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Name of Active Ingredient: Capsaicin		

SYNOPSIS

Title of Study: A Phase III, Double-blind, Randomized, Placebo-controlled, Multicenter Study Evaluating the Efficacy and Safety of QUTENZA® in Subjects with Painful Diabetic Peripheral Neuropathy.

Investigators/Coordinating Investigator: [redacted] MD, [redacted] United States.

Study Centers: This study was conducted at 29 sites in the United States.

Publication Based on the Study: Not applicable.

Study Period: February 2012 to February 2014

Study Initiation Date (Date of First Enrollment): 06 February 2012

Study Completion Date (Date of Last Evaluation): 13 February 2014

Phase of Development: Phase 3

Objectives:
Primary Objective: To evaluate the efficacy of a single application of QUTENZA compared to that of placebo in reducing pain intensity in patients 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 to evaluate safety and tolerability.

Methodology: This was a multicenter, two-arm, double-blind, placebo-controlled randomized study to assess the efficacy and safety of a single QUTENZA patch application in patients with PDPN. The duration of participation for each patient was up to 14 weeks and consisted of a screening period (from 12 days prior to first patch application visit), a treatment visit (baseline) where patients received a single QUTENZA or placebo patch application to the feet for 30 minutes, and visits at week 2, 4, 8 and 12 (end of study [EoS]).

Number of Patients (Planned, Enrolled and Analyzed): A total of 360 eligible patients were planned to be treated, and 369 patients were randomized into the study (186 received QUTENZA and 183 received placebo).

Diagnosis and Main Criteria for Inclusion: Patients were eligible for the study if they fulfilled the following criteria:

1. Institutional review board approved written Informed Consent and privacy language as per national regulations was to be 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, symmetrical, sensorimotor polyneuropathy which was due to diabetes, for at least 1 year prior to screening visit

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

4. Diagnosis of PDPN was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument
5. At least 1 medical record of glycosylated hemoglobin (HbA1c) ≤ 11% at 3 to 6 months before screening visit; HbA1c ≤ 11% at screening visit with variations of < 1% point between the screening visit and the 3 to 6 month pre-screening value; patients who had HbA1c > 11% or > 1% difference between the 2 values may have undergone a more intensive period of diabetes treatment for 3 months and required rescreening. Upon rescreening, the patient may have been enrolled if the HbA1c ≤ 11% or if the investigator attested that the diabetes mellitus was appropriately optimized for that patient
6. 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
7. A minimum of 6 consecutive pain recordings during the screening period
8. Stable doses of pain medications for more than 4 weeks prior to the screening visit
9. Patient agreed not to participate in another interventional study while on treatment.

Test Product, Dose, Mode of Administration and Batch Numbers: QUTENZA is a high-concentration (8%) capsaicin patch. Up to 4 patches of QUTENZA (1120 cm^2 in total) were applied for 30 minutes to the painful areas of the feet (as identified by the study physician). Each patch is 14 cm by 20 cm (280 cm^2) and contains a total of 179 mg of capsaicin or 640 µg of capsaicin per 1 cm^2 of patch (8% w/w). QUTENZA was provided as a patch stored in a paper coated aluminum foil sachet with acrylnitrile-acrylic acid copolymer heat sealed layer.

A topical anesthetic cream (e.g., 5% lidocaine cream) was applied for a period as determined by the prescribing information of the product used.

QUTENZA Batch: [redacted] (expiry date: June 2014).

Duration of Treatment (or Duration of Study, if applicable): The study period was between 13 and 14 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers: The placebo patches were visually and cosmetically indistinguishable from the active capsaicin patches.

Placebo Batches: [redacted] (expiry dates: July 2013 and January 2015).

Criteria for Evaluation: This study assessed efficacy, tolerability, impact on HRQoL and safety of single application with QUTENZA compared with a single application of placebo. The primary efficacy variable was 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 scores during weeks 2 to 8, compared to the average of baseline scores) in the active arm compared to the placebo arm. NPRS were recorded every day throughout the study. The secondary efficacy variables were: 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 (i.e., average of scores during weeks 2 to 12, compared to the average of baseline scores); percent change in the 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; proportion of patients achieving 30% and 50% decrease in the average daily pain

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

score (question 5 of the BPI-DN) from the average assessed during baseline run-in period to the average daily pain score assessed between weeks 2 and 8 and weeks 2 and 12; overall patient status using Patient Global Impression of Change (PGIC) questionnaire at weeks 2, 8 and 12; change in the European QoL questionnaire in 5 dimensions (EQ-5D) total score and depression and anxiety scores on the Hospital Anxiety and Depression Scale (HADS) from baseline to weeks 2, 8 and 12; treatment satisfaction using the Self-Assessment of Treatment (SAT-II) 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).

