (QUTENZA – SOC alone)	-1.6, -0.7	-1.5, -0.6	-
Pain interfered with sleep (Question 9f)			
Mean (SD)	-2.3 (2.93)	-2.6 (2.77)	-1.1 (2.56)
LS mean difference (QUTENZA – SOC alone)	-1.2	-1.5	-
90% CI for difference (QUTENZA – SOC alone)	-1.8, -0.7	-2.0, -0.9	-
Pain interfered with enjoyment of life (Question 9g)			
Mean (SD)	-2.1 (2.57)	-2.3 (2.80)	-0.8 (2.47)
LS mean difference (QUTENZA – SOC alone)	-1.3	-1.5	-
90% CI for difference (QUTENZA – SOC alone)	-1.8, -0.8	-2.0, -1.0	-

EoS: End of study; LOCF: Last observation carried forward; LS: Least squares; N: Number of patients; n: Number of patients in the sample; SOC: Standard of care.

Source: Table 12.3.1.2.1

Patient Global Impression of Change

A greater improvement in PGIC was observed in the Qutenza arms compared with the SOC alone arm at the end of the study. The overall status of patients was 'very much improved, much improved or minimally improved' in approximately 70% of patients in the Qutenza arms compared with 38.5% in the SOC alone arm.

European Quality of Life Questionnaire in 5 Dimensions

A greater improvement in EQ-5D visual analog scale score was observed from baseline to the end of study in the Qutenza 30 minutes (10.4) and Qutenza 60 minutes (11.2) arms compared with the SOC alone arm (5.5).

SAT Results

At the end of the study, a greater proportion of patients in the Qutenza arms reported improvements in pain level, activity level, and quality of life, based on the SAT questionnaire, compared with the SOC alone arm.

The observed improvements in average pain, pain severity and pain interference were maintained throughout the 12 month duration of the study.

Rescue medication

The proportion of patients who used rescue medication after Qutenza treatment was comparable in the Qutenza 30 minutes arm (22.4%) with the Qutenza 60 minutes arm (29.9%). The types of medication used, and the proportions of patients using them were comparable between Qutenza arms.

Use of concomitant medications

A decrease in medication use was not observed in any of the treatment arms from baseline to the end of the study. Around one third of patients were using antiepileptic drugs at baseline across treatment arms. In the Qutenza arms, the proportion of patients using antiepileptics at the end of the study was comparable with the proportion reported at baseline. In contrast, at the end of the study, the proportion of patients using antiepileptic drugs had increased by > 10% in the SOC alone arm. Use of antidepressants and opioids was relatively low (< 20%) and fairly comparable from baseline to the end of study in the Qutenza arms. Small increases were observed in antidepressant and opioid use in the SOC alone group from baseline to the end of study.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

STEP and PACE clinical trials have been conducted in diabetic patients diagnosed with painful distal symmetrical polyneuropathy for at least 1 year. In STEP, patients were required to have a glycosylated hemoglobin (HbA1c) value ≤ 11% and in PACE ≤ 9%. Patients were allowed to remain on stable background analgesic medication. Given these characteristics, patients enrolled in STEP and PACE studies can be considered to be representative of the target PDPN patient population.

The efficacy of Qutenza was evaluated using uni-dimensional pain scales and multi-dimensional assessment tools, in accordance with the Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain (CPMP/EWP/252/03 Rev. 1). The protocols were reviewed and endorsed by the CHMP.

In studies submitted with the original MAA, low-dose (0.004%) capsaicin patch was used as a comparator to assure blinding conditions. In the STEP study, however, an inert placebo patch without any active substance was used, as placebo response can be considerably higher in the PDPN population than in PHN trials. As concluded in the initial MAA procedure, there are strong reasons to believe that the control arm used in Qutenza trials contributed to reduce the relative therapeutic effect of the active arms. Accordingly, the MAH argued that it is unethical to expose patients to a low concentration capsaicin patch

as the control as it will potentially decrease the likelihood that a trial will show superiority of the active treatment when a true treatment effect exists, thereby increasing the possibility of a noninformative study. This argumentation was endorsed by the CHMP during the initial review of the study protocol, as the proposed measures to mitigate the perception of the capsaicin patch application and its impact on efficacy evaluation were considered sufficient.

The study personnel were considered to be adequately blinded. However, the proper blindness of the study subjects to the treatments has been questioned. It was stressed that the patient may or may not experience burning sensation during treatment and all patients were pre-treated with local anaesthetics. Patients were informed about the drug as follows: "…It contains the active substance capsaicin (8%). Capsaicin is the substance in chili peppers that gives them their perception of heat. […] The placebo is a patch that looks like Qutenza but has no drug or other active ingredient in it…." therefore the patient was aware of the hot nature of the test product. Despite local anaesthetics, covering the application site for 24 h after removal of patch and verbal reassurance of the subjects (....you may or may not experience burning sensation") more patients with Qutenza patch needed rescue medications (35%) than with placebo (10%). Perceiving burning /hot/ painful sensations upon patch application, a patient could conclude that they received active treatment. An inert placebo theoretically allows more precise estimate of treatment effect but in this specific case the blinding of the subjects may have been of concern, especially due to the self-report nature of measures.

Analgesic use by treatment group and by assessment time point has been provided to assess the possible bias on the estimated treatment effect. Two patterns of analgesic use were observed. The first pattern related to local site reaction. Understandably, the analgesic use in the Qutenza group was substantially larger but also longer than 5 days set as rescue period in the protocol. The second pattern was related to a small number of patients who required permanent analgesic use (7 out of 186 patients in Qutenza and 10 out of 183 in the placebo arm). As the number of patients in this group was very small, the CHMP determined that the impact of additional permanent analgesic use on the final outcome is minor.

It has also been shown that functional unblinding was unlikely as at week 12, patients on Qutenza experienced a greater percentage reduction in NPRS scores, compared to patients on placebo, regardless of whether or not application site reaction was experienced. The CHMP concluded that the initially higher analgesic use was not expected to have had an impact on pain assessment at the end of the trial.

Distal polyneuropathy typically shows a stocking-and-glove distribution in the distal extremities. The symptoms typically start in the toes, gradually ascending to the lower limbs. In advanced cases, it spreads to the upper limbs. Since painful diabetic neuropathy is generally localized to lower limbs, the need for application of Qutenza to the upper extremities is likely to be infrequent thus, application in other locations were not investigated in the clinical trials.

Accordingly , the MAH has updated section 4.4 of the SmPC to state: "Qutenza must be applied to intact, non-irritated, dry skin, and allowed to remain in place for 30 minutes for the feet (e.g. HIV-associated neuropathy, painful diabetic neuropathic pain) and 60 minutes for other locations (e.g. postherpetic neuralgia)." This recommendation has been agreed by the CHMP, considering that feet are the most likely location for PDPN.

