Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

SYNOPSIS

Title of Study: Tolerability of QUTENZA™ When Applied After Pre-Treatment With Lidocaine or Tramadol in Subjects With Peripheral Neuropathic Pain - A Randomized, Multi-center, Assessor-blinded Study

Investigators/Coordinating Investigator: [redacted], MD, DMSc, Professor

Study Center(s): This study was conducted in the following countries: Belgium, Slovakia, United Kingdom, Ireland, Denmark, Czech Republic, and Norway.

Publication Based on the Study: No publications based on the results of this study were available as of the time of finalization of this report.

Study Period: July 2011 to April 2012

Study Initiation Date (Date of First Enrollment): 6 July 2011

Study Completion Date (Date of Last Evaluation): 25 April 2012

Phase of Development: Phase 4

Objectives: The primary objective of this study was to evaluate the tolerability of QUTENZA treatment when applied after pre-treatment with topical lidocaine or oral tramadol. The secondary objective was to evaluate the safety of the QUTENZA application procedure after pre-treatment with topical lidocaine or oral tramadol.

Methodology: This was a multi-center, randomized, assessor-blinded study.
Prior to application of QUTENZA, subjects were randomized to 1 of 2 treatment arms, in a 1:1 ratio as follows:
Arm 1: Application of topical anesthetic (lidocaine 4%) to the area of pain for 60 min prior to patch application.
Arm 2: Administration of 50 mg of tramadol 30 min prior to patch application.
The subjects received a single treatment with QUTENZA (capsaicin 8% patch). The duration of participation for each subject was approximately 2 weeks.

Number of Patients (Planned, Enrolled and Analyzed): One hundred and twenty (120) QUTENZA-naïve subjects were to receive a single treatment with QUTENZA (capsaicin 8% patch). A total of 122 subjects were enrolled into the study and received randomized study drug treatment. All randomized subjects were included in safety analysis set (SAF).

Diagnosis and Main Criteria for Inclusion: Male or female subjects between 18 and 90 years of age, inclusive, in good health as determined by the investigator and with documented diagnosis at the treatment visit of either 1) PHN with pain persisting at least 3 months since shingles vesicle crusting, or 2) Neuropathic pain due to PNI including post-surgical neuropathic pain and post-traumatic peripheral neuropathic pain, persisting for a minimum of 3 months following the event, who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied were eligible for inclusion in this study.

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Test Product, Dose and Mode of Administration, Batch Numbers:

Arm 2: Tramadol was provided as tablets containing 50 mg of tramadol hydrochloride along with saccharine sodium and strawberry flavor. A single tramadol tablet of 50 mg was administered orally, 30 min prior to QUTENZA patch application. Batch number: [redacted]

Duration of Treatment (or Duration of Study, if applicable):

Arms 1 and 2: QUTENZA was available as a patch stored in a paper coated aluminum foil sachet with acrylnitrile-acrylic acid copolymer heat seal layer. Each patch was 14 cm by 20 cm (280 cm^2) and contained a total of 179 mg of capsaicin (640 mcg capsaicin per 1 cm^2 of patch [8% w/w]). QUTENZA is approved in the EU for the treatment of PNP in non-diabetic adults. Batch number: [redacted]

Reference Product, Dose and Mode of Administration, Batch Numbers:

Arm 1: Lidocaine 4% was provided as creme, 30 g tubes containing 40 mg/g of lidocaine, purified water, propylene glycol, hydrogenated soy lecithin, benzyl alcohol, polysorbate 80, carbomer 940, triethanolamine and cholesterol. Lidocaine 4% was applied for 60 min to the intended treatment area prior to QUTENZA patch application. Batch numbers: [redacted] and [redacted]

Criteria for Evaluation:

Tolerability: Evaluation of the tolerability of QUTENZA treatment when applied after pre-treatment with topical lidocaine or oral tramadol was the primary objective of this study. Efficacy, pharmacokinetics and pharmacodynamics were not evaluated in this study. A QUTENZA tolerant subject was defined as being a subject receiving at least 90% of the intended patch duration. For the 60 min application, this meant at least a 54 min exposure. Subjects receiving less than 90% of the intended patch duration or with missing patch duration were considered to be non QUTENZA tolerant.