Safety was assessed by evaluation of changes in vital signs (heart rate and blood pressure), laboratory assessments and adverse events (AEs). Sensory testing involved ratings of evoked sensations, including pain, by recording, either reduced or increased stimulus perception compared to a normal asymptomatic control site. Assessments of vibration, heat, cold and sharp sensations and deep tendon reflexes were performed at the baseline visit and at the planned EoS or discontinuation visit. Tolerability of patch application was assessed by: Dermal assessment (0 to 7 point severity score on Dermal Assessment Scale); "Pain now" NPRS scores before and after patch application; rescue pain medication use on days 1 to 5 (where rescue pain medication was defined as all pain medication that a patient was taking between day 1 and day 5 post patch application treatment).

Criteria for Evaluation, Posthoc Analyses: In this PDPN population the time to full effect was later than expected (see 'Figure 2'). In other indications full effect was already achieved after 2 weeks whereas in this PDPN population the full effect was 2 weeks later. To understand the impact of the later full effect on the primary and some secondary analyses, additional endpoint definitions were implemented; the percentage change from baseline to between weeks 4 and 8 and weeks 4 and 12, for average daily pain score as endpoint. Due to the later than expected onset of action of QUTENZA in this population, responders were also defined as those patients with at least 30% or at least 50% reduction in pain score from baseline to between weeks 4 and 8, weeks 4 and 12, at week 8 and at week 12. Patients were allowed into the study either with stable doses of permitted concomitant neuropathic pain medication (to remain stable throughout the study), or they could be on no neuropathic pain medications in the antiepileptic drug or antidepressant categories.

Statistical Methods: The intention to treat (ITT) analysis set included all randomized patients who received study patch application. This set was the primary analysis data set for efficacy endpoints. The per protocol set (PPS) was also used as a secondary analysis for efficacy variables. The safety analysis set (SAF) included all patients who received study patch application. All safety analyses were conducted on this dataset.

All data processing, summarization and analyses were performed using SAS® Version 9.1 or higher on UNIX.

For continuous variables, descriptive statistics include 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., add up to 100%. In general data is presented by treatment group and overall unless specified otherwise.

The primary efficacy variable (average daily pain score at week 2 to 8) was analyzed as:

- Descriptive statistics, shown for percent change from baseline

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

- A p-value, a least squares (LS) mean estimate and a CI reported for the difference between QUTENZA and placebo for percent change from baseline.

An analysis of covariance (ANCOVA) model was used for these inferential analyses. The model included treatment, gender, pain score at baseline, HbA1c at screening and site as factors/covariates and was a baseline and last observation carried forward (BLOCF) analysis.

Secondary efficacy variables included those based on the average pain score:

- BPI question 5: Descriptive statistics performed for BPI-DN questions 5 (average pain) as absolute values and as changes from baseline to between weeks 2 and 12 and weekly averages
- Reduction achievements: Patients achieving a 30% or 50% decrease in the average daily pain score between weeks 2 and 8 and weeks 2 and 12; the number and percentage of patients achieving these reductions and p-value, an LS mean estimate and a CI, reported for the odds ratio of QUTENZA and placebo for patients achieving reductions
- Time to treatment effect and treatment failure: estimated by Kaplan-Meier method and percentile 25, 50 (median) and 75, with corresponding 95% CI, together with the number of patients with and without treatment effect at EoS
- Subgroup analyses: Average daily pain score, analyzed by subgroups (grouped age, grouped baseline average daily pain, grouped duration of PDPN, grouped HbA1c, maximum Neuropathic Pain Symptom Inventory [NPSI] dimension/subscale, race, sex and site)
- Sensitivity analyses: To explore the impact of the BLOCF missing data imputation method 2 sensitivity analyses were performed for the primary endpoint (baseline observation carried forward [BOCF] and weekly average of daily pain score calculated without imputation)
- Exploratory analyses: An ANCOVA model with treatment, gender, pain score at baseline and PDPN duration as factors/covariates and an ANCOVA model with treatment, gender, pain score at baseline and NPSI total score at baseline as factors/covariates.

Secondary efficacy variables also included those based on:

- PGIC questionnaire: Counts by category at week 2, week 8, week 12, EoS and EoS (BLOCF)
- HRQoL questionnaires (EQ-5D and HADS): counts by category at week 2, week 8, week 12, EoS and EoS (BLOCF)
- SAT II questionnaire: Counts by category at week 2, week 8, week 12
- Concomitant medications: Change in use of concomitant pain medication was evaluated from screening visit to termination visit
- BPI question 9F: Average sleep interferences scores were analyzed similarly to the average daily pain scores, with the exception that the subgroup analyses were not performed.

Safety was assessed by evaluation of the following variables:

- AEs and serious AEs
- Vital signs (heart rate and blood pressure) on the day of patch application
- Laboratory analyses.