The pivotal STEP study was carried out in the US but the results can be extrapolated to the European population. The PACE study has been conducted in several regions in Europe and a large difference between the regional results has been observed. The background medication differed between geographical regions: in the EU, patients were most likely treated in line with neuropathic pain treatment guidelines (i.e. pregabalin, gabapentin, duloxetine, tramadol) while in Russia and particularly in Ukraine more emphasis was put on other treatment options, such as vitamin preparations. Baseline SOC treatment was also more frequent in the EU than in Ukraine. Efficacy differed between geographical

regions and was most pronounced in Ukraine (25% of the study population) where the majority of patients did not get any SOC. However, if the higher efficacy were due to the lower rate of background therapy of neuropathic pain, then it would be higher in patients without SOC treatment and this was not the case: for instance in Russia and Ukraine both mean percent change from baseline and responder rates were higher in those subjects who took standard of care. Qutenza was favoured over SOC in all regions. This suggests that other factors than differences in local SOC may have influenced the different efficacy between regions. However, as there was a clear preference towards Qutenza in all regions, the CHMP concluded that the regional variation does not impact on the overall validity of the study.

Efficacy data and additional analyses

Application time of 30 minutes was selected for the STEP study, based on prior results in HIV-AN and PHN studies. Additionally, a 60-minute Qutenza application was also evaluated in PACE study in order to obtain additional efficacy and safety data for the longer application duration. The safety profile of the 60-minute application was comparable to the 30-minute application in the PACE study.

Although the SOC group needed more anti-depressants and antiepileptics, the need for opioids was increased in Qutenza 60 min group. No additional benefit was demonstrated by using the 60-minute application. Therefore, the efficacy and safety data support the application of Qutenza for 30 minutes in patients with PDPN.

The treatment difference was statistically significant between Qutenza and placebo for the primary endpoint in STEP trial. The difference between the active and placebo arm was relatively small and the placebo effect higher compared to prior neuropathy trials. This was in line with literature data. i.e placebo response can be higher in the PDPN population than in PHN patients. However, a higher placebo effect (than in previous trials) was unexpected since an inert patch has been used instead of a low-dose capsaicin control.

In a recent publication (Christian Martini, et al., Pharmacodynamic analysis of the analgesic effect of capsaicin 8% patch (QutenzaTM) in diabetic neuropathic pain patients: detection of distinct response groups, Journal of Pain Research 2012:5 51-59) PDPN patients were classified into four groups regarding their treatment response to Qutenza. According to the authors, patients who reported significant pain relief at week 2 can be classified further as transient responders (Group 3 in the cited publication) or responders who have steady response after single a patch (Group 4). Following the CHMP's request the MAH repeated the analysis using the data of STEP and PACE studies. Following Martini et al. [2012], the MAH classified patients into four groups: full responders, partial responders with recurrent syndromes, no responders with stable syndromes and a group where the patients' conditions worsen despite the treatments. The MAH carried out this analysis only for patients in the Qutenza groups. It was hypothesized that the treatment response after the first patch application is predictive regarding the final outcome and if a patient does not show any response after the first application then any further treatment is a futile attempt. At end of study PACE, patients in each category showed improved pain levels, even the 5 patients that worsened after their first treatment application. Of the nonresponders after initial treatment, more than 50% became a responder after multiple treatments with an average improvement of 26%. These results indicate that patients not responding after 1 treatment application may benefit from subsequent treatments. The results from the PACE study are also comparable with those reported by Martini et al., though fewer patients in PACE showed maximum response with no return. In addition, the results from the STEP and PACE studies are very similar, especially when the responder groups are combined. In conclusion, the hypothesis with regard to the response categories has been confirmed. However, the hypothesis that nonresponders to the initial Qutenza patch application would continue to be nonresponders was not confirmed by the data. Instead, in the PACE study more than 50% of the

nonresponders after initial treatment became a responder after multiple treatments with an average improvement of 26%.

The percentage of patients who failed to experience any improvement in pain was consistently less in the Qutenza arm than in the placebo arm in the STEP study, and less in Qutenza plus standard of care arm compared to standard of care alone arm in the PACE study. The percentage of patients with no response at all was generally comparable in STEP (26% at week 12) to those in prior studies. In HIV-AN- and PNH-studies 29 % and 18% of patients respectively did not show any change or experienced worsening of pain from baseline to week 2-8.

Evaluation of the week 12 results for the PDPN study with those of the phase 3 studies conducted with Qutenza in patients with PHN and HIV-AN were conducted to compare the treatment effects across the aetiologies. The 30% responder rates for painful diabetic peripheral neuropathy showed 8% difference to placebo, with a p=0.049 (borderline significance). The responder rates at 30% level and the magnitude of percent reduction of average pain were comparable across approved and PDPN indications.

The effectiveness of Qutenza in PDPN was further demonstrated by the treatment effect seen with multiple applications in the PACE study where a 1.0-point separation on a pain numerical rating scale from standard of care after multiple treatments was observed.

A meta-analysis (a mixed treatment comparison) was presented to compare responder rates in Qutenza PDPN study with already approved medications for PDPN (pregabalin, gabapentin and duloxetine) and it was shown that Qutenza is as effective as other medications, though due to a smaller sample size the confidence interval of the effect size was larger for the Qutenza estimate.

Pathophysiology of PDPN is multifactorial as diabetes can damage the peripheral nervous system in a variety of ways, but the most common presentation is a distal symmetric polyneuropathy (DSP). Other patterns of injury include small fiber predominant neuropathy, radiculoplexopathy, and autonomic neuropathy, amongst others. While there are clear differences in the pathophysiology of PDPN, HIV-AN and PHN, the qualitative characteristics of the pain overlap between the aetiologies. In all cases the pain is neuropathic in origin, arising from injury to peripheral nerves, resulting in peripheral nociceptor hyper-excitability and altered central nervous signal processing secondary to changes in afferentation. The mechanism of action of capsaicin is considered to be similar in all 3 conditions. Comparable responder rates in the presented studies provide evidence that differences in aetiology do not appear to translate into a clinically meaningful difference in response to treatment with Qutenza.

2.4.4. Conclusions on the clinical efficacy

Based on the results of STEP and PACE studies, the CHMP concluded that the efficacy of Qutenza in the treatment of PDPN has been demonstrated.

2.5. Clinical safety

Introduction

The purpose of this assessment was to evaluate and compare the safety data collected in studies STEP and PACE with the data from the original MAA, which included 12 studies in patients with PHN, HIV-AN and PDPN.

In the studies included in this safety analysis, the Qutenza patch was applied for 30, 60 or 90 minutes, depending on the site of application, pain aetiology and study.

Patient exposure

The overall safety evaluation was based on 3 study pools.

Pool 1 (PDPN Patients from STEP and PACE)
Pool 1 comprised 499 patients and included all patients enrolled into PDPN studies, STEP and PACE, who received at least 1 dose of study drug. Pool 1 consisted of Qutenza data only, with no control comparison.

Pool 2 (Patients Included in the Original Submission Dossier)
Pool 2 comprised 1615 patients who received at least 1 dose of study drug in the 12 studies included in the original MAA: studies C102, C106, C107, C108, C109, C110, C111, C112, C116, C117, C118 and C119.

A subset of patients in C111 study included PDPN patients. To allow for the comparison between PDPN patients versus non-PDPN patients, the PDPN patients from the C111 study were excluded from Pool 2 (non-PDPN population of Pool 2) for these analyses, and comprised 1524 patients. Pool 2 consisted of Qutenza data only, with no control comparison.

