Clinical trial results:
Qutenza TM versus pregabalin in patients with Peripheral Neuropathic Pain (PNP) an Open-label, Randomized, Multicenter, Non-inferiority Efficacy and Tolerability Study.

Summary

EudraCT number	2011-005872-41
Trial protocol	SE CZ FI AT SK ES BE SI GB DE GR PT IT BG
Global end of trial date	26 September 2013

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	22 May 2015
Version creation reason	• Correction of full data set Updates required due to non-substantial reasons

Trial information

Trial identification

Sponsor protocol code	QTZ-EC-0004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01713426
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd.
Sponsor organisation address	2000 Hillswood Drive, Chertsey, United Kingdom, KT16 0RS
Public contact	Associate Medical Director - Pain Therapeutic Area, Astellas Pharma Europe Ltd. (APEL), Astellas.resultsdisclosure@astellas.com
Scientific contact	Associate Medical Director - Pain Therapeutic Area, Astellas Pharma Europe Ltd. (APEL), Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2013
Global end of trial reached?	Yes
Global end of trial date	26 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to compare the efficacy,tolerability and impact on health-related quality of life (HRQoL) of treatment with Qutenza (Capsaicin (8%) high-concentration patch) versus pregabalin in patients with Peripheral Neuropathic Pain (PNP) after 8 weeks.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal or and regional and national legislation related to the privacy and protection of personal information.The appropriate Competent Authority in each country approved the protocol prior to the start of the study. The original study protocol and the amendments were reviewed by the Independent Ethics Committee (IEC) at each study site. An IEC-approved written informed consent was obtained from each patient or legal guardian prior to the initiation of any study-specific procedures.

Background therapy:

Patients remained on existing neuropathic pain medication(s) if the doses were maintained stable for more than 4 weeks prior to the baseline visit. Patients in the Qutenza (Capsaicin (8%) high-concentration patch) arm received a topical anesthetic on their painful affected area(s) prior to placement of Qutenza (Capsaicin (8%) high-concentration patch). In addition patients may have received a short-acting pain medication (including short-acting opioids) during patch application or as needed following patch application, to reduce patch-related pain/discomfort. Short-acting opioids could have been administered for up to 5 days following patch application. Patients could also be give non-opioid pain medications (e.g., paracetamol, NSAIDs) administered for conditions other than neuropathic pain. Other medical therapy not specifically prohibited, includes non-opioid pain medications (e.g., paracetamol, NSAIDs) administered for conditions other than neuropathic pain. Any changes, additions or discontinuations to medications were assessed and recorded at every study visit. Doses of any concomitant medication for the treatment of neuropathic pain had to remain stable for the duration of the study.

Evidence for comparator:

Pregabalin belongs to the antiepileptic group of drugs and the active substance is a gamma-aminobutyric acid analogue. Pregabalin binds to an auxiliary subunit of voltage-gated calcium channels in the central nervous system, potently displacing 3H-gabapentin. Pregabalin is an anticonvulsant, which, along with tricyclic antidepressants such as amitriptyline can be considered the standard of care for the treatment of PNP. A flexible dose design has been chosen for pregabalin to best match clinical practice in Europe. The Summary of Product Characteristics (SmPC) for pregabalin states that the effective dose range is 150 to 600 mg/day. The SmPC advises that the dose of pregabalin should be up-titrated over a period of 10 to 14 days. To reduce the occurrence of dose-limiting side effects, up-titration of the dose in European clinical practice is often performed over a longer time period, using varying dose changes and frequency of up-titration steps. This study was designed to reflect as much as possible the current clinical practice and thus included an up-titration scheme performed over a period of 4 weeks, using gradual steps of 75 mg/day. This up-titration method was intended to provide a level of flexibility while minimizing variability and represents a compromise between the different clinical practices across Europe. Intolerance of any dose of pregabalin was recorded as an Adverse Event (AE).