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

AEs (coded by Medical Dictionary for Regulatory Activities [MedDRA] version 13.1) were assessed according to the schedule of assessments, were summarized as counts over the entire study and analyzed descriptively. Treatment-emergent AEs (TEAEs), serious TEAEs, drug-related TEAEs (TEAEs with probable or possible relationship to the study drug) and the proportion of patients who prematurely terminated from the study or study drug due to an AE were reported throughout the study. All AEs occurring during the study were to be followed up until resolved or judged to be no longer clinically significant, or until they became chronic to the extent that they could be fully characterized.

Sensory testing was summarized as the shift from baseline in the counts in each category (vibration, heat, cold and sharp sensations) for the left and right sides combined for each item at week 12 and EoS). Dermal assessments are summarized as counts in each category (and combined category ≥ 4 scores) at screening, before application of topical anesthetic, 15 minutes after patch removal, 60 minutes after patch removal, week 12 and EoS.

Statistical Methods, Posthoc Analyses: The data associated with the new definitions of percentage change from baseline for average pain score (baseline to between weeks 4 and 8 and weeks 4 and12), responder rates (30% and 50%, baseline to between weeks 4 and 8, week 4 and 12, week 8 and week 12) and for the additional subgrouping based on concomitant medication were analyzed as per the protocol-defined analyses for the primary endpoint. In addition it was stated in the study protocol that PGIC categories were to be analyzed with a Cochran-Mantel-Haenszel (CMH) test. As well as this general test, PGIC categories were combined as follows; i) Very Much + Much + Minimally Improved and ii) No Change + Minimally Worse + Much Worse + Very Much Worse. A p-value was reported for the difference between QUTENZA and placebo using Fishers Exact test for each of Week 2, Week 8, Week 12, EoS and EoS (BLOCF).

Summary of Results/Conclusions:

Patient Disposition: In total 369 patients were randomized into the study (186 to receive QUTENZA and 183 to receive placebo). The SAF and ITT comprised 369 patients in total (186 who received QUTENZA and 183 who received placebo). The PPS comprised a total of 338 patients (172 in the QUTENZA arm and 166 in the placebo arm). All patients who were randomized were dosed. A total of 17 patients discontinued from the study after treatment was initiated; discontinuation rates were 4.8% in the QUTENZA arm and 4.4% in the placebo arm. One patient in the placebo arm discontinued due to an AE. Three patients were lost to follow up (2 [1.1%] in the QUTENZA arm and 1 [0.5%] in the placebo arm). Thirteen patients chose to withdraw from the study (7 [3.8%] in the QUTENZA arm and 6 [3.3%] in the placebo arm). The overall completion rate for the SAF was 95.4% (95.2% for the QUTENZA arm and 95.6% for the placebo arm). A summary of patient disposition is provided in [Figure 1].

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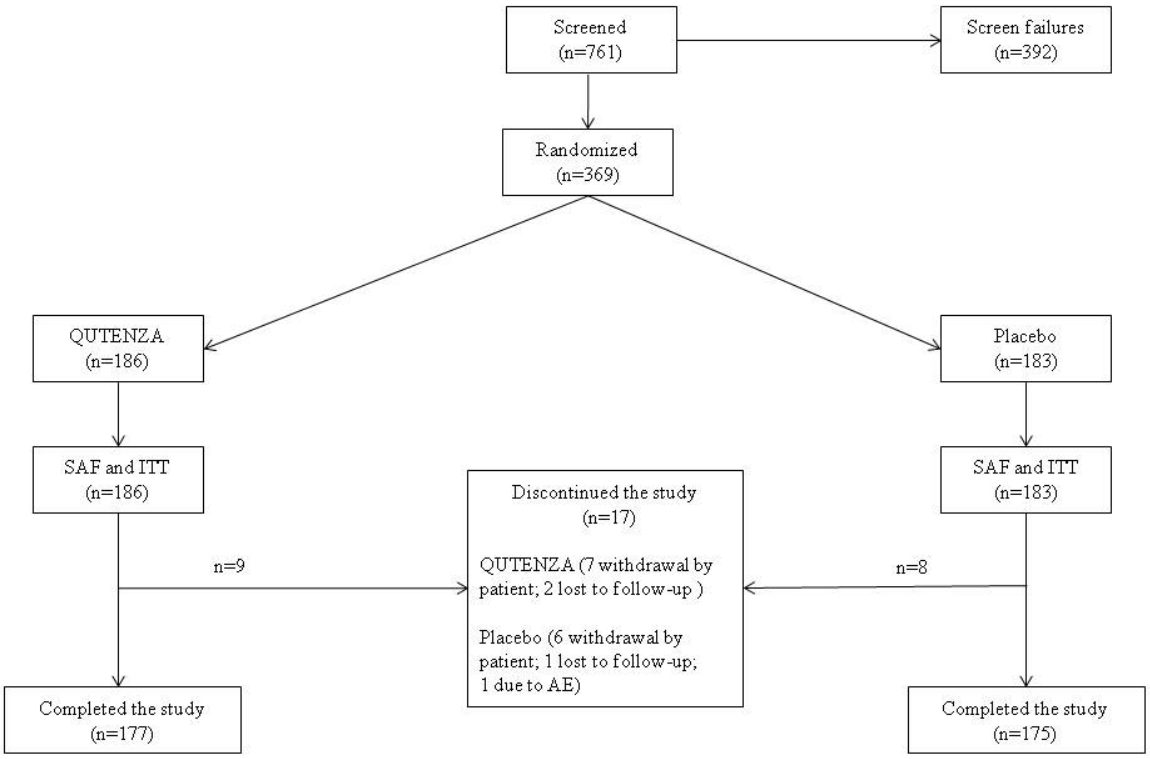
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Figure 1 Disposition of Patients