Pool 3 (Overall Safety Population)
Pool 3 comprised 2114 patients and provided the overall safety population (combination of all patients in Pool I and Pool 2). The results of the pooled studies were presented to enable a comparison of the data and to demonstrate their consistency, as well as to provide an assessment of the overall safety.

Adverse events

The AEs in this section are described for the STEP and PACE studies; the PDPN population (Pool 1); the PDPN population versus the non-PDPN population (Pool 1 versus Pool 2 excluding PDPN patients in the C111 study); and the overall safety population (Pool 3), where warranted.

The summary of adverse events is provided in Tables below.

Table 13 Overview of Adverse Events- Patients Administered Qutenza

	Number of Patients (%)		
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC [Total Active]) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications [total active]) (Pool 2†) (N = 1524)	Total Population (30, 60 and 90 Minute Applications [Total Active]) (Pool 3) (N= 2114)
TEAEs	296 (59.3)	1297 (85.1)	1648 (78.0)
Drug-related‡ TEAEs	198 (39.7)	1021 (67.0)	1251 (59.2)
Deaths	2 (0.4)	0	2 (0.1)
Serious TEAEs	35 (7.0)	114 (7.5)	155 (7.3)
Drug-related‡ serious TEAEs	2 (0.4)	3 (0.2)	5 (0.2)
TEAEs leading to permanent discontinuation from study	15 (3.0)	0	15 (0.7)
Application site reactions‡	194 (38.9)	1037 (68.0)	1266 (59.9)
TEAE of cardiac disorders within 7 days of patch application	0	9 (0.6)	9 (0.4)
TEAE of blood pressure changes within 7 days of patch application	7 (1.4)	29 (1.9)	38 (1.8)
TEAE related to vital signs	23 (4.6)	91 (6.0)	117 (5.5)

† Does not include the PDPN patients from study C111
‡ Possible or probable, as assessed by the investigator, or records where relationship is missing
N: Number of patients; PDPN: Painful diabetic peripheral neuropathy; SOC: Standard of care; TEAE: Treatment-emergent adverse event
Source: Table 3.1.1.1, Table 3.1.2.1.1 and Table 3.1.3.1.1

Table 14 Pool 1 Common† TEAEs (Occurring in at Least 3% of Patients in any Treatment Group)

MedDRA v13.1 System Organ Class Preferred Term	Treatment, Number of patients (%)		
	QTZ Active (30 min) (N = 186)	QTZ Active + SOC (30 min) (N = 156)	QTZ Active + SOC (60 min) (N = 157)
Overall	65 (34.9)	77 (49.4)	85 (54.1)
General disorders and administration site conditions	18 (9.7)	45 (28.8)	51 (32.5)
Application site pain	18 (9.7)	44 (28.2)	46 (29.3)
Application site erythema	0	12 (7.7)	14 (8.9)
Nervous system disorders	26 (14.0)	19 (12.2)	20 (12.7)
Burning sensation	26 (14.0)	15 (9.6)	15 (9.6)
Headache	5 (2.7)	5 (3.2)	7 (4.5)
Musculoskeletal and connective tissue disorders	21 (11.3)	19 (12.2)	20 (12.7)
Pain in extremity	20 (10.8)	8 (5.1)	13 (8.3)
Back pain	1 (0.5)	4 (2.6)	5 (3.2)
Arthralgia	0	8 (5.1)	4 (2.5)
Infestations and infestations	7 (3.8)	6 (3.8)	17 (10.8)
Upper respiratory tract infection	7 (3.8)	2 (1.3)	3 (1.9)
Bronchitis	0	0	6 (3.8)
Nasopharyngitis	0	4 (2.6)	9 (5.7)
Investigations	0	13 (8.3)	7 (4.5)
Blood triglycerides increased	0	7 (4.5)	3 (1.9)
Glycosylated haemoglobin increased	0	8 (5.1)	5 (3.2)
Skin and subcutaneous tissue disorders	3 (1.6)	5 (3.2)	6 (3.8)
Erythema	3 (1.6)	5 (3.2)	6 (3.8)
Vascular disorders	3 (1.6)	2 (1.3)	9 (5.7)
Hypertension	3 (1.6)	2 (1.3)	9 (5.7)

†TEAEs for which the incidence is ≥ 3% in at least one of the arms; the other TEAEs are excluded and the System Organ Class totals are derived from the common TEAEs only. All TEAEs by preferred term and System Organ Class are presented in Table 3.1.1.2.

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; n: number of patients; PDPN: Painful diabetic peripheral neuropathy; QTZ: QUTENZA; TEAE: Treatment-emergent adverse event; SAF: Safety analysis set; SOC: Standard of care

Source: Table 3.1.1.6

Table 15 Pool 1 and Non-PDPN Pool 2 TEAEs (Occurring in at Least 3% of Patients in Total Active Arm)

MedDRA v13.1 System Organ Class Preferred Term	Treatment, Number of patients (%)	
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC [Total Active]) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications [Total Active]) (Pool 2†) (N = 1524)
Common overall	227 (45.5)	1100 (72.2)
General disorders and administration site conditions	114 (22.8)	974 (63.9)
Application site pain	108 (21.6)	682 (44.8)
Application site erythema	26 (5.2)	661 (43.4)
Application site pruritus	0	142 (9.3)
Application site papules	(< 3)	81 (5.3)
Application site dryness	0	69 (4.5)
Application site swelling	0	67 (4.4)
Application site oedema	0	45 (3.0)
Nervous system disorders	65 (13.0)	105 (6.9)
Burning sensation	56 (11.2)	(< 3)
Headache	17 (3.4)	(< 3)
Infections and infestations	30 (6.0)	174 (11.4)
Upper respiratory tract infection	(< 3)	62 (4.1)
Nasopharyngitis	(< 3)	46 (3.0)
Gastrointestinal disorders	(< 3)	137 (9.0)
Nausea	(< 3)	77 (5.1)
Vomiting	(< 3)	56 (3.7)
Diarrhoea	(< 3)	45 (3.0)
Musculoskeletal and connective tissue disorders	60 (12.0)	62 (4.1)
Pain in extremity	41 (8.2)	(< 3)

† Does not include the PDPN patients from study C111

The table presents TEAEs which were reported in >3% in the total active arm for Pool 1 and non-PDPN Pool 2.

In the supplementary "common" tables the incidence of TEAEs is presented for events which occurred at an incidence of ≥ 3% in at least one of the arms [Table 3.1.1.6] and [Table 3.1.2.1.6]; the other TEAEs are excluded and the System Organ Class totals are derived from the common TEAEs only. All TEAEs by preferred term and System Organ Class are presented in [Table 3.1.1.2] and [Table 3.1.2.1.2].