Actual start date of recruitment	11 July 2012
Long term follow-up planned	No

Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Bulgaria: 54
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Belarus: 8
Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	Turkey: 49
Country: Number of subjects enrolled	Armenia: 40
Worldwide total number of subjects	568
EEA total number of subjects	415

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	413
From 65 to 84 years	155
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multinational, multicenter study was conducted at 92 contracted sites in a total of 22 countries. The study population consisted of males and females between 18 and 80 years of age with documented diagnosis of probable or definite PNP.

Pre-assignment

Screening details:

Patients were screened in a 12-day period between Day -12 and Day -4 during which informed consent,collection of demographic, medical and medication history, a physical examination, vital signs (blood pressure and pulse rate) and safety laboratory tests data was collected.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Qutenza [Capsaicin (8%) high-concentration patch]

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Qutenza (Capsaicin (8%) high-concentration patch)
Investigational medicinal product code	ASP0805
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical use

Dosage and administration details:

Qutenza is a high concentration (8%) capsaicin patch. Participants received a topical anesthetic cream (e.g., 4% lidocaine cream) on their painful affected area(s) prior to placement of Qutenza patches. Up to 4 patches of Qutenza (1120 cm2) were applied for 60 minutes to the painful areas of the body (as defined by the study physician), except the feet, where a 30 minute application time was used. The patches were removed after 30 minutes (feet) or 60 minutes (other body locations) and the treatment area(s) were cleansed using study-supplied cleansing gel. The rationale for the application times was to keep the mode of administration in full accordance with the approved SmPC.

Arm title	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Pregabalin [75 mg hard capsule to be taken orally gamma-aminobutyric acid analogue]
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pregablin was administered daily in 75-mg capsules to best match clinical practice in Europe. Patients were prescribed 150 to 600 mg/day of pregabalin, administered in 2 or 3 divided doses daily. All patients started with a daily dose of 75-mg which was up-titrated to 150 mg/day after 3 or 4 days. Further up-titration was at the discretion of the investigator, however patients were up-titrated to a maximum tolerated dose or until the patient experienced a clinically meaningful reduction in pain (≥ 30% reduction in pain from Baseline). Up-titration occurred in 75-mg steps every 3 to 4 days, up to a maximum dose of 600 mg/day. If the patient experienced unacceptable tolerability issues, a single

down-titration of pregabalin was permissible, back to the previously tolerated dose (to a minimum dose of 150 mg/day).

Number of subjects in period 1	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Started	286	282
Completed	276	236
Not completed	10	46
Discontinuation due to AE	-	24
Lack of efficacy	2	3
Consent withdrawn by subject	4	14
Randomized - Never received study drug	4	5

Baseline characteristics

Reporting groups	
Reporting group title	Qutenza [Capsaicin (8%) high-concentration patch]
Reporting group description: -	
Reporting group title	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Reporting group description: -	

Reporting group values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]	Total
Number of subjects	286	282	568
Age categorical Units: Subjects			
Age continuous			
Age values reported are for the Full Analysis Set (FAS) population. The FAS population includes all randomized patients who initiated the study treatment. The total number of patients for FAS population was 559, with 282 for Qutenza and 277 for pregabalin.			
Units: years			
arithmetic mean	55.4	56.3	
standard deviation	± 13.96	± 13.54	-
Gender categorical			
Gender values provided are for the Full Analysis Set (FAS) population. The FAS population includes all randomized patients who initiated the study treatment. The total number of patients for FAS population was 559, with 282 for Qutenza and 277 for pregabalin.			
Units: Subjects			
Female	159	155	314
Male	123	122	245
Not Recorded	4	5	9
Race			
Race values provided are for the Full Analysis Set (FAS) population. The FAS population included all randomized patients who initiated study treatment. The number of patients for FAS was as follows; Qutenza 282; pregabalin 277.			
Units: Subjects			
White	278	276	554
Asian	1	1	2
Other	3	0	3
Not Recorded	4	5	9
Type of neuropathic pain			
Postherpetic neuralgia (PHN) is a peripheral neuropathic pain (PNP) disorder that represents a complication of acute herpes zoster infection. Peripheral nerve injury (PNI) can lead to the development of neuropathic pain which results from a trauma or is a consequence of medical interventions such as surgery, injections or radiotherapy. In a majority of patients pain resulting from an injury to peripheral nerves resolves but in some it may become chronic. Non-diabetic painful Peripheral Polyneuropathy is a pattern of nerve damage.			
Units: Subjects			
Postherpetic Neuralgia (PHN)	63	73	136
Peripheral Nerve Injury (PNI)	146	137	283
Non-diabetic painful peripheral polyneuropathy	73	67	140