Safety: Changes in vital signs (heart rate and blood pressure) after patch application relative to baseline, laboratory interpretation at screening visit and at unscheduled visits (listed only), abnormal ECGs (clinically significant or not) at screening visit and at unscheduled visits (listed only), proportion of subjects at each dermal assessment score (from 0 [no evidence of irritation] to 7 [strong reaction spreading beyond test site]) before and at all time points after patch application, adverse events.

Statistical Methods: All relevant observations available in the analytical database were listed for subjects from the SAF. All derived variables were flagged in listing column titles.
All data was analyzed for the total SAF population, by treatment arm and visit/time point when applicable and unless stated otherwise.
For continuous variables, descriptive statistics included the number of subjects (n), mean, standard deviation, median, minimum, 25% percentile, 75% percentile and maximum. Frequencies and percentages were displayed

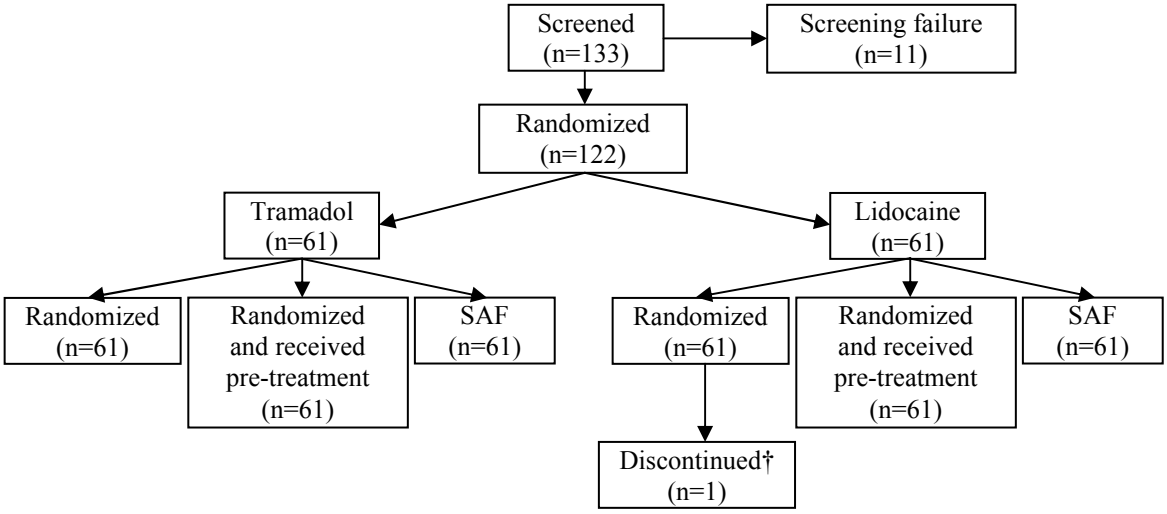
Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

for categorical data. Percentages by categories were based on the number of subjects with no missing data, i.e., will add up to 100%. When needed, 95% binomial confidence intervals were added.
All data processing, summarization, and analyses were performed using SAS® Version 8.2 or higher on Unix.

Summary of Results/Conclusions:

- A total of 122 subjects were enrolled into the study and received randomized study drug treatment. All randomized subjects received the study drug. The SAF comprised 122 subjects. Of these subjects, 121 (99.2%) completed the study and 1 subject from treatment Arm 1 (lidocaine 4%) prematurely discontinued the study due to AEs (erythema and application site pain). A summary of subject disposition is presented in [Figure 1].