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; TEAE: Treatment-emergent adverse event; SAF: Safety analysis set

Source: Table 3.1.1.6 and Table 3.1.2.1.6

Table 16 Pool 1 versus Non-PDPN Pool 2 Treatment Related TEAEs (occurring in at least 3 % of patients in the total active arm)

MedDRA v13.1 System Organ Class Preferred term	Treatment, Number of patients (%)	
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications (Pool 2†) (N = 1524)
Common overall	186 (37.3)	974 (63.9)
Nervous system disorders	55 (11.0)	(< 3)
Burning sensation	55 (11.0)	(< 3)
General disorders and administration site conditions	114 (22.8)	974 (63.9)
Application site pain	108 (21.6)	676 (44.4)
Application site erythema	26 (5.2)	658 (43.2)
Application site pruritus	(< 3)	139 (9.1)
Application site papules	(< 3)	80 (5.2)
Application site dryness	(< 3)	67 (4.4)
Application site swelling	(< 3)	65 (4.3)
Application site oedema	(< 3)	45 (3.0)
Musculoskeletal and connective tissue disorders	36 (7.2)	(< 3)
Pain in extremity	36 (7.2)	(< 3)

† Does not include the PDPN patients from study C111

In the supplementary "common" tables the incidence of related TEAEs is presented for events which occurred at an incidence of ≥ 3% in at least one of the arms [Table 3.1.1.7] and [Table 3.1.2.1.7]; the other TEAEs are excluded and the System Organ Class totals are derived from the common TEAEs only. All related TEAEs by preferred term and System Organ Class are presented in [Table 3.1.1.3] and [Table 3.1.2.1.3].

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; PDPN: Painful diabetic peripheral neuropathy; TEAE: Treatment-emergent adverse event; SOC: Standard of care

Source: Table 3.1.1.7 and Table 3.1.2.1.7.

Table 17 Pool 1 vs non-PDPN Pool 2 severe TEAEs (occurring in at least 1 % of patients in the total active arm)

MedDRA v13.1 System Organ Class Preferred Term	Treatment, Number of patients (%)	
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications (Pool 2†) (N = 1524)
Overall	12 (2.4)	162 (10.6)
General disorders and administration site conditions	5 (1.0)	140 (9.2)
Application site pain	5 (1.0)	120 (7.9)
Application site pruritus	(< 1)	18 (1.2)

† Does not include the PDPN patients from study C111

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; PDPN: Painful diabetic peripheral neuropathy; TEAE: Treatment-emergent adverse event; SOC: Standard of care

Source: Table 3.1.1.8 and Table 3.1.2.1.8

STEP Study

In STEP, more patients reported TEAEs in the Qutenza arm (46.8%) compared with the placebo arm (33.9%); however, most of the TEAEs reported were attributable to application site reactions, and were consistent with the established safety profile of Qutenza.

The proportion of related TEAEs was higher in the Qutenza arm (34.9%) compared with the placebo arm (12.6%); however, this was mainly attributable to the application of the patch. 2 patients in the Qutenza arm reported serious AEs (SAEs) (dehydration and convulsion), neither considered related to study drug. No patients in the Qutenza arm had a TEAE resulting in discontinuation from the study.

PACE Study

In PACE, more patients reported TEAEs in the Qutenza arms (68.4%) compared with the SOC alone arm (48.4%), which was mainly attributable to the higher incidence of application site reactions. A comparable proportion of patients reported serious TEAEs in the Qutenza arms (10.5%) compared with the SOC alone arm (9.7%).

Less than 10% of patients in the Qutenza arms reported TEAEs resulting in discontinuation of the treatment or the study.

Common Adverse Events

Pool 1 (PDPN Patients from STEP and PACE)

As expected, application site reactions were the most common TEAEs; burning sensation, application site pain, application site erythema and pain in extremity were the most commonly reported TEAEs in the PDPN population (Pool 1). The incidence of hypertension was higher in the Qutenza (60 minutes) arm (5.7%) compared to the Qutenza (30 minutes) arm (1.5% without SOC and 1.3% with SOC).

Pool 1 versus Pool 2 (PDPN Patients versus Non-PDPN Patients)

Fewer patients in the Qutenza arms reported common TEAEs in the PDPN population (Pool 1; 45.5%) compared to the non-PDPN population (Pool 2 excluding PDPN patients in the C111 study; 72.2%). The type of common TEAEs were comparable in the PDPN population with the non-PDPN population; fewer patients in the PDPN population reported general disorders and administration site conditions compared to the non-PDPN population (22.8% and 63.9%, respectively) including application site pain and application site erythema. However, erythema, burning sensation, and pain in extremity were more commonly reported in PDPN population with burning sensation only being reported in Pool 1 (11% patients).

Comparison of the 30-minute Qutenza application showed that fewer patients reported common TEAEs in the PDPN population (Pool 1; 41.5%) compared with the non-PDPN population (Pool 2 excluding PDPN patients in the C111 study; 67.1%), which was consistent with the analysis for all application durations.

Pool 3 (Overall Safety Population)

Consistent with Pool 1 and Pool 2, the most commonly reported TEAEs in the overall safety population (Pool 3) were application site reactions.

Treatment-related events of general disorders and administration site conditions were reported by fewer patients in the PDPN population (Pool 1; 22.8%) compared to the non-PDPN population (Pool 2 excluding the PDPN patients in the C111 study; 63.9%). Consequently, fewer patients reported related events, by Preferred Term, of application site pain (21.6% and 44.4%) and application site erythema (5.2% and 43.2%) in the PDPN population and non-PDPN population, respectively.

Burning sensation, pain in extremity and erythema were commonly reported treatment related TEAEs in the PDPN population (Pool 1) but not in the non-PDPN population (Pool 2 excluding the PDPN patients in Study C111). However, these TEAEs are the expected application site reactions consistent with the safety profile of Qutenza.

Dermal Assessment

Pool 1 (PDPN Patients from STEP and PACE)

In the PDPN population (Pool 1), 63.3% of patients had no evidence of irritation following patch application (a score of 0 on the dermal assessment scale; an 8-point scale ranging from 0 [no evidence of irritation] to 7 [strong reaction spreading beyond the test site]). No patients scored higher than 3. PDPN patients who were administered Qutenza alone (i.e., without SOC) and who were administered Qutenza for 30 minutes (compared with 60 minutes) reported less irritation.

Pool 1 versus Pool 2 (PDPN Patients versus Non-PDPN Patients)

Fewer PDPN patients (Pool 1) who received Qutenza for 30 minutes reported irritation or application site reactions compared to the non-PDPN patients; 68.3% of PDPN patients had no irritation compared with 33.4% of non-PDPN patients. In addition, 4.1% of PDPN patients had a maximum increase of ≥ 2 points on day 1 compared with 34.1% of non-PDPN patients.