Not Recorded	4	5	9

Duration of neuropathic pain diagnosis			
Duration of neuropathic pain diagnosis values are provided for the Full Analysis Set (FAS) population. The FAS population includes all randomized patients who initiated study treatment. The total number of patients randomized for FAS population was 559 with 282 for Qutenza and 277 for pregabalin.			
Units: Years			
arithmetic mean	2.58	2.12	
standard deviation	± 4.32	± 2.9	-

End points

End points reporting groups

Reporting group title	Qutenza [Capsaicin (8%) high-concentration patch]
Reporting group description: -	
Reporting group title	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Reporting group description: -	

Primary: Proportion of patients who achieved ≥30% change in the "Average Pain for the Past 24 hours" Numeric Pain Rating Scale (NPRS) Score from Baseline to Week 8 (BOCF) (FAS)

End point title	Proportion of patients who achieved ≥30% change in the "Average Pain for the Past 24 hours" Numeric Pain Rating Scale (NPRS) Score from Baseline to Week 8 (BOCF) (FAS)

End point description:

The proportion of patients in each arm who achieved at least ≥30% change in the "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Week 2 (Day 8) to Week 8 (Day 57) was analyzed to compare the efficacy of Qutenza versus pregabalin in patients with Peripheral Neuropathic Pain (PNP). 'Baseline' refers to the mean of all NPRS "average pain for the past 24 hours" scores recorded during the screening period for 4 consecutive days. Week 8 Baseline-Observation Carried Forward (BOCF) refers to the mean of all "average pain for the past 24 hours" NPRS scores for the 7 days up to and including the Week 8 visit if non-missing and the Baseline value if missing assessment at Week 8.

End point type	Primary

End point timeframe:

Week 2 (Day 8) and Week 8 (Day 57)

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of patients				
number (not applicable)				
Responders, Number of patients	157	151		

Statistical analyses

Statistical analysis title	Proportion of patients who achieved ≥ 30% change

Statistical analysis description:

The analysis of the primary efficacy variable was performed using a Generalized Linear Model (GLM) with logit link function, the hypothesis was tested using Odds Ratio (OR) using the non-inferiority margin of -8.5%, which translated into a margin on the OR of 0.693. The null hypothesis of inferiority was therefore to be rejected if the 2-sided 95% Confidence Interval (CI) for the OR of Qutenza versus pregabalin fell completely above 0.693.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]

Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.86
Method	Generalized Linear Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.715
upper limit	1.496

Secondary: Proportion of patients in each arm who achieved "optimal therapeutic effect" from Week 2 to Week 8 (FAS)

End point title	Proportion of patients in each arm who achieved "optimal therapeutic effect" from Week 2 to Week 8 (FAS)

End point description:

The key secondary efficacy endpoint was the proportion of patients who achieved optimal therapeutic effect defined as no change in chronic background pain medication (assessed by the Independent Data Review Board [IDRB]) and no discontinuation of study drug due to lack of efficacy or tolerability prior to Week 8 and at least 30% reduction in the "average pain for the past 24 hours" NPRS score, from Baseline to Week 8 and no moderate or severe Adverse Drug Reaction (ADRs) during the stable treatment period.