AE: Adverse event; ITT: Intention to treat set (all randomized patients who received patch application; grouped by randomization assignment); n: Number of patients in the sample; SAF: Safety analysis set (all randomized patients who received study patch application; grouped by actual treatment)

Patient Demographics: The mean age of patients enrolled in the study was 63.9 years (range 36 to 89 years) in the QUTENZA arm and 62.0 years (range 33 to 89 years) in the placebo arm. 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%).

The mean duration of PDPN was 5.83 years (range 1.2 to 22.7 years) in the QUTENZA arm and 5.72 years (range 1 to 22.7 years) in the placebo arm. The majority of patients in both treatment arms had a PDPN duration of between 3 and 10 years (106 patients in the QUTENZA arm and 109 patients in the placebo arm) ([Table 1]).

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Table 1 Summary of Demographics and Baseline Characteristics for Patients in the 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 (3.98)
Median	4.84	4.55	4.62
Min - Max	1.2 – 22.7	1.0 – 22.7	1.0 – 22.7

All randomized patients who received study patch application (grouped by randomization assignment)
BMI: Body mass index (weight [kg]/height [m^2]); N: Number of patients in the intention to treat Set; n = Number of patients in the sample; PDPN: Painful diabetic peripheral neuropathy; n: Number of patients in the sample.

All randomized patients who received study patch application (grouped by randomization assignment).

Prior and Concomitant Medications: Overall, the number of patients who used pain medications prior to treatment was comparable between the treatment arms (125 patients [67.2%] in the QUTENZA arm and 132 patients [72.1%] in the placebo arm). The most commonly used medications to treat pain prior to treatment were: Gabapentin (30.6% of patients in the QUTENZA arm and 38.8% in the placebo arm); ibuprofen (10.2% of patients in the QUTENZA arm and 12.6% in the placebo arm); and naproxen (10.2% of patients in the QUTENZA arm and 8.7% in the placebo arm).

Overall, the number of patients who used opioid medications prior to treatment was comparable between the treatment arms (15 patients [8.1%] in the QUTENZA arm and 16 patients [8.7%] in the placebo arm). The most commonly used opioids prior to treatment were tramadol (2.7% of patients in the QUTENZA arm and 3.3% in the placebo arm) and vicodin (2.2% of patients in the QUTENZA arm and 2.7% in the placebo arm).

Overall, pain medications used at or after baseline were comparable between the treatment arms. The most commonly used medications to treat pain at or after baseline were (by preferred World Health Organization

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEBV)		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

[WHO] name): Gabapentin (31.2% of patients in the QUTENZA arm and 38.8% in the placebo arm); ibuprofen (16.1% of patients in the QUTENZA arm and 12.6% in the placebo arm); naproxen (11.3% of patients in the QUTENZA arm and 8.2% in the placebo arm); and paracetamol (11.3% of patients in the QUTENZA arm and 6.6% in the placebo arm).

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%]). Of the 13 patients in the QUTENZA arm who were administered vicodin at or after baseline, 11 patients were administered vicodin as rescue medication (following patch application) and 2 patients were administered vicodin for other reasons. Of the 11 patients who were administered vicodin as a rescue medication, the majority (8) took it for less than 5 days and had stopped on or before day 5.

Efficacy Results:

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

The efficacy of a single application of QUTENZA was compared to that of placebo in reducing pain intensity in patients with PDPN. A statistically significant greater pain reduction was observed from baseline to between week 2 and 8 (BLOCF) in the QUTENZA arm than in the placebo arm. For the primary analysis set (ITT), the mean (SD) percent reduction in pain score from baseline was -27.44 (26.79) for the QUTENZA arm and was -20.85 (28.92) for the placebo arm, the corresponding LS mean difference (QUTENZA - placebo) was -6.6 (95% CI: -12.3, -0.8); the difference was statistically significant (p = 0.025). Results based on the PPS were consistent with results based on the ITT dataset, the LS mean difference (QUTENZA – placebo) was -6.3 (95% CI: -12.4, -0.2); the difference was statistically significant (p = 0.042) ([Table 2]).