Table 18 Pool 1 versus Non-PDPN Pool 2 application site reactions (occurring in at least 3% of patients in any treatment group)

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MedDRA v13.1 System Organ Class Preferred Term	Treatment, Number of Patients (%)	
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications (Pool 2†) (N = 1524)
Overall	194 (38.9)	1037 (68.0)
General disorders and administration site conditions	117 (23.4)	1010 (66.3)
Application site pain	108 (21.6)	685 (44.9)
Application site erythema	26 (5.2)	662 (43.4)
Application site pruritus	0	139 (9.1)
Application site papules	4 (0.8)	81 (5.3)
Application site dryness	0	69 (4.5)
Application site swelling	0	69 (4.5)
Application site oedema	0	47 (3.1)
Application site vesicles	1 (0.2)	31 (2.0)
Nervous system disorders	60 (12.0)	22 (1.4)
Burning sensation	55 (11.0)	0
Musculoskeletal and connective tissue disorders	36 (7.2)	8 (0.5)
Pain in extremity	36 (7.0)	2 (0.1)
Muscle spasms	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	21 (4.2)	20 (1.3)
Erythema	13 (2.6)	0

† Does not include the PDPN patients from study C111

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; PDPN: Painful diabetic peripheral neuropathy; SOC: Standard of care

Source: Table 3.1.1.10 and Table 3.1.2.1.10

Cardiac Disorders and Adverse Events Associated with Blood Pressure Changes

Cardiac Disorders

No TEAEs in the “Cardiac disorders” System Organ Class with an onset within 7 days following treatment were reported in the PDPN population (Pool 1). In total, 7 patients (0.5%) in the Qutenza arms of the non-PDPN population had cardiac disorders (3 had palpitations, 2 had atrioventricular block first degree and 2 had tachycardia) within 7 days following treatment.

Blood Pressure Changes

In total, 7 (1.4%) Qutenza treated patients in the PDPN population had TEAEs associated with blood pressure changes with onset within 7 days following treatment (3 patients had blood pressure increased

and 4 patients had hypertension). All the patients who experienced TEAEs associated with blood pressure changes were from the PACE study and were, therefore, also receiving SOC medication.

In the non-PDPN population 29 (1.9%) patients had TEAEs associated with blood pressure changes with onset within 7 days following treatment (17 had increased blood pressure, 9 had hypertension, 2 had tachycardia and systolic blood pressure increased and heart rate increased were each reported by 1 patient).

A similar proportion of patients experienced TEAEs associated with blood pressure changes occurring at any time during study (i.e., not just within 7 days of Qutenza patch application) in the PDPN population and non-PDPN population.

Treatment-emergent Adverse Events Associated with Neurological Function

TEAEs associated with neurological function were analysed in the integrated safety analysis. Overall, more patients in the PDPN population experienced TEAEs associated with neurological function (11.8%) compared to the non-PDPN population (4.4%). The difference between the aetiologies was mainly due to the difference in the reports of burning sensation (11.2% versus 0.7%, respectively).

Table 19 Pool 1 vs Non-PDPN Pool 2 Treatment emergent adverse events associated with neurological function.

MedDRA v13.1 System Organ Class Preferred term	Treatment, Number of Patients (%)	
	PDPN Population (30 and 60 Minute Applications on Active or Active + SOC) (Pool 1) (N = 499)	Non-PDPN Population (30, 60 and 90 Minute Applications (Pool 2†) (N = 1524)
Overall	59 (11.8)	67 (4.4)
Nervous system disorders	59 (11.8)	40 (2.6)
Burning sensation	56 (11.2)	11 (0.7)
Hypoaesthesia	3 (0.6)	15 (1.0)
Dysaesthesia	1 (0.2)	0
Paraesthesia	0	9 (0.6)
Hyperaesthesia	0	4 (0.3)
Sensory loss	0	2 (0.1)
Ageusia	0	1 (0.1)
Allodynia	0	1 (0.1)
Sensory disturbance	0	1 (0.1)
General disorders and administration site conditions	0	28 (1.8)
Application site paraesthesia	0	16 (0.1)
Application site hyperaesthesia	0	9 (0.6)
Application site anaesthesia	0	3 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)	0
Skin burning sensation	1 (0.2)	0

† Does not include the PDPN patients from study C111

Within a System Organ Class, a patient may have reported more than 1 type of adverse event.

A TEAE was defined as an adverse event which started or increased in severity after intake/application of the study drug.

Sorting order: Descending frequency by System Organ Class, and within that descending frequency by preferred term based on the total number of patients with TEAEs.

N: Number of patients in the population per treatment arm; PDPN: Painful diabetic peripheral neuropathy; SOC: Standard of care

Source: Table 3.1.1.19 and Table 3.1.2.1.19

Serious adverse event / deaths / other significant events

There were 4 deaths in the PACE study (2 patients in the Qutenza arm and 2 patients in the SOC alone arm), none of which were considered related to study drug. No deaths were reported in the STEP study. During the overall clinical development program, 13 deaths were reported, none of which were considered related to study drug.

Laboratory findings

In the STEP and PACE studies, routine laboratory evaluations (haematology, biochemistry and urinalysis) were completed at screening and, if clinically indicated, later in the study. For both studies, clinical laboratory findings did not reveal any safety concerns.

Neurological and Sensory Testing

The neurological tests performed depended on the aetiology of the pain in the study. The PHN-targeted neurological/sensory examination consisted of light brush, pinprick, vibration, warmth and cold, while the HIV-AN and PDPN-targeted neurological/sensory examination consisted of deep tendon reflex, vibration, warm sensation, cold sensation and sharp (pinprick) sensation. The PACE study also included the Norfolk Quality of Life Diabetic Neuropathy (QOL-DN) questionnaire as the primary safety variable and the Utah Early Neuropathy Scale (UENS) as a secondary safety variable.

STEP Study

Results of sensory testing based on dichotomous scoring in the STEP study over 12 weeks showed that a similar proportion of patients in both the Qutenza and placebo arms reported a reduction in sensitivity from screening to week 12. However, the majority of patients in both groups reported the same or increased sensitivity for all sensory modalities.

Pool 1 versus Pool 2 (PDPN Patients versus Non-PDPN Patients)

For all sensory modalities, as well as reflexes, the proportion of patients with the same scores post-treatment compared to baseline was greater for the 30-minute Qutenza treatment in the PDPN population (Pool 1) compared to the non-PDPN population. Conversely, the proportions of patients reporting either decreased or increased responses were higher in the non-PDPN population (Table 20).

Table 20 PACE study percent change from baseline to end of study in Norfolk QOL-DN Total and Subscale Scores (Safety Analysis Set)

EoS (LOCF)	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
Total Score			
n	134	139	123
Mean (SD)	-27.6 (49.95)	-32.8 (53.21)	-6.7 (54.12)
LS mean difference (QUTENZA – SOC alone)	-20.9	-26.1	
90% CI for difference (QUTENZA – SOC alone)	-31.7, -10.1	-36.8, -15.4	
Physical functioning/large fiber			
n	142	143	131
Mean (SD)	-34.2 (51.83)	-30.9 (86.71)	-11.8 (59.86)
LS mean difference (QUTENZA – SOC alone)	-20.6	-19.1	-
90% CI for difference (QUTENZA – SOC alone)	-34.2, -7.0	-32.6, -5.5	-
Activities of daily living			
n	108	117	105
Mean (SD)	-16.4 (118.78)	-10.6 (136.73)	15.9 (119.74)
LS mean difference (QUTENZA – SOC alone)	-32.3	-26.5	-
90% CI for difference (QUTENZA – SOC alone)	-60.8, -3.9	-54.4, 1.4	-
Symptoms			
n	147	153	144
Mean (SD)	-15.9 (51.30)	-26.8 (46.32)	-2.9 (43.12)
LS mean difference (QUTENZA – SOC alone)	-13.0	-23.9	-
90% CI for difference (QUTENZA – SOC alone)	-22.1, -3.9	-32.9, -14.9	-
Small fiber			
n	114	123	107
Mean (SD)	-12.2 (99.45)	-14.6 (109.82)	-0.2 (114.63)
LS mean difference (QUTENZA – SOC alone)	-12.0	-14.4	-
90% CI for difference (QUTENZA – SOC alone)	-36.0, 12.0	-38.0, 9.1	-
Autonomic			
n	74	65	68
Mean (SD)	-32.8 (94.14)	-30.0 (93.87)	-21.7 (97.15)
LS mean difference (QUTENZA – SOC alone)	-11.1	-8.3	-
90% CI for difference (QUTENZA – SOC alone)	-37.5, 15.3	-35.5, 19.0	-

Pairwise comparison with SOC alone using a one-way ANOVA with treatment group as fixed effect.