End point type	Secondary

End point timeframe:

Week 2 (Day 8) to Week 8 (Day 57)

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of patients				
number (not applicable)				
Responders, Number of patients	147	124		

Statistical analyses

Statistical analysis title	Optimal therapeutic effect Week 8 BOCF

Statistical analysis description:

The Generalized Linear Model (GLM) models optimal therapeutic effect dependent on treatment, countries [countries were pooled due to a small numbers of patients within the country] gender with logit linkage and binomial distribution. Baseline Observation Carried Forward (BOCF) and Full Analysis Set (FAS) was used for data analysis.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v

	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.064
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	1.423
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.979
upper limit	2.066

Notes:

[1] - Generalized Linear Model

Secondary: Proportion of patients who achieved at least a 30% change in the "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Baseline to the mean of all scores recorded between Week 2 and Week 8 (FAS)

End point title	Proportion of patients who achieved at least a 30% change in the "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Baseline to the mean of all scores recorded between Week 2 and Week 8 (FAS)

End point description:

Proportion of patients who achieved at least a 30% decrease in the "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Baseline to the mean of all scores recorded between Week 2 and Week 8. BOCF: Baseline Observation Carried Forward and NC [Non-compliant].

End point type	Secondary

End point timeframe:

Baseline to the mean of all scores recorded between Week 2 and Week 8 including complete 8 weeks of treatment.

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
number (not applicable)				
Week 8 BOCF+NC	150	146		
Week 8 [Mean of all observed data]	157	151		

Statistical analyses

Statistical analysis title	At least 30% Pain Change Achievement Week 8
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]

Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.303
Method	Generalized Linear Model
Parameter estimate	Odds ratio (OR)
Point estimate	0.812
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.547
upper limit	1.206

Notes:

[2] - The GLM models optimal therapeutic effect dependent on treatment, country (pooled), gender with logit linkage and Binomial Distribution.The Odds Ratio (OR) compares Qutenza to pregabalin.

Statistical analysis title	At least 30% Pain Change Achievement Week 8BOCF+NC
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.98
Method	Generalized Linear Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.695
upper limit	1.452

Notes:

[3] - The GLM models optimal therapeutic effect dependent on treatment, country (pooled), gender with logit linkage and Binomial Distribution.The Odds Ratio compares Qutenza to pregabalin.

Secondary: Proportion of patients who achieved at least a 50% change in the "average pain for the 24 hours" Numeric Pain Rating Scale (NPRS) score from Baseline to Week 8 and from Baseline to the mean of all scores recorded between Week 2 and Week 8 (FAS)

End point title	Proportion of patients who achieved at least a 50% change in the "average pain for the 24 hours" Numeric Pain Rating Scale (NPRS) score from Baseline to Week 8 and from Baseline to the mean of all scores recorded between Week 2 and Week 8 (FAS)

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Week 8, and from Baseline to the mean of all scores recorded between Week 2 and Week 8 including proportion of patients in both arms who completed 8 weeks of treatment.

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of Patients				
number (not applicable)				
Week 8 [Responders, Number of Patients]	114	106		
Week 8 (BOCF) [Responders, Number of Patients]	114	106		
Week 2 to Week 8 [Responders, Number of Patients]	96	60		

Statistical analyses

Statistical analysis title	At least 50% Pain Change Achievement Week 8

Statistical analysis description:

Full Analysis Set (FAS) used for analysis.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in Proportion
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	5.8

Notes:

[4] - The difference in proportion method was used to analyse large sample normal approximation and compare Qutenza to Pregabalin.

Statistical analysis title	At least 50% Pain Reduction Achievement Week 8BOCF

Statistical analysis description:

Full Analysis Set (FAS) was used for analysis.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Difference in Proportion
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	10.3

Notes:

[5] - The difference in proportion method was used to analyse large sample normal approximation and compare Qutenza to Pregabalin.

Statistical analysis title	At Least 50% Reduction Achievement Week 2 to 8

Statistical analysis description:

Full Analysis Set (FAS) was used for analysis.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Difference in Proportion
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	19.6

Notes:

[6] - The difference in proportion method was used to analyse large sample normal approximation and compare Qutenza to Pregabalin.

Secondary: Absolute and percent change in "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Week 2 to Week 8 (FAS)

End point title	Absolute and percent change in "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score from Week 2 to Week 8 (FAS)

End point description:

Full Analysis Set (FAS) was used for data analysis.

