SYNOPSIS

Title of Study: 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

Investigators/Coordinating Investigator: [redacted], Czech Republic

Study Center(s): This study was conducted at 71 centers in a of total 11 countries in Europe

Publication Based on the Study: Not applicable

Study Period: November 2011 to February 2014

Study Initiation Date (Date of First Enrollment): 10 Nov 2011

Study Completion Date (Date of Last Evaluation): 27 Feb 2014

Phase of Development: phase 3

Objectives:

Primary Objective: to assess the safety of repeat applications of QUTENZA administered over a period of 12 months in patients with painful diabetic peripheral neuropathy (PDPN).

Secondary Objectives: to assess the efficacy of repeat applications of QUTENZA administered over a period of 12 months in patients with PDPN.

Methodology: This was a multicenter, 3-arm, randomized study to assess the long-term safety of repeated applications of QUTENZA patch applications with standard of care (SOC) versus SOC alone in patients with PDPN. The active arms (arms I and II) included QUTENZA patch(es) with an application time of 30 or 60 minutes, respectively) with SOC. The control arm (arm III) included SOC only. Patch re-applications took place either at scheduled bi-monthly visits or at unscheduled visits. No patients could receive more than 7 QUTENZA patch applications during the study. No study patch application was to be made later than at week 52. Patients and investigators were not blinded but physicians assessing neurological function were blinded to treatment.

Number of Patients (Planned, Enrolled and Analyzed): A total of 300 eligible patients were planned to be treated; in total 468 patients were randomized into the study (156 patients received QUTENZA [30 minutes] + SOC, 157 patients received QUTENZA [60 minutes] + SOC, and 155 patients received SOC alone).

Diagnosis and Main Criteria for Inclusion: Patients were required to meet all of the following criteria:

1. Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations were obtained from the patient or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable)
2. Male or female ≥ 18 years of age
3. Diagnosis of painful, distal, symmetric, sensorimotor polyneuropathy, which was due to diabetes, for at least 1 year prior to screening visit

4. Diagnosis of PDPN confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI)

5. At least one medical record of glycosylated hemoglobin (HbA1c) of ≤ 9% at 3 to 6 months before screening visit and an HbA1c of ≤ 9% at screening visit. A patient who had an HbA1c of > 9% at the screening visit, for whom the pre-screening value was ≤ 9%, may have undergone a more intensive period of diabetes treatment for 3 months and be re-screened. Upon rescreening, the patient may have been enrolled if the HbA1c was ≤ 9% or if the investigator attested that Diabetes Mellitus (DM) was appropriately optimized for that patient

6. Stable glycemic control for at least 6 months prior to screening visit, i.e., on antidiabetic drugs (including insulin and/or oral hypoglycemic agents [OHA])

7. Average Numeric Pain Rating Scale (NPRS) score over the last 24 hours of ≥ 4 at the screening and the baseline visit.

Test Product, Dose and Mode of Administration, Batch Numbers: Each patch contained a total of 179 mg of capsaicin or 640 µg of capsaicin per cm^2 of patch (8% w/w). Up to 4 patches (1120 cm^2) could be applied at each application. The patches were applied for 30 minutes (arm I) or 60 minutes (arm II) to painful areas.

Material	Batch number	Expiry date
QUTENZA	Manufacturer batch # of patch: [redacted]	
	Astellas batch # of kit : [redacted]	June 2014
EMLA	[redacted]	Feb 2014
EMLA	[redacted]	April 2014

Duration of Treatment (or Duration of Study, if applicable): The study period was up to 52 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers: The choice of medication and dose of SOC was at the discretion of the investigator. Patients randomized to arm III received treatment optimized on an individual basis.

Criteria for Evaluation: This open-label, safety study assessed the safety of repeat applications of QUTENZA plus SOC administered over a period of 12 months compared with SOC alone. The primary variable was the percentage change from baseline to end of study in the Norfolk Quality of Life Questionnaire - Diabetic Neuropathy (QOL-DN) total score. A reduction in score indicated the absence of functional deterioration related to changes in underlying peripheral neuropathy. The Norfolk QOL-DN is a self-administered questionnaire, designed to capture and quantify the impact of diabetic neuropathy on the quality of life of individual patients with diabetic neuropathy. The secondary safety variables were: change from baseline to end of study in Norfolk QOL-DN subscale scores; change from baseline to end of study in Utah Early Neuropathy Scale (UENS) total and subscale scores; change from baseline to end of study in the average sensory testing score, involving ratings of evoked sensations, including pain; tolerability of patch application assessed by dermal assessment (0 to 7 point severity score on the Dermal Assessment Scale); “Pain now” NPRS scores before and after patch application; and rescue pain medication use on days 1 to 5 (where rescue pain medications were used on days 1 to 5 for pain associated with patch applications). Safety was assessed by

evaluation of adverse events (AEs), laboratory assessments, and changes in vital signs (blood pressure and pulse rate).

Secondary efficacy variables were: Change from baseline to end of study in average pain (Question 5 of the Brief Pain Inventory Diabetic Peripheral Neuropathy (BPI-DN), Pain Severity Index, and Pain Interference; change from baseline to end of study in Questions 3, 4, 6, 8, and 9a to g of the BPI-DN; change from baseline to end of study in patient global impression of change (PGIC); change from baseline to end of study in the European Quality of Life Questionnaire in 5 Dimensions (EQ-5D); change from baseline to end of study in self-assessment of treatment (SAT); and use of concomitant medications.