EoS: End of study; LOCF: Last observation carried forward; LS: Least squares; N: Number of patients; n: Number of patients in the sample; SOC: Standard of care; QOL - DN: Quality of life - diabetic neuropathy.

Source: [E05-CL-3002, Table 18, Table 27 and Table 12.6.5.2.1]

Table 21 Mean change from Baseline to End of Study in UENS Total Score (Safety Analysis Set)

	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
EoS (LOCF)			
n	149	153	142
Mean (SD)	-2.1 (5.03)	-3.0 (5.05)	-1.2 (4.22)
LS mean difference (QUTENZA – SOC alone)	-0.9	-1.7	
90% CI for difference (QUTENZA – SOC alone)	-1.8, 0.1	-2.7, -0.8	

EoS: End of study; LOCF: Last observation carried forward; N: Number of patients; n: Number of patients in the sample; UENS: Utah Early Neuropathy Scale.

Source: [E05-CL-3002 Table 19 and Table 12.6.6.2]

Safety in special populations

Special populations have not been specifically studied.

Safety related to drug-drug interactions and other interactions

N/A

Post marketing experience

As the current indication in Europe does not include diabetic patients, treatment of these patients is considered to be off-label. Therefore, too few patients with PDNP have been treated to estimate market exposure in this population.

2.5.1. Discussion on clinical safety

The safety of the diabetic population was analysed in comparison with other approved populations. Safety data were presented in 3 pools: Pool 1 (STEP+PACE studies - PDNP population), Pool 2 (all non-diabetic patients safety set from prior studies) and pool 3 (overall safety set).

Overall, 2114 patients received Qutenza during the clinical development program. 1524 patients had pain of non-PDPN aetiology and 590 had pain due to PDPN (91 patients from study C111 and 499 patients from STEP and PACE).

Most of the TEAEs reported in the Qutenza arms in STEP and PACE studies were attributable to application site reactions, and were consistent with the previously established safety profile. The most common adverse drug reactions were: application site pain, burning sensation, pain in extremity, application site erythema and erythema.

The incidence of TEAEs, drug-related TEAEs and application site reactions were lower in the PDPN- compared to the non-PDPN pool. The techniques of reporting of application site reactions were, however, different in PDPN and non-PDPN studies, which hampered the comparison between the pools. In studies submitted in the initial MAA, patients were actively asked if they had experienced an application site reaction (a separate CRF page was utilized), while in STEP and PACE this was not done. Additionally, in the STEP study the application site was covered throughout treatment and 24 h after removal of the patch to limit the probability of unblinding the study at an individual patient level.

The reason for the differences in reporting between PDPN and non-PDPN studies was that the pattern of local reactions with Qutenza had been well characterized in the initial development program. It was determined that since multiple dermal and neurological assessments were included in STEP and PACE studies, spontaneous reporting of AEs would provide sufficient signal for any unique events. Therefore, standard methods of AE elucidation and reporting were used in STEP and PACE, in line with common practice in clinical studies. The protocols for both studies were submitted to EMA prior to starting the studies to confirm that the studies would meet regulatory expectations for the follow-up measures.

Difference in respect of TEAE capture may have influenced the difference in application site reactions that are presented in these studies. Inter-study variation may also have been due to developmental stage of Qutenza. AEs reported pre-approval could have been more numerous and diverse than those reported post-approval due to the familiarity of the Investigator with the drug. The MAH clarified that a standard method of reporting of adverse events was used to avoid bias of overreporting some dedicated adverse

events and underreporting some others. The CHMP was of the opinion that this approach can be acceptable, particularly since dermal assessment and monitoring was carried out very carefully and no new adverse events emerged and the safety profile in diabetic patients is comparable to the safety profile in the non-PDPN population.

Burning sensation and pain in extremity were more commonly reported in the PDPN population (N= 55 vs. 0 and N=36 vs. 2, respectively, in PDPN vs. non-PDPN pools). Both burning sensation and pain in extremity can be due to the underlying neuropathy. However, an imbalance observed between diabetic and non-diabetic population was most likely due to the different reporting of AEs in both pools.

Most events of burning sensations and pain in extremity were related to application site reactions, were mild to moderate and resolved without long-term sequelae. The pattern of the appearance also confirmed that most reactions emerged shortly or immediately after patch application which suggest that these AEs were related to the study drug. The frequency categories of both burning sensation and pain in extremity were changed from uncommon to common in the SmPC.

Patients with painful diabetic peripheral neuropathy may have coexisting peripheral autonomic neuropathy with vasomotor and sudomotor dysfunction, which may lead to an increase in the vulnerability of the skin to breakdown. Application of capsaicin 8% in such areas may have a greater irritant effect, and result in cutaneous lesions at the treatment site. Therefore, an appropriate warning has been added to section 4.4 of the SmPC to instruct the physician to perform careful visual examination of the patients' feet prior to every application of Qutenza.

An increase in hypertension and burning pain was observed after 60-minute application in PACE study. This finding may have been due to the fact that those patients receiving the 60-minute application experienced more pain, which was associated with a temporary increase in blood pressure.

The observed mean blood pressure changes, regardless of timing, were small in both painful diabetic peripheral neuropathy (PDPN) and non-PDPN studies. In PDPN patients the mean increases in systolic blood pressure at 15 minutes after patch removal were 2.0, 1.1 and 2.2 mm Hg for Qutenza 30 minutes, 30 minutes + standard of care (SOC) and 60 minutes + SOC, respectively. This compares with 2.1 and 6.0 mm Hg for Qutenza 30 minutes and 60 minutes, respectively, in non-PDPN patients at 5 minutes after patch removal.

The diabetic population is considered to be at higher risk for cardiovascular events and the transient increase in blood pressure is a well-known effect of treatment with Qutenza. Therefore, a warning that particular attention should be given to diabetic patients with significant comorbidities has been added to the SmPC.

No significant decrease in sensory and neurological function was detected by the Norfolk questionnaire and UENS scale in the PACE trial. Both of these instruments were compliant with the CHMP guideline for peripheral neuropathy. A greater reduction (i.e., a lack of deterioration) was observed in Norfolk QOL-DN total scores (primary endpoint in PACE) in the Qutenza arms compared with the standard treatment, suggesting the absence of neuropathy-related functional deterioration and improved quality of life in the Qutenza arms. The reduction in total score was greater in the Qutenza-60 min arm compared to the Qutenza-30 min arm. Greater reduction was observed in all subscale scores in the Qutenza arms than in the SOC alone arm. However, mean values suggest that in activities of daily living, patients in the SOC alone arm experienced some worsening.