Table 2 Percent Change from Baseline to Weeks 2 to 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	

BLOCF: Baseline and last observation carried forward; BPI-DN: Brief pain inventory-diabetic neuropathy; ITT: Intention to treat; LS: Least squares: N: Number of patients in the population per treatment arm; PPS: Per protocol set; QTZ: QUTENZA.

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

Sensitivity Analyses: Results for the sensitivity analyses (average change in daily pain score from baseline to between weeks 2 and 8 using either BOCF imputation, or repeated measures mixed model analysis with either autoregressive (AR) or unstructured (UN) covariance structures were consistent with those for the primary analysis, in that a greater percentage reduction in pain score was observed in the QUTENZA arm than in the

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEBV)		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

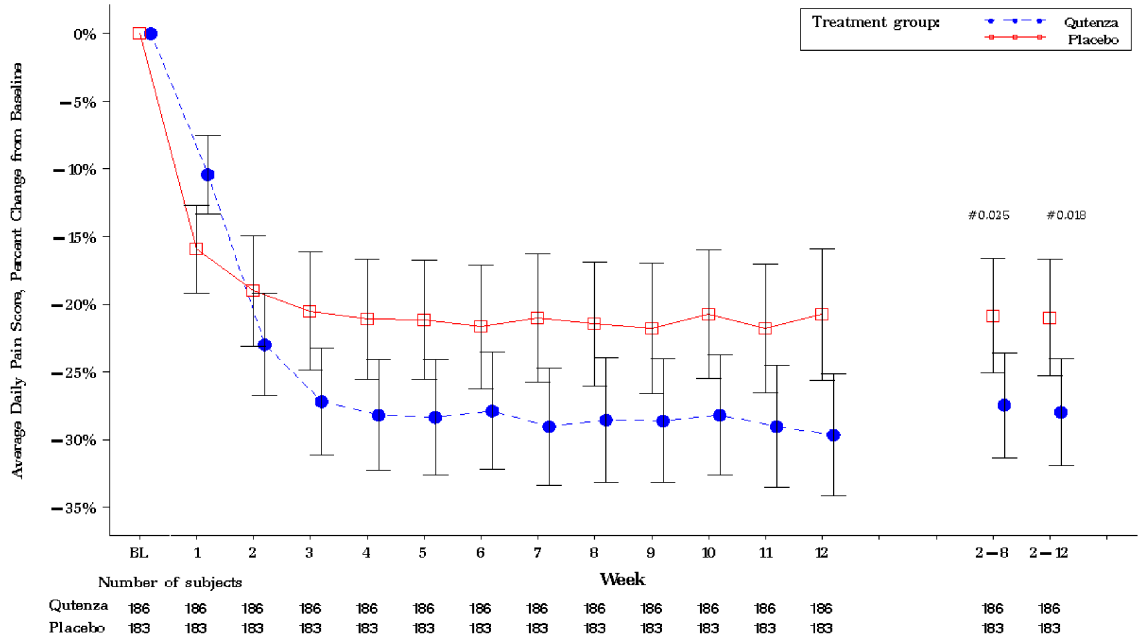
placebo arm; this was statistically significant for the mixed model analyses but not for the BOCF analysis. The LS mean difference (QUTENZA – placebo) for the UN and AR (1) analyses were similar (-6.6 [95% CI: -12.3, -0.8] and -6.5 [95% CI: -12.1, -1.0]) and the reduction in pain score for both analyses was statistically significant (p = 0.026 and p = 0.022). The LS mean difference (QUTENZA - placebo) for the BOCF analysis was -4.7 (95% CI: -9.7, -0.4); the reduction in pain score was not statistically significant (p = 0.072) in this case.

Secondary Efficacy Analyses Based on the BPI-DN:

Average Daily Pain Score (Question 5 of the BPI-DN) Change from Baseline:

A greater percentage reduction in pain score was observed in the QUTENZA arm than in the placebo arm from week 2 onwards. The percentage reduction in pain score was statistically significant from week 3 onwards apart from week 6 (p < 0.05, no adjustment for multiple comparisons) ([Figure 2]).

Figure 2 Average Daily Pain Score Percent Change from Baseline



A statistically significant greater pain reduction was observed from baseline to between weeks 2 and 12 in the QUTENZA arm than in the placebo arm (p = 0.018); the difference in pain relief between the treatment groups was numerically more pronounced in favor of QUTENZA for this analysis (LS mean difference [QUTENZA - placebo] -7.1) than for baseline to between weeks 2 and 8 (primary) analysis.

From week 3, the percentage reduction in pain score was statistically significant (p-values ranged from 0.005 [week 12] to 0.036 [week 3]) with the exception of week 6 (p = 0.051).

A greater proportion of patients achieved at least a 30% reduction in average daily pain score from baseline to between week 2 and 8 and week 2 and 12 in the QUTENZA arm than in the placebo arm but the differences were not statistically significant. The same trend was observed for the proportion of patients achieving a 50% reduction in daily pain score.