Criteria for Evaluation, Posthoc Analyses: To further understand the tolerability and efficacy of QUTENZA following repeated applications, posthoc analyses were performed in a subset of patients who had received all 7 QUTENZA patches to assess: change from baseline to the end of study in UENS total score by visit; onset of treatment emergent AEs (TEAEs) by patch application; and change from baseline to end of study in the Pain Severity Index.

Statistical Methods: Only 1 analysis set was defined, the safety analysis set (SAF); this was used for all analyses (both safety and efficacy).

All data processing, summarization, and analyses were performed using SAS® Version 9.3.

For continuous variables, descriptive statistics included the number of patients (n), mean, SD, minimum, maximum, Q1, median, and Q3. Frequencies and percentages are displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., added up to 100%.

The primary safety variable (Norfolk QOL-DN total score) was analyzed as:

- Descriptive statistics are for absolute value at end of study
- Descriptive statistics are for change from baseline at end of study
- Descriptive statistics are for percent change from baseline at end of study
- A 90% CI was reported for the difference between each of the active treatment arms against SOC control for change from baseline and percent change from baseline at end of study.

An additional sensitivity analysis was performed on the Norfolk QOL-DN total score as descriptive statistics shown for absolute values and as changes from baseline to end of study

The secondary safety variables were analyzed as:

- Norfolk QOL-DN subscale scores: descriptive statistics for absolute values and as changes from baseline to end of study
- UENS total score: descriptive statistics for absolute values and as changes from baseline to end of study, and counts by clinically significant decrease category (a decrease of at least 4 points versus a decrease of less than 4 points) reported at each post baseline analysis visit
- UENS total grouped by the number of patch applications: : descriptive statistics for absolute values and as changes from baseline to end of study, and counts by clinically significant decrease category (a decrease of at least 4 points versus a decrease of less than 4 points) reported at the end of the study

- UENS total score: descriptive statistics for absolute values and as changes from baseline to end of study
- Sensory testing scores: descriptive statistics for absolute values, dichotomous scores (average sensory score) analyzed as counts by category (decrease versus same or increased) for each modality reported for each post baseline analysis visit, original scores summarized as the shift from baseline in the combined counts in each category for the left and right sides for each item at each post baseline analysis visit, and worst finding for each modality summarized as counts by category and counts by combined category (below normal versus. not below normal)
- Dermal assessments: counts in each category and combined category ≥ 4 scores (definite edema or higher), dermal assessments at each patch application are summarized as counts by category (and combined category ≥ 4 scores): before and after patch application, worst post application response, and worst post baseline response
- "Pain now" NPRS scores: descriptive statistics shown for absolute values at each patch application
- AEs (coded by Medical Dictionary for Regulatory Activities [MedDRA] v13.1) were defined as either a: post randomization adverse event (PRAE) (an AE observed on or after the day of randomization); or treatment-emergent adverse event (TEAE) (an AE observed after starting administration of the test drug). Day 1 was set as each patch application date for the QUTENZA arms. The number of patients with AEs by days was counted from day 1 to day 55 by patch applications. TEAEs, serious TEAEs, drug-related TEAEs (TEAEs with probable or possible relationship to the study drug) and TEAEs resulting in discontinuation of the treatment or the study, were reported throughout the study
- Laboratory test results of HbA1c and lipids profiles (total cholesterol, low-density lipoprotein -cholesterol, high-density lipoprotein -cholesterol, and triglycerides): Descriptive statistics for absolute values and as changes from baseline to end of study
- Vital signs associated with patch applications (QUTENZA arms only), and collected at screening and end of study: descriptive statistics for absolute values and as changes from screening to end of study

The efficacy variables were analyzed as:

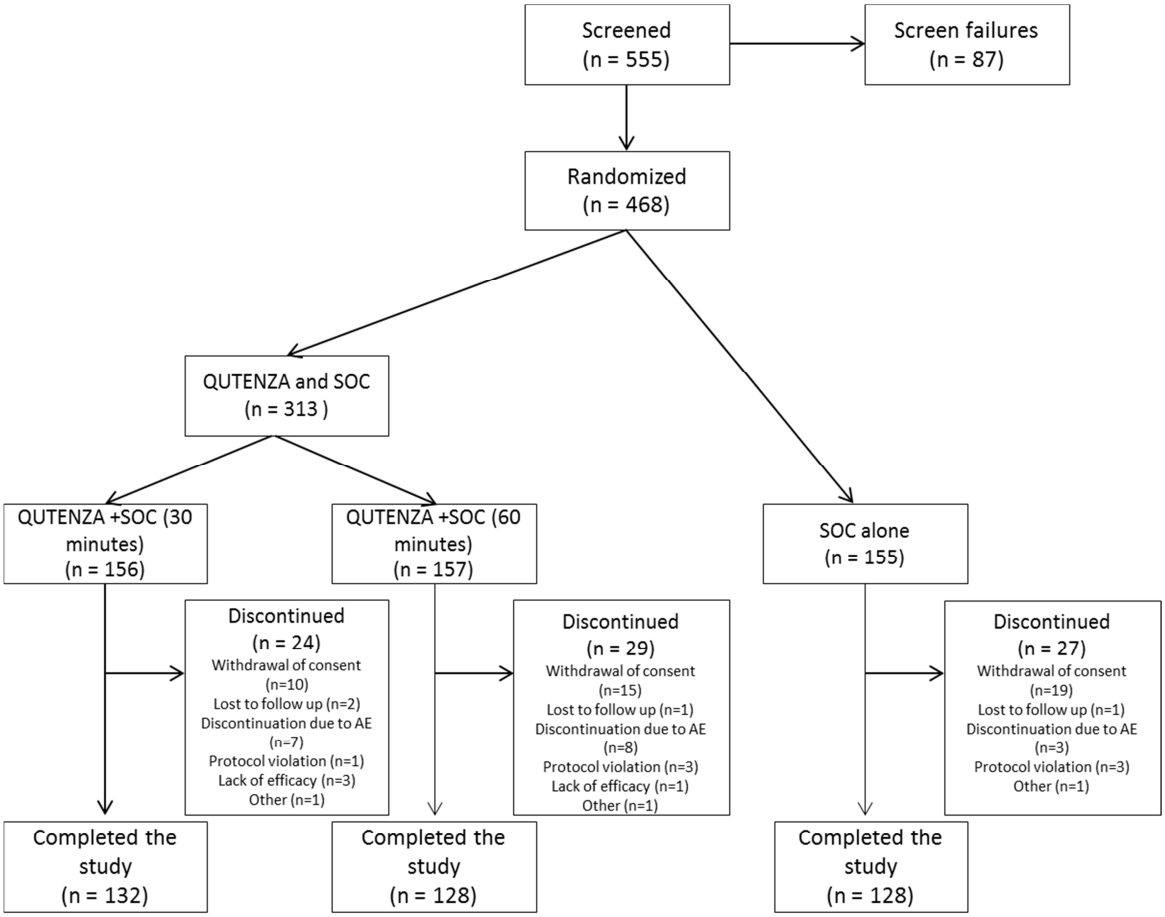
- Average pain (Question 5 of the BPI-DN), Pain Severity Index, Pain Interference, and BPI-DN Questions 3, 4, 5, 6, 8, and 9a to g: absolute values at each analysis visit and change from baseline at each post baseline analysis visit
- PGIC: counts by category and counts by combined categories at each analysis visit
- EQ-5D Questionnaire: descriptive statistics for absolute values and as changes from baseline to end of study
- SAT: counts by category and counts by combined categories at the end of study
- Use of concomitant medications: antidepressants, antiepileptic drugs, and opioids were summarized by visit. The number of patients with at least one medication in the class was counted.

Summary of Results/Conclusions

Patient Disposition: 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, with the most common reason for study discontinuation as withdrawal of consent (Figure 1).

Figure 1 Patient Disposition



SOC: standard of care.

Patient Demographics: the demographic and baseline characteristics were similar across treatment arms. The mean (SD) age of patients was 60.4 (10.52) years.

Table 1 Summary of Demographics and Baseline Characteristics for Patients (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 (14.48)	86.71 (16.35)	89.62 (17.64)
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 (8.89)	169.70 (9.05)	169.32 (10.91)
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 (4.56)	30.07 (4.97)	31.19 (4.91)
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

Prior and Concomitant Medications: the proportion of patients using opioids for pain, psychoanaleptics, and antiepileptic drugs increased from prior to treatment to baseline or after in all treatment arms. A greater increase from prior treatment to baseline or after was observed in antiepileptic and psychoanaleptics use in the SOC alone arm compared with the QUTENZA arms. Non medication therapies prior to treatment were used by less than 10% of patients across treatment arms, the most common being surgical and medical procedures. An increase in the proportion of patients using non medication therapy was observed, at or post baseline, in more than 10% of patients in all treatment arms. The greatest increase was observed in the QUTENZA (30 minutes) arm from 3.8% prior to treatment, to 24.4% at or after baseline compared with an increase of 1.9% to 17.2% in the QUTENZA (60 minutes) arm and 5.8% to 16.1% in the SOC alone arm.

Efficacy Results

Primary Efficacy Variable: this study did not include a primary efficacy endpoint.

Secondary Efficacy Variables

Brief Pain Inventory - Diabetic Neuropathy Question 5 (Average Pain): A reduction in average pain was observed from baseline to the end of study in all treatment arms. Patients treated with QUTENZA had a greater reduction in average pain compared to the SOC alone arm.

During the study, more patients in the QUTENZA arms (105/156 patients [67.3%] in the QUTENZA [30 minutes] arm, and 106/157 patients [67.5%] 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 of patients 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%).

During the study, more patients in the QUTENZA (30 minutes) arm (44.8%) and QUTENZA (60 minutes) arm (48.4%) had at least a 50% reduction in average pain compared with the SOC alone arm (23.8%). Of those patients, 20% of patients 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 subjects demonstrated this effect in the SOC alone arm.

During the study, loss of treatment effect was observed in a comparable proportion of subjects 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 > 5 subjects in each month from month 3 to month 13.

Brief Pain Inventory - DN (Pain Severity Index): a reduction in pain severity was observed from baseline to the end of study in all treatment arms. Patients treated with QUTENZA had a greater reduction in pain severity compared with SOC alone. The improvement in pain severity was comparable between QUTENZA arms.

Brief Pain Inventory - DN (Pain Severity Index) by Visit: patients in the QUTENZA arms showed sustained improvement in pain severity from baseline to month 1 and up to the end of study, and greater improvements compared with the SOC alone arm. The reductions in pain severity were comparable between the QUTENZA arms over time.

Brief Pain Inventory - DN (Pain Interference): a reduction in pain interference was observed from baseline to the end of study in all treatment arms. Patients treated with QUTENZA had a greater reduction in pain interference compared with patients treated with SOC alone. The improvement in pain interference was comparable between QUTENZA arms.