End point type	Secondary

End point timeframe:

Mean of all scores from Week 2 (Day 8) to Week 8 (Day 57).

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	275		
Units: Number of Patients				
arithmetic mean (standard deviation)				
Week 2 to 8 Absolute Change from Baseline	-2.5 (± 2.17)	-1.8 (± 1.67)		
Week 2 to 8 Percent Change from Baseline	-37.1 (± 30.43)	-27.5 (± 24.03)		

Statistical analyses

Statistical analysis title	Numeric Pain Rating Scale (NPRS) Absolute Change

Statistical analysis description:

The LS mean and LS mean difference between Qutenza and pregabalin and its corresponding 95% CI are derived using an analysis of covariance (ANCOVA) model adjusted for gender, pooled country and baseline.

Comparison groups	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated] v Qutenza [Capsaicin (8%) high-concentration patch]
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.4

Statistical analysis title	Numeric Pain Rating Scale (NPRS) Percent Change

Statistical analysis description:

The LS mean and LS mean difference between Qutenza and pregabalin and its corresponding 95% CI are derived using an ANCOVA model adjusted for gender, pooled country and baseline.

Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-5.2

Secondary: Time to onset of pain relief (in days) as assessed by at least a 30% change in "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score (FAS)

End point title	Time to onset of pain relief (in days) as assessed by at least a 30% change in "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score (FAS)

End point description:

Time to onset of pain relief was assessed using the analysis of the time to ≥ 30% change (for 3 consecutive days) in "average pain for the past 24 hours" NPRS score. Onset date of pain relief is the date of the first questionnaire recorded with a 30% change. The Time to Onset is derived as Onset Date - Baseline Date + 1 Day. Hazard ratio was estimated using a Cox Model with country (pooled), gender and "average pain for the last 24 hours" NPRS score at baseline as covariates.

End point type	Secondary

End point timeframe:

Baseline, Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 29), Week 6 (Day 43), and Week 8 (Day 57)
.

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of Patients				
number (not applicable)				
Day 7 [Number of Patients with Events]	141	64		
Day 14 [Number of Patients with Events]	170	107		
Day 29 [Number of Patients with Events]	185	136		
Day 43 [Number of Patients with Events]	186	147		
Day 57 [Number of Patients with Events]	189	158		

Statistical analyses

Statistical analysis title	Time to Onset of Pain Relief
Statistical analysis description:	
Time to onset of pain relief was assessed using the analysis of the time to ≥ 30% change (for 3 consecutive days) in "average pain for the past 24 hours" NPRS score. Time to onset of pain relief was provided by the Cox model, adjusted on country, gender and NPRS score at baseline.	
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	2.08

Secondary: Overall patient status using Patient Global Impression of Change (PGIC) questionnaire at Week 4 and Week 8 (FAS)

End point title	Overall patient status using Patient Global Impression of Change (PGIC) questionnaire at Week 4 and Week 8 (FAS)

End point description:

Difference between Qutenza and pregabalin for counts by category were completed using a Cochran-Mantel-Haenszel test. The Patient Global Impression of Change (PGIC) scores ranged from 1 = Very Much Improved to 7 = Very Much Worse. Full Analysis Set (FAS) was used for data analysis and Last Observation Carried Forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

Week 4 and Week 8 End of Study (LOCF)

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of Patients				
number (not applicable)				
Week 4 [Very Much Improved]	21	12		
Week 4 [Much Improved]	110	104		
Week 4 [Minimally Improved]	74	73		
Week 4 [No Change]	52	36		
Week 4 [Minimally Worse]	10	8		
Week 4 [Much Worse]	1	6		
Week 4 [Very Much Worse]	0	0		
Week 8 [Very Much Improved]	50	40		
Week 8 [Much Improved]	94	83		
Week 8 [Minimally Improved]	67	77		
Week 8 [No Change]	53	40		
Week 8 [Minimally Worse]	6	14		
Week 8 [Much Worse]	6	7		
Week 8 [Very Much Worse]	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Medical Outcomes Study (MOS) 6-item Cognitive Functioning Scale from Baseline to Week 8 (FAS)