Figure 1 Disposition of Subjects



SAF: Safety analysis set.
† Due to erythema and application site pain adverse events after treatment visit.
Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3 and Listing 13.2.7.5

- The mean age of subjects enrolled in the study was 55.3 years (range 18 to 88 years). The majority of subjects were White (97.5%) and more female subjects were enrolled in the study (57.4%). Subjects' mean body weight was 79.77 kg and mean BMI was 28.03 kg/m^2. For all subjects, the mean duration of neuropathic pain was 4.2 years and it was higher in the lidocaine treatment arm (4.93 years) compared to tramadol treatment arm (3.43 years). Postherpetic neuralgia (PHN) occurred in 23% of the subjects, whereas 77% had PNI (of which 73.4% post-surgical and 26.6% post-traumatic). The occurrence of the type of neuropathic pain was similar between the 2 treatment arms. A summary of subject demographics and baseline characteristics is presented in [Table 1].

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Table 1 Summary of Demographics and Baseline Characteristics, SAF

Parameter Category/Statistics	**Lidocaine n = 61**	**Tramadol n = 61**	**Total n = 122**
Sex, n (%)			
Male	24 (39.3)	28 (45.9)	52 (42.6)
Female	37 (60.7)	33 (54.1)	70 (57.4)
Race, n (%)			
White	59 (96.7)	60 (98.4)	119 (97.5)
Black or African	1 (1.6)	1 (1.6)	2 (1.6)
Other†	1 (1.6)	0	1 (0.8)
Age, years			
Mean (SD)	57.1 (15.94)	53.6 (16.74)	55.3 (16.37)
Median	59.0	54.0	56.0
Min–Max	25-88	18-87	18-88
Weight, kg			
n	60	61	121
Mean (SD)	81.50 (18.05)	78.07 (15.75)	79.77 (16.95)
Median	79.00	76.80	78.00
Min–Max	53.0-140.0	47.0-115.5	47.0-140.0
Height, cm			
n	60	61	121
Mean (SD)	167.39 (9.630)	169.51 (10.438)	168.46 (10.060)
Median	167.50	170.00	168.70
Min–Max	143.0-186.0	148.0-190.1	143.0-190.1
Body Mass Index‡, kg/m^2			
n	60	61	121
Mean (SD)	28.97 (5.279)	27.11 (4.775)	28.03 (5.096)
Median	28.34	26.70	27.54
Min–Max	19.0-44.7	18.4-42.4	18.4-44.7
Duration of neuropathic pain, years§			
n	61	61	122
Mean (SD)	4.93 (5.834)	3.43 (3.657)	4.18 (4.907)
Median	2.81	2.61	2.72
Min–Max	0.3-29.8	0.3-22.9	0.2-29.7
Type of neuropathic pain, n (%)			
Postherpetic Neuralgia	13 (21.3)	15 (24.6)	28 (23.0)
Peripheral Nerve Injury	48 (78.7)	46 (75.4)	94 (77.0)
Post-surgical	32 (66.7)	37 (80.4)	69 (73.4)
Post- traumatic	16 (33.3)	9 (19.6)	25 (26.6)
Other	0	0	0

SAF: Safety analysis set.

† Not Asian, American Indian, Alaskan native, native Hawaiian or other Pacific islander.

‡ Derived as: Weight (kg) / (Height (m)* Height (m)).

§ Derived as: (Date of screening visit -'Date of Diagnosis' + 1 day)/365.25.

Source: Tables 12.1.2.1.1 and 12.1.3.2

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

Tolerability Results:

- In total 121 subjects (99.18%) were QUTENZA tolerant. In both treatment arms similar proportions of QUTENZA-tolerant subjects were observed (98.36% and 100.0% for lidocaine and tramadol, respectively) with overlapping 95% confidence interval. One subject in the lidocaine treatment arm was non QUTENZA tolerant (15 min instead of 60 min duration of QUTENZA patch application). The tolerability of QUTENZA is presented in [Table 2].

Table 2 QUTENZA Tolerability, SAF

QUTENZA tolerability† Statistics‡	**Lidocaine n = 61**	**Tramadol n = 61**	**Total n = 122**
QUTENZA tolerant			
n (%)	60 (98.36)	61 (100.00)	121 (99.18)
95% CI	(91.20, 99.96)	(94.13, 100.00)	(95.52, 99.98)
Non QUTENZA tolerant			
n (%)	1 (1.64)	0	1 (0.82)
95% CI	(0.04, 8.80)		(0.02, 4.48)

SAF: Safety analysis set.