Brief Pain Inventory – DN (Questions 3, 4, 6, 8 and 9a to g): a greater improvement in BPI-DN pain scores were observed from baseline to the end of study (EoS) in the QUTENZA arms compared with the SOC alone arm. The improvements were comparable between QUTENZA arms.

Question 8 of the BPI-DN enquires into the patients' assessment of how much relief pain treatments or medications provided in the last 24 hours in terms of percentage reduction, rather than by use of a rating scale.

Greater pain relief was observed in the QUTENZA arms compared with the SOC alone arm. The magnitude of this relief appeared greater for QUTENZA (60 minutes) arm compared with the QUTENZA (30 minutes) arm. This result is consistent with the overall trend seen for the BPI-DN pain and pain interference assessments, which generally showed a relatively greater treatment effect versus SOC alone for the QUTENZA (60 minutes) arm compared with the QUTENZA (30 minutes) arm.

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 + minimally improved' in approximately 70% of patients in the QUTENZA arms

compared with 38.5% in the SOC alone arm, whereas the overall status was 'no change + minimally worse + much worse + very much worse' in approximately 30% of patients in the QUTENZA arms compared with 61.5% in the SOC alone arm.

EQ-5D Questionnaire: overall, a greater proportion of patients in the QUTENZA arms had no problems with their health at the end of the study, based on according to each of the five dimensions of the EQ-5D, compared with the SOC alone arm.

A greater improvement in EQ-5D visual analog scale score was observed from baseline to the end of study in the QUTENZA arms compared with the SOC alone arm, and the improvement in score was comparable between QUTENZA arms.

Self-assessment of Treatment: 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 compared with the SOC alone arm. The improvements 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 subjects 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 more than 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.

Safety Results

Primary Safety Analysis: Change in Norfolk QOL-DN total score from baseline to end of study: The Norfolk QOL-DN scale was used to detect the impact on patient functioning associated with changes in nerve fiber-specific functions, including small-fiber sensation, which may have been related to the potential adverse effect of long term exposure to QUTENZA on peripheral nerve endings. A reduction in Norfolk QOL-DN score indicated the absence of functional deterioration related to changes in underlying peripheral neuropathy.

A greater reduction in Norfolk QOL-DN total score was observed in the QUTENZA arms compared with the SOC alone arm, suggesting an improvement in QOL and the absence of neuropathy-related functional deterioration in the QUTENZA arms. The reduction in total score was greater in the QUTENZA (60 minutes) arm compared with the QUTENZA (30 minutes) arm (Table 2 and Figure 2).

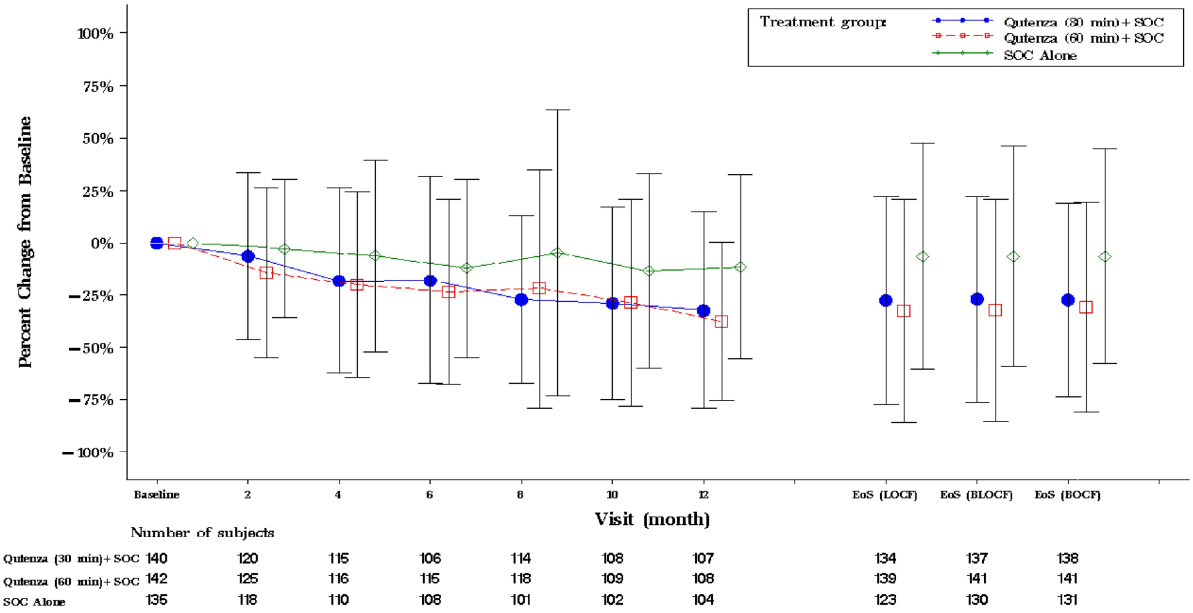
Table 2 **Percent Change from Baseline to EoS in Norfolk QOL-DN Total Score (Safety Analysis Set)**

EoS (LOCF)	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
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	

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 subjects; n: Number of subjects in the sample; SOC: Standard of care.

Figure 2 **Mean (+/- SD) Norfolk QOL-DN Scale Percent Change from Baseline to EoS (Safety Analysis Set)**



BOCF: baseline observation carried forward; BLOCF: baseline and last observation carried forward; EoS: end of study; LOCF: last observation carried forward; SOC: standard of care.