End point title	Change in the Medical Outcomes Study (MOS) 6-item Cognitive Functioning Scale from Baseline to Week 8 (FAS)

End point description:

The MOS Cognitive Functioning Scale is a patient reported outcome instrument which measures a range of less severe, day-to-day problems in 6 aspects of cognitive functioning,
including reasoning, concentration and thinking, confusion, memory, attention and psychomotor.The MOS 6-item Cognitive Functioning Scale absolute values are presented by treatment arm for the FAS.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Percent Change from Baseline [N=276; N=274]	12.4 (± 27.27)	6.9 (± 54.23)		
Absolute Change from Baseline [N=276; N=274]	4 (± 8.47)	0.5 (± 10.79)		

Statistical analyses

Statistical analysis title	Percent Change (MOS) Cognitive Function
Comparison groups	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated] v Qutenza [Capsaicin (8%) high-concentration patch]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	15.1

Statistical analysis title	Absolute Change (MOS) Cognitive Function
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	5.7

Secondary: Medical Outcomes Study (MOS) – Sleep Scale from Baseline to Week 4 and Week 8 (FAS)

End point title	Medical Outcomes Study (MOS) – Sleep Scale from Baseline to Week 4 and Week 8 (FAS)

End point description:

Disturbed sleep is prevalent in people with chronic pain, and its assessment is also important in chronic pain trials. The MOS Sleep Scale measures 6 dimensions of sleep, including initiation, maintenance (e.g., staying asleep), quantity, adequacy, somnolence (e.g.,drowsiness) and respiratory impairments (e.g., shortness of breath, snoring). Disturbed sleep has a major impact on Quality of Life (QoL) and is often a common symptom of many other chronic conditions, such as neuropathic pain. The reliability and validity of the MOS Sleep Scale have been evaluated in a number of disease areas, including neuropathic pain. Patients completed the MOS Sleep Scale at Baseline Visit, Week 4 Visit (Visit 4) and End of Treatment (EOT).

End point type	Secondary

End point timeframe:

Baseline to Weeks 4 and 8

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Week 4 [Absolute Change N=263; N=239]	4.3 (± 8.75)	6.4 (± 8.76)		
Week 4 [Percent Change N=263; N=239]	12.3 (± 24.6)	17.6 (± 25.43)		
Week 8/EoS [Absolute Change N=257; N= 244]	5.1 (± 8.88)	6.2 (± 8.79)		
Week 8/EoS [Percent Change N=257; N=244]	14 (± 25.45)	16.5 (± 24.41)		
Week 8/EoS BOCF [Absolute Change N=276; N=273]	4.7 (± 8.66)	5.5 (± 8.52)		
Week 8/EoS BOCF [Percent Change N=276; N=273]	13 (± 24.81)	14.7 (± 23.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Euroqol-5 dimensions (EQ-5D-5L) total score from Baseline to Week 8 (FAS)

End point title	Change in the Euroqol-5 dimensions (EQ-5D-5L) total score from Baseline to Week 8 (FAS)

End point description:

The EQ-5D-5L was used as a measure of respondents' Health-related quality of life (HRQoL) and health status. The EQ-5D-5L provides a simple descriptive profile and a single index value for health status.

The EQ-5D-5L patient-rated questionnaire includes a visual analog scale (VAS), which records the respondent's patient-rated health status on a graduated scale (0 to 100), with higher scores for higher HRQoL. It also includes the EQ-5D-5L descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The responses record 5 levels of severity (i.e., no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

End point type	Secondary
End point timeframe: Baseline and Week 8 /EoS (BOCF).	