† QUTENZA tolerant subject: received at least 90% (54 min or 27 min for foot-treated subjects) of intended patch duration; Non QUTENZA tolerant subject: received less than 90% of intended patch duration or patch duration was missing.

‡ 95% confidence intervals of proportion were calculated using binomial distribution.

Source: Table 12.3.1

- There was no difference between the treatment arms for QUTENZA tolerability by type of neuropathic pain [Table 3].

Table 3 QUTENZA Tolerability by Type of Neuropathic Pain, SAF

QUTENZA tolerability† Statistics‡	**Type of Neuropathic Pain**					
	Postherpetic Neuralgia Subjects			**Peripheral Nerve Injury Subjects**		
	Lidocaine n = 13	**Tramadol n = 15**	**Total n = 28**	**Lidocaine n = 48**	**Tramadol n = 46**	**Total n = 94**
QUTENZA tolerant						
n (%)	13 (100.00)	15 (100.00)	28 (100.00)	47 (97.92)	46 (100.00)	93 (98.94)
95% CI	(75.29, 100.00)	(78.20, 100.00)	(87.66, 100.00)	(88.93, 99.95)	(92.29, 100.00)	(94.21, 99.97)
Non QUTENZA tolerant						
n (%)	0	0	0	1 (2.08)	0	1 (1.06)
95% CI				(0.05, 11.07)		(0.03, 5.79)

SAF: Safety analysis set.

† QUTENZA tolerant subject: received at least 90% (54 min or 27 min for foot-treated subjects) of intended patch duration; Non QUTENZA tolerant subject: received less than 90% of intended patch duration or patch duration was missing.

‡ 95% confidence intervals of proportion were calculated using binomial distribution.

Source: Table 12.3.1

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

- The percent duration of QUTENZA patch application was comparable between the 2 treatments groups.
- Pain relief was observed after pre-treatment administration up to 15 min prior to QUTENZA application. The pain relief was more pronounced in the lidocaine arm compared with tramadol arm (considered to be related to the difference between the onset of an effect of a topical anesthetic and a systemic analgesic, and also because lidocaine was administered 70 min before the start of QUTENZA application vs 30 min for tramadol administration). The pain level increased to the same extent in subjects in both treatment arms during the patch application up to 55 min following QUTENZA patch application. Subjects in the tramadol treatment arm experienced a greater pain relief at 85 min and 115 min after QUTENZA patch removal, compared to the lidocaine treatment arm.
- The difference in mean change from baseline in NPRS 'Pain Now' score between the tramadol and lidocaine treatment arms appeared to be slightly larger in subjects with PHN compared with subjects with PNI. However, no formal statistical testing was performed.
- Numerically lower, although not statistically significant, tolerability scores were observed in the tramadol treatment arm compared with the lidocaine treatment arm at both assessments.

Safety Results:

- The most common QUTENZA-emergent AEs (which started or worsened in severity during or after application of QUTENZA until the subject's completion of the study) occurring in at least 5% of subjects were application site pain, erythema, application site erythema, pain and nausea. [Table 4] and [Table 12.6.1.12]. The majority of QUTENZA-emergent AE were mild and moderate in intensity. There were several severe QUTENZA-emergent AE including application site pain, skin burning sensation, erythema and nausea. These AE were probably or possibly related to QUTENZA treatment. Most of them required drug treatment and non-medication therapy.

Table 4 Number of QUTENZA-Emergent AE Occurring in at Least 5% of the Subjects by SOC and PT (MedDRA v13.1), SAF

System organ class Preferred term (MedDRA v13.1)†, n (%)	**Lidocaine n = 61**	**Tramadol n = 61**	**Total n = 122**
Overall	54 (88.5)	49 (80.3)	103 (84.4)
General disorders and administration site conditions	47 (77.0)	41 (67.2)	88 (72.1)
Application site pain	37 (60.7)	34 (55.7)	71 (58.2)
Application site erythema	13 (21.3)	10 (16.4)	23 (18.9)
Pain	8 (13.1)	5 (8.2)	13 (10.7)
Skin and subcutaneous tissue disorders	21 (34.4)	23 (37.7)	44 (36.1)
Erythema	20 (32.8)	19 (31.1)	39 (32.0)
Gastrointestinal disorders	5 (8.2)	6 (9.8)	11 (9.0)
Nausea	4 (6.6)	3 (4.9)	7 (5.7)

A QUTENZA-emergent AE was defined as an AE which started or worsened in severity during or after application of QUTENZA until subject's completion of the study.