Sensitivity Analysis on Norfolk QOL-DN Total Score: no notable differences were observed between the sensitivity analyses and the SAF analysis without imputed missing values.

Secondary Safety Variables:

Norfolk QOL-DN Subscale Scores: a reduction in Norfolk QOL-DN subscale scores was observed across all treatment arms from baseline to end of study Table 3. A greater reduction in score was observed in the QUTENZA arms compared with the SOC alone arm for subscales "physical functioning/large fiber", "symptoms", "small fiber" and "autonomic", suggesting no functional deterioration in "activities of daily living". There was a marginal improvement in score in the QUTENZA (30 minutes) arm compared with the SOC alone arm for subscale "activities of daily living" Table 3.

Table 3 Percent Change from Baseline to EoS in Norfolk QOL-DN Subscale Scores (Safety Analysis Set)

EoS (LOCF)	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
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	-

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

Utah Early Neuropathy Scale Scores: the UENS is a sensitive clinical examination scale which was specifically developed to detect changes or progression in the severity and anatomical distribution of sensory neuropathy. The UENS places most emphasis on the severity and anatomical distribution of sharp sensation in the lower limbs. A reduction in the UENS score indicates a lack of deterioration in neurological function including no increase in small-fiber sensory loss.

Utah Early Neuropathy Scale Total Score: 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 with the SOC alone arm.

Utah Early Neuropathy Scale Total Score by Visit: in patients who received the maximum of 7 QUTENZA patch applications, no increase in the UENS total score was noted with an increasing number of applications. Improvements in score were greater in the QUTENZA (60 minutes) arm compared with the QUTENZA (30 minutes) arm.

Utah Early Neuropathy Scale Subscale Scores: the improvements in UENS subscale scores from baseline to end of study were similar between the QUTENZA arms compared with the SOC alone arm, with the exception of the sharp sensation subscale.

A greater improvement in the sharp sensation subscale score from baseline to end of study was observed in the QUTENZA arms compared with the SOC alone arm. The decrease in score represented an improvement in

sharp sensation Table 4. In the overall study population, there was no evidence of an adverse effect of repeated applications of QUTENZA on sharp sensation.

Table 4 Mean Change from Baseline to EoS in UENS Sharp Sensation Subscale Score (Safety Analysis Set)

EoS (LOCF)	QUTENZA (30 min) + SOC (N = 156)	QUTENZA (60 min) + SOC (N = 157)	SOC alone (N = 155)
Sharp sensation			
n	150	155	144
Mean (SD)	-1.4 (3.84)	-2.2 (3.99)	-0.7 (3.14)
Median (min, max)	-1.0 (-16, 12)	-1.0 (-18, 8)	0.0 (-11, 9)

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

Sensory Testing: more than 65% of patients in the QUTENZA arms and SOC alone arm showed no deterioration in sensation at the end of the study. The proportions of patients with the same or improved scores for vibration, reflexes, warm and cold were marginally greater in the QUTENZA (60 minutes) arm compared with the QUTENZA (30 minutes) arm and SOC alone arm. The proportion of patients with the same or improved scores for sharpness were comparable between QUTENZA arms, and greater compared with the SOC alone arm.

Dermal Assessment: at screening, there was no evidence of dermal irritation in the majority of patients (>95%) in all treatment arms. Less than 3% of patients in each treatment arm had "minimal erythema barely perceptive" (Category 1) or "definite erythema, readily visible; minimal edema or minimal papular response" (Category 2).

Prior to the application of the topical anesthetic and prior to the patch applications (first to seventh), there was no evidence of dermal irritation in the majority of patients (> 90%) in all treatment arms. Fifteen minutes after patch removal, the proportion of patients with evidence of dermal irritation increased; however, most patients showed no evidence. Approximately 30% of patients showed "minimal erythema barely perceptive" (Category 1) and less than 10% showed "definite erythema (readily visible); minimal edema or minimal papular response" (Category 2). Less than 2% of patients had "erythema and papules" (Category 3) after the first and seventh applications. A similar trend was observed 60 minutes after patch removal.

Based on the worst post baseline response (prior to or after patch application), and the worst post application response, most patients showed either no evidence of irritation (40.6%) or "minimal erythema barely perceptive" (43.1%). No patient had "definite edema or higher" (Category 4).

Rescue Medications: 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.

"Pain Now" NPRS Scores: overall, based on the pain score scale of 1 to 10, the mean pain scores after patch application were low (≤ 3.5). The peak mean pain was observed 15 minutes and 60 minutes after the first QUTENZA patch application. Pain score reduced after the second patch and remained relatively stable from the fifth patch to the last patch.

Adverse Events: post randomization AEs (PRAEs) were AEs observed on or after the day of randomization and were collected to allow for comparison of the QUTENZA arms with the SOC alone arm. Treatment-emergent AEs (TEAEs) were AEs observed after starting administration of the test drug (QUTENZA); hence, there are no TEAEs in the SOC alone arm.

The proportion of patients reporting PRAEs were comparable between QUTENZA arms, and as expected, were greater for QUTENZA combined with SOC compared with the SOC alone. Four deaths were reported: 2 patients in the QUTENZA arms and 2 in the SOC alone arms, none of which were considered treatment-related.

The incidence of TEAEs considered by the investigator to be drug-related was comparable between the 2 QUTENZA arms, with the majority being application site reactions.