Name of Sponsor/Company: Astellas Pharma Europe B.V. (APEBV)		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

In a posthoc analysis, a higher proportion of patients in the QUTENZA arm had reached treatment effect (a 30% reduction in pain score for 3 consecutive days) compared to the placebo arm at all time points tested (day 14, 28, 56 and 84).

The median time to pain relief (where 50% of patients had a 30% reduction in the average daily pain score) for the ITT was numerically shorter for the QUTENZA arm; 19 days for the QUTENZA arm versus 72 days for the placebo arm.

A greater reduction in sleep interference score between baseline and week 2 to 12 was observed in the QUTENZA arm than in the placebo arm (LS mean difference [QUTENZA – placebo] -9.5). The difference was statistically significant ($p = 0.020$).

Secondary Efficacy Analyses Based on the PGIC

At week 8, there was a numerical difference in the proportion of patients who reported they were "very much improved + much improved" between the QUTENZA arm (39.4%) and the placebo arm (30.2%) however the CMH test for general association was not statistically significant ($p = 0.075$), and an association between treatment and PGIC category could not be concluded.

Secondary Efficacy Analyses Based on the EQ-5D:

A slightly greater increase in EQ-5D visual analogue scale (VAS) total score change from baseline was observed at week 8 in the QUTENZA arm (4.0) than in the placebo arm (3.5); the difference (LS mean) was not statistically significant ($p = 0.320$).

Secondary Efficacy Analyses Based on the SAT II:

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

At week 12, for the following questions/subquestions, there was evidence of a statistically significant association between treatment and outcome favoring QUTENZA: "Over the past 7 days, how much has the study treatment improved your pain level?" and "Over the past 7 days, how much has the study treatment improved the following aspects of your life; sub question emotional wellbeing, such as mood, temperament or outlook on life?"

Subgroup Analyses: Subgroup analyses were performed for patients with different types of pain, based on NPSI dimension scores (paroxysmal pain, paresthesia/dysesthesia, burning [superficial] spontaneous pain, evoked pain and pressing [deep] spontaneous pain). Patients with paroxysmal pain had a greater change from baseline to week 2 to 8 daily pain score in the QUTENZA arm compared with the placebo arm, which was more pronounced than the change seen for the ITT population. Patients with paresthesia/dysesthesia and with burning (superficial) spontaneous pain responded similarly to 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 improvements were not as pronounced as in the ITT population particularly in the pressing (deep) spontaneous pain subgroup.

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

There was no evidence that the duration of PDPN was predictive of the treatment response for QUTENZA. For the QUTENZA arm, all subgroups based on the duration of PDPN responded similarly in that a reduction of daily pain score from baseline to between weeks 2 and 8 similar to that of the ITT was observed. However, in the placebo group, the percent change in daily pain score for patients with PDPN for ≥ 10 years was higher than for the ITT and between treatment groups; patients responded similarly to both treatments (QUTENZA and placebo).

There was no evidence that patients with an average daily pain baseline score ≥ 7 responded any better to QUTENZA than those with a score of < 7.

Exploratory Analyses: The effect of 2 important covariates (PDPN duration and NPSI total score at baseline) on the primary endpoint were investigated by including each as factors in the primary endpoint analysis model (exploratory analyses). Results for the exploratory analyses were consistent with those for the primary analysis, in that a greater percentage reduction in pain score was observed in the QUTENZA arm than in the placebo arm, but neither covariate was significant in the models.

Posthoc Analyses:

Reduction in Average Daily Pain Score (Posthoc): A statistically significant greater pain reduction was observed from baseline to between weeks 4 and 8 and weeks 4 and 12 (BLOCF) in the QUTENZA arm than in the placebo arm ($p = 0.020$ and $p = 0.016$). The difference in pain relief between the treatment groups was numerically more pronounced in favor of QUTENZA for these analyses than for baseline to between weeks 2 and 8 (primary) analysis and were similar to the baseline to between weeks 2 and 12 analysis.

Patients who were not taking concomitant PDPN pain medications had an increased response to QUTENZA (a greater decrease in pain scores) compared with those who were taking concomitant PDPN pain medications. A numerically greater pain reduction was seen in the subgroup of patients who were not taking concomitant PDPN pain medications between QUTENZA and placebo at both baseline to between weeks 2 and 8 and baseline to between weeks 2 and 12, the reduction was statistically significant at baseline to between weeks 2 and 12. Pain reduction was similar between QUTENZA and placebo from baseline to between weeks 2 and 8 and from baseline to between weeks 2 and 12 between QUTENZA and placebo for patients who were taking concomitant PDPN pain medications; no statistically significant differences between the treatment groups were observed for this subgroup.

Responder Analysis (Posthoc): A statistically significantly greater proportion of patients achieved at least a 30% reduction in average daily pain score from baseline to between weeks 4 and 12 and at week 12 in the QUTENZA arm than in the placebo. A statistically significantly greater proportion of patients also achieved at least a 50% reduction in average daily pain score from baseline to week 12 only in the QUTENZA arm than in the placebo arm.