AE: Adverse event; PT: Preferred term; SAF: Safety analysis set; SOC: System organ class.

Footnotes continued on next page

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

† Sorting order: descending in number of total column by system organ class, and within that descending order by preferred term. Preferred term 'off label use' corresponds to QUTENZA application on foot for subject [redacted] documented as protocol violation.

Source: Table 12.6.1.2.2

- Two subjects experienced QUTENZA-emergent QUTENZA-related SAEs: 1 hypertension (moderate in severity) and 1 off label use on foot (mild in severity). Both SAEs were probably related to QUTENZA treatment and subjects recovered on the same day. The off label use was reported as an SAE because of the prolonged application time on the foot within the context of this trial (i.e., for 60 min rather than the 30 min specified in the approved product labeling). Therefore, this was considered to be a medically significant SAE in accordance with regulatory requirements. The subject reporting the off label use did not experience any other AE. The number of QUTENZA-emergent SAEs which started or worsened in severity during or after application of QUTENZA until subject's completion of the study is presented in [Table 5].

Table 5 Number of Serious QUTENZA-Emergent AE by SOC and PT (MedDRA v13.1), SAF

System organ class Preferred term (MedDRA v13.1), n (%)	**Lidocaine n = 61**	**Tramadol n = 61**	**Total n = 122**
Overall	1 (1.6)	1 (1.6)	2 (1.6)
Surgical and medical procedures	0	1 (1.6)	1 (0.8)
Off label use†	0	1 (1.6)	1 (0.8)
Vascular disorders	1 (1.6)	0	1 (0.8)
Hypertension	1 (1.6)	0	1 (0.8)

A serious QUTENZA-Emergent AE was defined as an AE which started or worsened in severity during or after application of QUTENZA until subject's completion of the study.

AE: Adverse event; PT: Preferred term; SAF: Safety analysis set; SOC: System organ class.

† Preferred term 'off label use' corresponds to QUTENZA application on foot for subject [redacted] documented as protocol violation.

Source: Table 12.6.1.7

- No deaths were reported in this study.
- The number of subjects reporting AEs and SAEs was identical in both treatment arms, but there was a higher number of AEs reported in the lidocaine treatment arm compared to the tramadol treatment arm. Two AEs leading to permanent discontinuation were reported by one subject in the lidocaine treatment arm.
- One application site pain and 1 erythema QUTENZA-emergent AE (possibly or probably related) that resulted in permanent discontinuation were reported by one subject in the lidocaine treatment arm.
- The most common QUTENZA-emergent AE of special interest (pain/burning sensation/heat/pruritus) were application site pain and pain in both lidocaine and tramadol treatment arm, respectively.
- One hypertension and 1 off label used SAE were reported as serious QUTENZA-related QUTENZA-emergent AEs in the lidocaine and tramadol treatment arm, respectively (QUTENZA application on foot for subject [redacted] also documented as protocol violation).

Name of Sponsor/Company: Astellas Pharma Europe Limited		
Name of Finished Product: QUTENZA		
Name of Active Ingredient: Capsaicin		

- The mean painful area size was similar between the 2 treatment arms at each visit. In both treatment arms, there was a decrease in mean painful area size at the EoS compared to screening and treatment time points. The reduction in mean painful area size was more pronounced in the tramadol treatment arm compared with the lidocaine treatment arm.

CONCLUSIONS:

There was no difference in QUTENZA tolerability when applied after pre-treatment with topical lidocaine or oral tramadol. In addition, QUTENZA application after pre-treatment with topical lidocaine or oral tramadol is well tolerated in subjects with PNP.

Date of Report: Sep 2012