In the QUTENZA (60 minutes) arm, 2 patients experienced 3 serious TEAEs considered to be drug-related [Section 9.3.1.7.2], and 4 patients experienced 4 TEAEs leading to permanent discontinuation of study drug, which were considered to be drug-related. There were no drug-related serious TEAEs or drug-related TEAEs leading to permanent discontinuation of study drug in the QUTENZA (30 minutes) arm [Table 5].

Table 5 Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	QUTENZA (30 min) + SOC (N = 156)		QUTENZA (60 min) + SOC (N = 157)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
TEAEs	104 (66.7)	463	106 (67.5)	453
Drug-related TEAEs †	62 (39.7)	217	71 (45.2)	267
Serious TEAEs	20 (12.8)	46	13 (8.3)	18
Drug-related serious TEAEs †	0	0	2 (1.3)	3
TEAEs leading to permanent discontinuation of study drug	7 (4.5)	24	8 (5.1)	10
Drug-related AEs leading to permanent discontinuation of study drug †	0	0	4 (2.5)	4
Application site reactions	60 (38.5)	208	69 (43.9)	254
Deaths	1 (0.6)	-	1 (0.6)	-

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

A treatment-emergent adverse event is an AE observed after starting administration of the test drug (QUTENZA).

SAEs include those upgraded by the sponsor based on review of the Sponsor's lists of Always Serious terms, if any upgrade was done.

AE: Adverse event; N: Number of patients; SAE: Serious adverse event; SOC: Standard of care.
TEAE: Treatment-emergent adverse event

† Possible or probable, as assessed by the investigator, or records where relationship is missing.

The reported TEAEs in the QUTENZA arms were consistent with the established safety profile of QUTENZA. The most frequently reported TEAEs were application site reactions.

The incidence of TEAEs reported in at least 5% of patients in the QUTENZA arms are presented in [Table 6]. There were no notable differences between QUTENZA arms, and there were no differences in AEs related to sensory loss in the System Organ Class "Nervous System Disorders" including hypoaesthesia between the QUTENZA arms.

Table 6 Incidence of Treatment Emergent Adverse Events (Reported by ≥ 5% of Patients in Any Treatment Arm) (Safety Analysis Set)

MedDRA v13.1 System Organ Class Preferred term	QUTENZA (30 min) + SOC (N = 156) n (%)	QUTENZA (60 min) + SOC (N = 157) n (%)
All systems		
Any AE	104 (66.7)	106 (67.5)
General disorders and administration site conditions		
Application site erythema	12 (7.7)	14 (8.9)
Application site pain	44 (28.2)	46 (29.3)
Infections and infestations		
Bronchitis	0	8 (5.1)
Nasopharyngitis	4 (2.6)	9 (5.7)
Investigations		
Blood triglycerides increased	8 (5.1)	3 (1.9)
Glycosylated hemoglobin increased	9 (5.8)	5 (3.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	8 (5.1)	4 (2.5)
Pain in extremity	8 (5.1)	14 (8.9)
Nervous system disorders		
Burning sensation	15 (9.6)	15 (9.6)
Vascular disorders		
Hypertension	3 (1.9)	9 (5.7)

Sorting order: Alphabetically by System Organ Class and PT.

A treatment-emergent adverse event is an AE observed after starting administration of the test drug. There are therefore no TEAEs in the SOC arm. If an AE has missing date parts and missing value for the flag of onset timing that prevent a definitive determination that it was prior to the first patch application, it was considered a TEAE.

† Drug related TEAEs had a possible or probable relationship to study drug, as assessed by the investigator, or had a missing relationship.

AE: Adverse event; N: Number of patients; n: Number of patients in the sample; SAE: Serious adverse event; SOC: Standard of care; TEAE: treatment-emergent adverse event.

More than one third of TEAEs were identified as application site reactions in the QUTENZA arms. The type and frequency of application site reactions were comparable between QUTENZA arms. More than one third of TEAEs were identified as application site pain in the QUTENZA (30 minutes) arm (36.5%) and in the QUTENZA (60 minutes) arm (40.8%). The type and frequency of application site pain TEAEs were comparable between QUTENZA arms. A comparable proportion of patients reported TEAEs identified as application site dermal changes in the QUTENZA (30 minutes) arm (10.3%) and in the QUTENZA (60 minutes) arm (12.7%). The type and frequency of application site dermal changes were comparable between QUTENZA arms.

In general, there were no increases in the proportion of patients reporting TEAEs relative to the first exposure after repeated QUTENZA applications over the course of the study.

The most frequently reported drug-related TEAEs were application site reactions. No patients reported drug-related TEAEs that were considered serious in the QUTENZA (30 minutes) arm; 3 patients reported drug-related TEAEs that were considered serious in the QUTENZA (60 minutes) arm.

Severe TEAEs were considered to be drug-related by the investigator in a total of 7 patients in the QUTENZA arms (< 5%).

Serious TEAEs by System Organ Class and Preferred Term are presented in Table 7. Less than 15% of patients reported serious TEAEs during the study, and the majority of serious TEAEs were reported in a single

patient. The frequency of serious events was comparable between the QUTENZA arms and no notable differences in the type or frequency of events were observed.