For the subgroup of patients who were not taking concomitant PDPN pain medication, statistically significant differences between QUTENZA and placebo were observed in the proportion of patients who achieved at least a 30% reduction in average daily pain score at all time points measured. However, for the subgroup of patients who were taking concomitant PDPN medication, there were no statistical differences in the proportion of

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Name of Active Ingredient: Capsaicin		

patients who achieved at least a 30% reduction in average daily pain score observed at any time points between the QUTENZA arm and the placebo arm.

Analyses Based on the PGIC (Posthoc): For the posthoc analysis, which combined the PGIC categories as follows; i) very much + much + minimally improved and ii) no change + minimally worse + much worse + very much worse, an overall improvement in patients' status was observed which was more pronounced in the QUTENZA arm than the placebo arm. The p-values reported for the difference between QUTENZA and placebo for week 2, week 8, and week 12 were statistically significant and in favor of QUTENZA.

Safety Results:

Adverse Events: The proportion of patients with TEAEs was higher, and more TEAEs were reported in the QUTENZA arm compared with the placebo arm; 87 (46.8%) patients reported 157 TEAEs in the QUTENZA arm and 62 (33.9%) patients reported 91 TEAEs in the placebo arm. The TEAE reported by the highest proportion of patients was burning sensation; a higher proportion of patients reported this TEAE in the QUTENZA arm (26 [14%]) compared with the placebo arm (5 [2.7%]). The next most common TEAEs were pain in extremity and application site pain (Table 3).

The proportion of patients with drug-related TEAEs was also higher, and more events were reported, in the QUTENZA arm than in the placebo arm; 65 (34.9%) patients reported 73 drug-related TEAEs in the QUTENZA arm and 23 (12.6%) patients reported 25 drug-related TEAEs in the placebo arm. The drug-related TEAE reported by the highest proportion of patients was burning sensation. Only 1 patient reported burning sensation as a TEAE that was not considered to be drug-related (in the placebo arm). A higher proportion of patients reported drug-related pain in extremity in the QUTENZA arm (17 [9.1%]) compared with the placebo arm (8 [4.4%]) and a higher proportion of patients reported application site pain in the QUTENZA arm (18 [9.7%]) compared with the placebo arm (4 [2.2%]). Only 5 patients reported pain in extremity as a TEAE that was not considered to be drug-related (3 in the QUTENZA arm and 2 in the placebo arm) and all reports of application site pain were considered to be drug-related.

The proportions of patients with application site reactions and application site pain was investigated. The proportion of patients with application site reactions was higher, and more application site reactions were reported in the QUTENZA arm compared with the placebo arm; 63 (33.9%) patients reported 68 application site reactions in the QUTENZA arm and 15 (8.2%) patients reported 16 application site reactions in the placebo arm. The majority of the application site reactions involved pain; patients who had an application site reaction had 1 or more of the following: burning sensation, application site pain or pain in extremity. The majority of TEAEs identified as application site reactions and pain were mild or moderate. Only 3 patients in the QUTENZA arm had TEAEs that were severe application site reactions. Overall, a larger proportion of rescue pain medications for pain caused by patch application was given to patients in the QUTENZA arm (35 patients [18.8%]), compared with the placebo arm (10 patients [5.5%]).

There was a peak in the percentage of patients reporting TEAEs for QUTENZA on day 2 (32% of patients), but the percentage of patients reporting TEAEs had plateaued by day 6 and there was only 1 patient who reported a severe TEAE after day 13. For placebo, the number of patients reporting TEAEs did not peak after patch application.

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

No deaths were reported in the study. The proportions of patients with serious TEAEs were low in both treatment arms; fewer were reported in the QUTENZA arm than in the placebo arm: 2 (1.1%) patients reported 2 serious TEAEs in the QUTENZA arm and 7 (3.8%) patients reported 9 serious TEAEs in the placebo arm ([Table 4]).

There were no drug-related serious TEAEs reported. Only 1 (0.3% of the total population) had a TEAE leading to discontinuation and this event (worsening hypertension) was not drug-related; there were no drug-related TEAEs that led to discontinuation.