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Percent Change [N=275; N=272]	26.5 (± 62.24)	20.4 (± 47.09)		
Absolute Change [N=276; N=272]	9.9 (± 19.57)	8.1 (± 18.83)		

Statistical analyses

Statistical analysis title	Percent Change from Baseline (HRQoL) EQ-5D-5L
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	19.2

Statistical analysis title	Absolute Change from Baseline (HRQoL) EQ-5D
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference

Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	5.9

Secondary: Treatment Satisfaction for Medication (FAS)

End point title	Treatment Satisfaction for Medication (FAS)

End point description:

Endpoint was assessed by TSQM evaluating proportion of patients who discontinued study drug or withdrew due to lack of efficacy or tolerability, or their willingness to continue treatment. The LS mean and LS difference of means between Qutenza and pregabalin and corresponding 95% CI were derived using an ANCOVA model adjusted for gender and pooled country. Factor Score = [(Sum of Obtained Score - Sum of Lowest Possible Score)/ Possible Sum Score Range] x 100, ranging from 0 to 100.

End point type	Secondary

End point timeframe:

Week 8 and Week 12

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Week 4 [TSQM Scale: Effectiveness]	57.7 (± 24.59)	57.8 (± 20.15)		
Week 8 (LOCF)[TSQM Scale: Effectiveness]	61.5 (± 25.57)	57.5 (± 23.14)		
Week 4 [TSQM Scale: Side effects]	95.6 (± 13.81)	80.3 (± 27.32)		
Week 8 (LOCF) [TSQM Scale: Side effects]	97 (± 12.27)	76.3 (± 31.19)		
Week 4 [TSQM Scale: Convenience]	71.7 (± 20.08)	74.5 (± 16.24)		
Week 8 (LOCF) [TSQM Scale: Convenience]	72.8 (± 20.52)	73.6 (± 17.46)		
Week 4 [TSQM Scale: Global Satisfaction]	60.7 (± 27.06)	58.5 (± 22.53)		
WEek 8 (LOCF) TSQM Scale: Global Satisfaction	62.6 (± 29.02)	56.1 (± 26.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach optimal maintenance dose for Pregabalin (Days) (FAS)

End point title	Time to reach optimal maintenance dose for Pregabalin (Days)

	(FAS)[7]

End point description:

Patients who withdrew before reaching the maintenance dose were censored at their last available visit date. The time to optimal maintenance dose was derived as the date when Optimal Maintenance Dose was reached - Baseline Date + 1 Day. Optimal Maintenance Dose is defined as the last dose collected and Date Optimal Maintenance Dose reached is the start of the Interval of the Optimal Maintenance Dose.

End point type	Secondary

End point timeframe:

VIsit (Week 1; [Days: 7]), (Week 2; [Days: 14]), (Week 4 [Days 29]), (Week 6 [Days 43]),(Week 8 [Days 57])

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint measures optimal maintenance dose for pregabalin only, which is why qutenza arm was excluded from the statistics report for this endpoint.

End point values	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]			
Subject group type	Reporting group			
Number of subjects analysed	277			
Units: Number of Patients				
number (not applicable)				
Week 1 [Day 7]	10			
Week 2 [Day 14]	60			
Week 4 [Day 29]	216			
Week 6 [Day 43]	248			
Week 8 [Day 57]	248			

Statistical analyses

No statistical analyses for this end point

Secondary: Resource use (number of contacts with health professionals)

End point title	Resource use (number of contacts with health professionals)

End point description:

Details of healthcare resource use (number of contacts with a healthcare professional both related to neuropathic pain and for other causes) were collected at each visit during the study.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment [EOT}

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Visits related to neuropathic pain[Baseline]	0.1 (± 0.61)	0.2 (± 0.59)		
Visits related to neuropathic pain[Week 2]	0.1 (± 0.41)	0.1 (± 0.62)		
Visits related to neuropathic pain[Week 4]	0.1 (± 0.77)	0.1 (± 0.68)		
Visits related to neuropathic pain[Week 8]	0.1 (± 0.52)	0.1 (± 0.72)		
Visits related to neuropathic pain[During Study]	0.4 (± 1.76)	0.5 (± 2.04)		
Visits due to other causes[Baseline]	0.1 (± 0.62)	0.2 (± 0.47)		
Visits due to other causes[Week 2]	0.3 (± 0.78)	0.3 (± 0.76)		
Visits due to other causes[Week 4]	0.2 (± 0.62)	0.2 (± 0.56)		
Visits due to other causes[Week 8]	0.4 (± 0.93)	0.3 (± 0.76)		
Visits due to other causes[During Study]	1.1 (± 1.97)	0.9 (± 1.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability (FAS)