Table 7 Serious Treatment-Emergent Adverse Events without an Outcome of Death (Safety Analysis Set)

MedDRA v13.1 System Organ Class Preferred term	QUTENZA (30 min) + SOC (N = 156) n (%)	QUTENZA (60 min) + SOC (N = 157) n (%)
All systems		
Any serious AE	20 (12.8)	13 (8.3)
Cardiac disorders	4 (2.6)	1 (0.6)
Angina pectoris	0	1 (0.6)
Atrial fibrillation	2 (1.3)	0
Atrial flutter	1 (0.6)	0
Cardiac failure acute	1 (0.6)	0
Coronary artery diseases	1 (0.6)	0
Myocardial infarction	1 (0.6)	0
Endocrine disorders	1 (0.6)	0
Hypothyroidism	1 (0.6)	0
Gastrointestinal disorders	3 (1.9)	0
Gastric ulcer	1 (0.6)	0
Gastrointestinal perforation	1 (0.6)	0
Hemarochezia	0	0
Nausea	1 (0.6)	0
General disorders and administration site conditions	3 (1.9)	0
Brain death	1 (0.6)	0
Multi-organ failure	1 (0.6)	0
Pyrexia	1 (0.6)	0
Hepatobiliary disorders	2 (1.3)	0
Cholecystitis	1 (0.6)	0
Cholecystitis chronic	1 (0.6)	0
Infections and infestations	6 (3.8)	2 (1.3)
Bronchopneumonia	1 (0.6)	0
Central nervous system infection	1 (0.6)	0
Chronic sinusitis	0	1 (0.6)
Endocarditis	1 (0.6)	0
Gastroenteritis	1 (0.6)	0
Herpes zoster	1 (0.6)	0
Mastitis	0	1 (0.6)
Pyelonephritis acute	1 (0.6)	0
Sepsis	1 (0.6)	0
Upper respiratory tract infection	1 (0.6)	0
Urinary tract infection	3 (1.9)	0
Injury, poisoning and procedural complications	2 (1.3)	0
Ankle fracture	1 (0.6)	0
Multiple injuries	1 (0.6)	0
Metabolism and nutrition disorders	1 (0.6)	3 (1.9)
Diabetes mellitus	0	1 (0.6)
Diabetes mellitus inadequate control	0	1 (0.6)
Fluid overload	1 (0.6)	0
Hypoglycemia	0	1 (0.6)

Table continued on next page

MedDRA v13.1 System Organ Class Preferred term	QUTENZA (30 min) + SOC (N=156) n (%)	QUTENZA (60 min) + SOC (N=157) n (%)
Musculoskeletal and connective tissue disorders	4 (2.6)	3 (1.9)
Intervertebral disc disorder	0	1 (0.6)
Intervertebral disc protrusion	1 (0.6)	0
Musculoskeletal pain	0	1 (0.6)
Osteoarthritis	2 (1.3)	1 (0.6)
Rotator cuff syndrome	1 (0.6)	0
Spinal column stenosis	1 (0.6)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (1.9)
Gastric cancer	0	1 (0.6)
Lung neoplasm malignant	0	1 (0.6)
Rectal cancer	0	1 (0.6)
Nervous system disorders	2 (1.3)	1 (0.6)
Hypoglycaemic coma	1 (0.6)	0
Intracranial hypotension	0	1 (0.6)
Nervous system disorder	1 (0.6)	0
Neuromyopathy	1 (0.6)	0
Transient ischaemic attack	1 (0.6)	0
Psychiatric disorders	1 (0.6)	0
Depression	1 (0.6)	0
Renal and urinary disorders	0	1 (0.6)
Renal failure	0	1 (0.6)
Reproductive system and breast disorders	1 (0.6)	0
Uterine polyp	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0
Acute respiratory failure	1 (0.6)	0
Hydrothorax	1 (0.6)	0
Pulmonary hypertension	1 (0.6)	0
Skin and subcutaneous tissue disorders	1 (0.6)	0
Skin ulcer	1 (0.6)	0
Vascular disorders	0	2 (1.3)
Accelerated hypertension	0	1 (0.6)
Arterial thrombosis	0	1 (0.6)
Hypotension	0	1 (0.6)

Sorting order: Alphabetically by System Organ Class and Preferred Term. All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF). Within a System Organ Class, a patient may have reported > 1 type of adverse event.

A treatment-emergent adverse event was an AE observed after starting administration of the test drug. There are therefore no TEAEs in the SOC arm. If an AE has missing date parts and missing value for the flag of onset timing that prevent a definitive determination that it was prior to the first patch application, it was considered a TEAE.

N: Number of patients; n: Number of patients in the sample; SOC: Standard of care; TEAE: Treatment-emergent adverse event.

No serious TEAEs were considered as related in the QUTENZA (30 minutes) arm. In the QUTENZA (60 minutes) arm, a total of 2 patients reported 3 drug-related serious TEAEs (angina pectoris, rectal cancer, and accelerated hypertension).

Less than 10% of patients (less than 10 patients per arm) reported TEAEs resulting in discontinuation of the treatment or the study in the QUTENZA arms. There were no notable differences between the QUTENZA arms. No TEAEs resulting in discontinuation were considered as drug-related in the QUTENZA (30 minutes) arm. In the QUTENZA 60 min arm, a total of 4 patients reported TEAEs of muscle spasms, rectal cancer, neuralgia, and psoriasis, which were considered as related to study drug.

Application site pain was the most frequently reported TEAE in both QUTENZA arms. For TEAEs reported in more than 1 patient, the mean duration of event was no longer than 4 days.

The majority of drug related TEAEs were reported in the first few days following each patch application, with the majority being reported in the first 7 days following patch application. A similar pattern occurred after each patch application, and there was no trend towards an increase in AEs following the later patches. This pattern was similar in the QUTENZA (30 minutes) and QUTENZA (60 minutes) arms.