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Name of Active Ingredient: Capsaicin		

Table 3 Summary of Patients with TEAEs (Reported by ≥ 2.0% of Patients in either Treatment Arm) (SAF)

MedDRA v13.1 System Organ Class Preferred Term	**Treatment, Number of Patients (%)**	
	QUTENZA N = 186	**Placebo N = 183**
Overall	87 (46.8)	62 (33.9)
Musculoskeletal and connective tissue disorders	25 (13.4)	17 (9.3)
Pain in extremity	20 (10.8)	10 (5.5)
Nervous system disorders	29 (15.6)	11 (6.0)
Burning sensation	26 (14.0)	5 (2.7)
Headache	5 (2.7)	3 (1.6)
General disorders and administration site conditions	24 (12.9)	7 (3.8)
Application site pain	18 (9.7)	4 (2.2)
Infections and infestations	16 (8.6)	13 (7.1)
Upper respiratory tract infection	7 (3.8)	1 (0.5)
Injury poisoning and procedural complications	7 (3.8)	6 (3.3)
Skin and subcutaneous tissue disorders	9 (4.8)	3 (1.6)
Respiratory thoracic and mediastinal disorders	6 (3.2)	5 (2.7)
Gastrointestinal disorders	3 (1.6)	5 (2.7)
Metabolism and nutrition disorders	3 (1.6)	5 (2.7)
Investigations	2 (1.1)	5 (2.7)
Psychiatric disorders	2 (1.1)	4 (2.2)

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

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.

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Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Table 4 Summary of Patients with Serious TEAEs (SAF)

MedDRA v13.1 System Organ Class Preferred Term	**Treatment; Number of Patients (%)**			
	QUTENZA N = 186		**Placebo N = 183**	
Overall	2	(1.1)	7	(3.8)
Respiratory, thoracic and mediastinal disorders	0	(0)	2	(1.1)
COPD	0	(0)	2	(1.1)
Cardiac disorders	0	(0)	1	(0.5)
Coronary artery disease	0	(0)	1	(0.5)
Myocardial infarction	0	(0)	1	(0.5)
General disorders and administration site conditions	0	(0)	1	(0.5)
Noncardiac chest pain	0	(0)	1	(0.5)
Infections and infestations	0	(0)	1	(0.5)
Postprocedural infection	0	(0)	1	(0.5)
Metabolism and nutrition disorders	1	(0.5)	0	(0)
Dehydration	1	(0.5)	0	(0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	(0)	1	(0.5)
Oesophageal carcinoma	0	(0)	1	(0.5)
Nervous system disorders	1	(0.5)	0	(0)
Convulsion	1	(0.5)	0	(0)
Surgical and medical procedures	0	(0)	1	(0.5)
Knee arthroplasty	0	(0)	1	(0.5)
Vascular disorders	0	(0)	1	(0.5)
Hypotension	0	(0)	1	(0.5)

COPD: Chronic obstructive pulmonary disease; N: Number of patients in the population per treatment arm; TEAE: Treatment-emergent adverse event; SAF: Safety analysis set.

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 severe TEAEs.

Laboratory Analyses: The majority of hematology and biochemistry abnormalities observed at screening were not clinically significant and did not warrant additional testing.

Vital Signs: The majority of patients had normal vital signs. The mean change in systolic blood pressure was numerically greater (2.0 mmHg) for the QUTENZA arm compared with the placebo arm (0.4 mmHg).

Sensory Function and Reflex Assessment: More patients in the QUTENZA arm reported decreased responses to sharpness and vibration at week 12 (34.9% and 19.5%, respectively) than in the placebo arm (27.5% and 14.0%, respectively). The converse was true for the response to warmth; fewer patients in the QUTENZA arm (34.3%) reported a decreased response to warmth at week 12 than in the placebo arm (40.9%). There were no differences between treatment arms with respect to cold responses. There were no differences between treatment arms with respect to reflexes at week 12 compared with baseline. Shifts (both decreases and increases) in sensitivity were observed for all the sensory modalities (warm, cold, sharp, vibration) and for reflexes; shifts were observed in both treatment groups for the warm, cold and sharp modalities.

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Name of Finished Product: QUTENZA		
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Tolerability Assessment – Dermal Changes: There were no notable differences between treatment arms with respect to dermal assessments except for at 15 minutes within patch removal and at 60 minutes after patch removal. At these time points, a higher proportion of patients in the QUTENZA arm had barely perceptible, minimal erythema than in the placebo arm and a lower proportion of patients in the QUTENZA arm had no evidence of irritation than in the placebo arm.

CONCLUSIONS: In conclusion, a single treatment with QUTENZA patches was generally well tolerated. The majority of TEAEs experienced were local, transient, and related to the application procedure. QUTENZA was effective in relieving pain in patients with PDPN over a period of 12 weeks; treatment with QUTENZA significantly reduced pain intensity in patients with PDPN compared to placebo.

Date of Report: 3 October 2014

Summary of Protocol Substantial Amendments

Protocol Amendment Number†	Date	Summary of Changes
Original Protocol	17 Aug 2011	● Original Protocol
Substantial Amendment 1	14 Oct 2011	● Detailed the additional use of the neuropathic pain symptom inventory (NPSI) questionnaire in the study
Substantial Amendment 3	06 May 2013	● The requirement for patients to be on stable glycemic control was removed ● An update of the exclusion and inclusion criteria; addition of inclusion criterion 9 and exclusion criterion 33

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

Appendix 13.1.4 – Investigator Information

Investigator	Site Information	
[redacted]	[redacted]	UNITED STATES [redacted]
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