An improvement in UENS total score was observed from baseline to the end of study in all treatment arms. There were no relevant differences in score between Qutenza arms compared to the standard treatment. The proportion of patients with the same scores in all sensory modalities and reflexes were greater for PDPN than in the non-PDPN population, while the proportion of patients reporting either

decreased or increased responses was higher in the non-PDPN population. Despite being an open-label study, PACE results suggest that neurological-sensory functions were not compromised.

The clinical safety data suggests no clear evidence for neurological impairment with multiple patch applications or dermal injuries which may have been associated with sensory loss. However, in the PACE study there was one case of hypoaesthesia which was considered possibly related to use of Qutenza and did not resolve 2 years after end of study. It was acknowledged that hypoaesthesia could have been caused by the worsening of the underlying disease but the role of study drug cannot be excluded. Post-marketing safety data did not show neurological impairment in the non-diabetic neuropathy indications to date, however, pharmacodynamic studies showed that in diabetic patients with neuropathy, recovery of epidermal nerve fibre density impaired by capsaicin treatment may be decreased. Tissue regeneration is known to be impaired in diabetic patients, particularly in those who suffer from a complicated disease. Persistent hypoaesthesia of the feet is therefore considered a particular risk for diabetic patients because of the risk of development of diabetic foot. Section 4.4 of the SmPC was updated to add this particular warning.

Patients with retinopathy have generally more severely complicated diabetes with signs of microvasculopathy. Therefore, the CHMP requested data on local reactions and sensory changes in this subset of patients.

The number of patients with retinopathy was low and the results should be interpreted with caution. In the STEP study, the proportion of patients with decreased sensitivity to below normal was higher in the retinopathy population, particularly for thermal stimuli and sharp sensations. However, these results cannot be attributed to capsaicin since this could be observed for both Qutenza and placebo arms, perhaps with minimally worse outcomes in the placebo group. The seemingly worse sensory outcomes could not be seen following multiple applications in the PACE study in which sample size of retinopathy subjects was considerably higher than in STEP.

A similar pattern was observed for local reactions: in STEP a slightly higher incidence of local reactions were observed in retinopathy subjects but the sample size was low and these differences less consistent than in sensory assessment. Furthermore this was not confirmed in the PACE study. Overall, the data do not suggest a worse safety profile of Qutenza in patients with diabetic retinopathy in terms of neurosensory functions and local reactions.

2.5.2. Conclusions on clinical safety

The CHMP concluded that the safety profile of Qutenza in diabetic patients was similar to the safety profile previously characterised in the broader neuropathic pain population. The most common AEs were local reactions of short duration.

The SmPC has been updated to highlight the particular importance of cardiovascular risk, neurosensory loss and intactness of skin in diabetic patients. Events of interest will be closely reviewed and reported in the Periodic Safety Update Reports.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP, requested changes to be made to the RMP to align it with the SmPC changes. The MAH submitted an updated RMP version 18.3 to bring the RMP in line with the updated SmPC. The CHMP agreed with the RMP version 18.3.

Summary of the safety specifications:

Summary of safety concerns	
Important identified risks	• Application site reactions • Accidental exposure • Transient increase in blood pressure • Lack of response to oral analgesics in those subjects with a high opioid tolerance when treated for acute pain during and following the procedure • Reductions in sensation, which are generally minor and temporary, at the application site including to thermal and sharp stimuli • Second degree burns
Important potential risks	• Loss of neurosensory function after repeated treatments • Lack of efficacy • Off label use
Missing information	• Interaction between capsaicin and topical local anaesthetic agents

Risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Application site reactions	Posology in section 4.2 of the SmPC Special warning and precaution for use in section 4.4 of the SmPC Listed in section 4.8 of the SmPC	Prescribers' Administration Guide
Accidental exposure	Posology, Method of administration and Instruction for use in section 4.2 of the SmPC Special warning and precaution for use in section 4.4 of the SmPC Special precaution for disposal and other handling in section 6.6 of the SmPC Listed in section 4.8 of the SmPC	Prescribers' Administration Guide
Transient increase in blood pressure	Special warning and precaution for use in section 4.4 of the SmPC Listed in Section 4.8 of the SmPC	Prescribers' Administration Guide
Lack of response to oral analgesics in those subjects with a high opioid tolerance when treated for acute pain during and following the procedure	Special warning and precaution for use in section 4.4 of the SmPC	Prescribers' Administration Guide
Reductions in sensation, which are generally minor and temporary, at the application site including to thermal and sharp stimuli	Special warning and precaution for use in section 4.4 of the SmPC Listed in section 4.8 of the SmPC	Prescribers' Administration Guide
Second degree burns	Posology in section 4.2 Special warning and precaution for use in section 4.4 of the SmPC Listed in Section 4.8 of the SmPC	Prescribers' Administration Guide
Loss of neurosensory function after repeated treatments	Special warning and precaution for use in section 4.4 of the SmPC	Prescribers' Administration Guide
Lack of efficacy	Clincial efficacy and safety in section 5.1 of the SmPC	None
Off label use	Therapeutic indications in section 4.1 Posology in section 4.2 of the SmPC Special warning and precaution in section 4.4 of the SmPC	Prescribers' Administration Guide
Interaction between capsaicin	Posology in section 4.2 of the	Prescribers' Administration Guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
and topical local anaesthetic agents	SmPC	

Pharmacovigilance plan:

Study / activity Type, title and category	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
QAPSA* (FR-QTZ-NI-001)	QUTENZA: a prospective and multicenter cohort study in standard clinical practice. Study required by the French Authority for reimbursement (Haute Autorité de Santé)	Long-term effects of repeated applications of capsaicin in terms of impact on pain perception, on quality of life.	Ongoing	December 2015

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template and SmPC guideline, which were reviewed and accepted by the CHMP.

2.7.1. User consultation

No user consultation with target patient groups on the package leaflet has been performed on the basis of the justification provided. The MAH considers that the main change in the patient leaflet is the wording of the indication. All other changes to the patient leaflet are considered minor and do not alter the key safety and efficacy messages. Therefore additional readability testing is considered unnecessary. The CHMP accepted this justification as valid.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the STEP study, Qutenza provided prolonged pain relief after a single patch application. The 30% responder rates for diabetic peripheral neuropathy showed 8% difference to placebo.The mean time to

maximal analgesic effect was approximately 3 weeks and the effect was maintained over the subsequent 9 weeks of the study.

Sustained efficacy was seen with repeat applications in the long-term PACE study. A higher proportion of patients achieved a clinically meaningful reduction in pain (> 30% reduction from baseline) in Qutenza treated patients compared to those receiving SOC treatment (67.3% versus 40.6%). Approximately twice as many Qutenza patients achieved a 50% reduction in pain from baseline compared to those receiving SOC treatment (46.6% versus 23.8%, respectively).

Treatment with Qutenza was associated with improvement in the general well-being of patients with PDPN, as observed by less interference with activities of daily living, less interference with sleep, and improved emotional well-being. Assessment of patient satisfaction with treatment was favourable for Qutenza and a positive effect on quality of life was observed compared to SOC.