Clinical Laboratory Evaluations: there were no notable differences in clinical laboratory results from screening to the end of study within the QUTENZA arms.

Vital Signs: most patients (> 80%) had normal systolic BP during the study in the QUTENZA arms. The mean change in diastolic BP below the normal range from screening to after all applications in the QUTENZA (30 minutes) arm was 14.7%. The mean change in diastolic BP below the normal range from screening to after all applications in the QUTENZA (60 minutes) arm was 7.0%. Patient [redacted] in the QUTENZA (60 minutes) arm, experienced accelerated hypertension on day 72, which was considered as serious and related to study drug.

The majority (> 98%) of patients in the QUTENZA arms had a normal pulse rate during the study.

CONCLUSIONS: based on the findings from the Norfolk QOL-DN total score, the treatment of PDPN with QUTENZA (30 minute or 60 minute application) and SOC does not result in a deterioration of sensory function when compared to SOC treatment alone. Similarly, a greater reduction in Norfolk QOL-DN subscale scores were observed in the QUTENZA arms compared with the SOC alone arm. The results provided no evidence of adverse functional consequences arising from the repeated administration of QUTENZA (up to 7 applications over a period of 12 months).

The decrease in the Norfolk QOL-DN score observed in the QUTENZA arms with up to 7 QUTENZA applications suggests that large fiber, small fiber and autonomic neuropathy is not negatively impacted by repeated exposure to QUTENZA, over the 12 month study period.

Although this study was designed to detect an effect of QUTENZA on the total score on the Norfolk QOL-DN scale, a positive effect of study treatment was also seen for all 3 treatment groups. This effect was notably larger for both QUTENZA treatment arms compared with SOC alone arm, for both the total score on the Norfolk QOL-DN scale and the subscales for “physical functioning/large fiber”, “symptoms”, “small fiber” and “autonomic” control of diabetic status. Active treatment of PDPN resulted in an overall improvement in quality of life for all treatments. This result may have arisen from a combination of improved control of neuropathic pain and, possibly a smaller AE burden, which may be the result of less use of concomitant oral neuropathic pain medication in the QUTENZA treatment groups by the end of the study.

A greater improvement in UENS total score was observed in the QUTENZA arms compared with the SOC alone arm, and no increase in the UENS total score was noted after repeated applications of QUTENZA, suggesting a lack of deterioration in neurological function, including no increase in small-fiber sensory loss, in the QUTENZA arms. A greater improvement in the UENS sharp sensation subscale score from baseline to end of study was observed in the QUTENZA arms compared with the SOC alone arm. For the remaining subscales, improvements in score were similar in the QUTENZA arms and the SOC alone arm. In the overall study population, there was no evidence of an adverse effect of QUTENZA on sharp sensation. A potential limitation of the UENS for the detection of loss of sharp sensation is that only 2 of the UENS testing areas were in the foot, with the others in areas where Qutenza was not applied. Notwithstanding this observation, an apparent

improvement (in the context of an open-label study) in sharp sensation was observed in this study for all treatments with a larger apparent treatment effect being seen in the QUTENZA treatment arms.

The safety data obtained from the UENS are consistent with scores from the Norfolk QOL-DN. There was no apparent progression in the severity or distribution of small-fiber sensory neuropathy with repeated applications of QUTENZA.

The safety profile of QUTENZA observed in patients with PDPN is consistent with the known safety profile of the product. Additionally, with repeated applications of QUTENZA, there was no increase in the incidence of TEAEs or evidence of progressive neurosensory dysfunction. Safety in the QUTENZA (60 minutes) arm was comparable with that of QUTENZA (30 minutes) arm suggesting that the application of QUTENZA patches for up to 1 hour does not raise any safety concerns.

QUTENZA treatment is efficacious compared to standard of care alone, and efficacy was maintained with repeated exposure.

Date of Report: 13 October 2014

Summary of Protocol Substantial Amendments

Protocol Amendment Number†	Date	Summary of Changes
Original Protocol	11 April 2011	• Original Protocol
Substantial Amendment 1	11 July 2011 (prior to study enrolment)	• Included removal of an exclusion criterion for diabetic retinopathy (exclusion criterion 6), an amendment to exclusion criterion 2 to provide a more precise definition of onychomycosis and to clarify that questionnaires were to be completed on paper. There were also some administrative changes to correct minor errors to the protocol.
Substantial Amendment 3	17 April 2013	• Included 2 substantial amendments: - The first described the comprehensive foot examination to be conducted at every scheduled visit, to identify high risk foot conditions, and the optional use of the previously mandatory comprehensive diabetes foot exam form. - The second was an update to the safety section of the patient information sheet to reflect new safety information in the Risk Management Plan, Investigator's Brochure and SmPC. There were also various nonsubstantial amendments included in amendment 3: an extension of the study period, administrative changes (including the Sponsor's location), clarifications on medication and documenting of serious adverse events (SAEs), and the addition of a new major contributing author.

†Amendment 2 issued on 16 May 2012 was a nonsubstantial amendment

Appendix 13.1.4 – Investigator Information

Investigator	Site Information	
[redacted]	[redacted]	BELGIUM [redacted]
[redacted]	[redacted]	CZECH REPUBLIC [redacted]
[redacted]	[redacted]	CZECH REPUBLIC [redacted]
[redacted]	[redacted]	CZECH REPUBLIC [redacted]
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† Cancelled/stopped sites