Uncertainty in the knowledge about the beneficial effects

The difference between Qutenza and placebo was relatively small although comparable to other neuropathy studies. This is considered noteworthy considering that an inert placebo has been used in STEP in contrast to the low concentration capsaicin patch used as control in prior Qutenza studies. The use of inert placebo raised questions regarding the blinding of the STEP study, since the study subjects were aware of the irritative nature of Qutenza. This concern was considered to be especially valid as the efficacy evaluation relied on self-assessment questionnaires.

The efficacy was considered to be weak with regards to responder rates. The 30% responder rate in the STEP study was borderline significant (p= 0.049). The majority of secondary outcomes in the STEP study were not statistically significant.

According to literature data, lower concentration capsaicin could be effective in the management of PDPN, however, the results of those studies are inconclusive. The lowest exposure to capsaicin, which can be effective, is not known. Based on the consideration that the most likely localisation of PDPN is on lower limbs, only foot applications were investigated.

Risks

Unfavourable effects

The most frequent AEs in diabetic patients were application site reactions, which is consistent with the safety profile observed in the non-diabetic population. The most common AEs were: application site pain, burning sensation, pain in extremity, application site erythema and erythema.

Patients with diabetic peripheral neuropathy could have coexisting peripheral autonomic neuropathy with vasomotor and sudomotor dysfunction, which may lead to an increase in the vulnerability of the skin to breakdown. Application of Qutenza in such areas may have a greater irritant effect, and result in cutaneous lesions at the treatment site.

Transient increase in blood pressure is a known risk associated with treatment-related pain. Diabetic patients with complicated disease may be at higher risk of cardiovascular events. Diabetes is also linked to the theoretical risk of a reduction or loss of neurosensory function following repeated Qutenza treatment.

Uncertainty in the knowledge about the unfavourable effects

The comparison of application site reactions between PDPN and non-PDPN populations is hindered by the difference in AEs reporting technique between older and new studies.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

PDPN is characterized by pain, paraesthesia and sensory loss. Existing pharmacological treatments are limited and the pain is often challenging to treat. Efficacy of current neuropathic pain treatments is variable: few patients experience complete pain relief, response may vary over time, and none of the treatments are without potential side effects.

The efficacy of Qutenza was limited in the placebo-controlled trial. However, incremental effectiveness was demonstrated when Qutenza was added to a background of 'standard of care' treatment.

The most common AEs are local reactions of short duration, which are particularly important in the diabetic population. However, the safety profile was not worse than in other neuropathy subjects studied in clinical trial settings.

With regards to the specific risks in the PDPN population, specific guidance has been added to the SmPC and educational material. Firstly, it was recommended that the feet of diabetic patients should be visually examined prior to each treatment with Qutenza to detect skin lesions associated with underlying neuropathy and/or peripheral vascular disease.

Furthermore, it was advised to clinically assess distal sensation in patients with pre-existing sensory impairment prior to each application of Qutenza therapy. Finally, the risk of cardiovascular events in diabetic patients has been addressed in the SmPC and educational material, with the advice to pay particular attention to those patients with comorbid coronary artery disease, hypertension and cardiovascular autonomic neuropathy.

Benefit-risk balance

The benefit-risk balance of Qutenza in the treatment of peripheral neuropathic pain in diabetic patients is considered positive.

Discussion on the Benefit-Risk Balance

The demonstration of efficacy for Qutenza in PDPN has been considered in the context of the unmet medical need that characterizes this group of patients. Only approximately 50% of patients show a 30% reduction in pain from baseline levels and many patients require treatment with a combination of drugs from different classes such as tricyclic antidepressants, duloxetine or pregabalin. These drugs are all characterized by a substantial adverse events burden.

Qutenza is a topical formulation with limited dermal penetration and minimal systemic absorption that provides an alternative to combination oral treatments. Because a single treatment with Qutenza may be associated with sustained reductions in pain that persists for up to 3 months, the high-concentration capsaicin patch is considered to provide a valuable addition to existing pharmacological treatments for PDPN, which are typically administered 1 or more times each day.

The safety profile of Qutenza in PDPN including patients who have confirmed retinopathy was generally consistent with what was observed in the previously studied populations of PHN and HIV-AN submitted with the initial MAA. The differences in the aetiology of these three neuropathies do not appear to translate into a clinically meaningful difference in response to treatment with Qutenza, thus supporting a broad neuropathic pain label.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE) for Qutenza.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Annex II, Labelling and Package Leaflet are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives for Belgium in the Package Leaflet. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and Package Leaflet.

An updated RMP (version 18.3) has been approved as part of the application.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

This CHMP recommendation is subject to the following amended conditions:

Other Conditions and Requirement of the Marketing Authorisation

- **Periodic Safety update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the details of an educational programme for health care practitioners with the National Competent Authorities and implement such programme nationally before launch.
This educational programme will include:

- recommendations regarding the general handling and disposal measures for Qutenza
  - administration of capsaicin should only be done under medical supervision
  - because of the risk of accidental exposure, the use of nitrile gloves, a mask and protective glasses are recommended
  - administration of Qutenza in a well ventilated area to reduce the risk of occupational exposure
- instructions regarding the administration of Qutenza
- warnings and precautions, including the need:
  - to undertake a visual examination of the feet prior to each application of Qutenza and at subsequent clinic visits to detect skin lesions related to underlying neuropathy and vascular insufficiency in patients with painful diabetic peripheral neuropathy
  - to be aware of the risk of reductions in sensory function which are generally minor and temporary (including to thermal and sharp stimuli) following administration of Qutenza
  - to use caution when administering Qutenza in patients with reduced sensation in the feet and in those at increased risk for such changes in sensory function
  - to clinically assess patients for increased sensory loss prior to each application of Qutenza in all patients with pre-existing sensory deficits. If sensory loss is detected or worsens, Qutenza treatment should be reconsidered
  - to monitor blood pressure during the treatment procedure
  - to provide supportive treatment if patients experience increased pain during Qutenza administration
  - in patients with unstable or poorly controlled hypertension or cardiovascular disease: to evaluate, prior to initiating Qutenza treatment, the risk of adverse cardiovascular eventsdue to the potential stress of the procedure. Particular attention should be given to diabetic patients with comorbidities of coronary artery disease, hypertension and cardiovascular autonomic neuropathy
  - in patients using high doses of opioids and with suspected high opioid tolerance: to put in place an alternative pain reduction strategy prior to initiating Qutenza treatment, as these patients may not respond to oral opioid analgesics when used for acute pain during and following the treatment procedure
  - to warn patients about the risk of causal local reactions (e.g. contact dermatitis) and of irritation of the eyes and mucous membranes associated with the cleansing gel of Qutenza.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include treatment of diabetic patients with peripheral neuropathic pain based on the results of studies E05-CL-3004 (STEP) and E05-CL-3002 (PACE) for Qutenza. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet Annex II and Labelling are updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives for Belgium in the Package Leaflet. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II, labelling and Package Leaflet. An updated RMP (version 18.3) has been approved as part of the application.

Summary

Please refer to the scientific discussion Qutenza-H-C-909-H-C-II-39.