End point title	Tolerability (FAS)

End point description:

The tolerability of treatment was assessed using Adverse Drug Reaction (ADRs) reported by patients in each arm. To increase the sensitivity of Adverse Events (AEs) collection and to limit recall bias on behalf of the patient, patients were asked to assess tolerability between visits, via self-report. In a patient reported outcome, terms such as "adverse event" were not appropriate. Instead, patients were asked open questions as to whether they have any health-related concerns or complaints and the number of complaints. Patients were asked to rate severity as follows; Mild (You could perform your normal daily activities), Moderate (You were limited in performing your normal daily activities) and Severe (You were not able to perform your daily activities).

End point type	Secondary

End point timeframe:

Baseline to End of Treatment [EOT]

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number of patients				

number (not applicable)				
Patients without TEAEs	72	100		
Patients without drug-related TEAEs	109	126		
Patients without moderate/severe TEAEs	135	153		
Patients without drug-related moderate/severe TEAE	174	173		
Patients without severe TEAEs	226	229		
Patients without severe drug-related TEAEs	247	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in intensity and area of allodynia from Baseline to Week 8

End point title	Change in intensity and area of allodynia from Baseline to Week 8

End point description:

The area(s) of dynamic mechanical allodynia was mapped with the patient in a comfortable position, as for assessment of the painful area. The intensity of pain associated with the allodynia was rated by the patient using a numeric rating scale.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment (EOT)

End point values	Qutenza [Capsaicin (8%) high-concentration patch]	Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	277		
Units: Number				
arithmetic mean (standard deviation)				
Intensity[Absolute change fromBaselineN=282;N=276]	-3 (± 3.07)	-2.3 (± 2.68)		
Intensity[Percent change from BaselineN=254;N=238]	-48.2 (± 44.15)	-38.2 (± 41.36)		
Area cm2[Absolute change from BaselineN=282;N=273]	-101 (± 177.32)	-69.7 (± 215.56)		
Area cm2[Percent change from BaselineN=255;N=235]	-43.6 (± 93.46)	-33.6 (± 64.02)		

Statistical analyses

Statistical analysis title	Intensity Absolute change from Baseline
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]

Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.2

Statistical analysis title	Intensity Percent change from Baseline
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference)
Point estimate	-10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	-3.5

Statistical analysis title	Area (cm2) Absolute change from Baseline
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference)
Point estimate	-30.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.5
upper limit	-2.7

Statistical analysis title	Area (cm2) Percent change from Baseline
Comparison groups	Qutenza [Capsaicin (8%) high-concentration patch] v Pregabalin [Oral Hard 75 mg Capsule Up-titrated as tolerated]
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	other

Parameter estimate	LS Mean Difference
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.3
upper limit	2.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for Treatment-Emergent Adverse Event (TEAE) was up to 30 days following the last treatment (follow-up window).

Adverse event reporting additional description:

All safety analyses was conducted on the Safety Analysis Set (SAF) data, and it included all patients who have received the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Pregabalin [oral hard 75 mg capsules]
Reporting group description: -	
Reporting group title	Qutenza [Capsaicin (8%) high-concentration patch]

Reporting group description: -

Serious adverse events	Pregabalin [oral hard 75 mg capsules]	Qutenza [Capsaicin (8%) high-concentration patch]	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 277 (2.53%)	10 / 282 (3.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
Vascular disorders			
Wegener's granulomatosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incorrect drug administration duration	Additional description: In the course of the study there was 1 patient who had a patch application with a duration of 60 mins to the feet, which was recorded as an SAE (incorrect drug administration duration), although there were no clinical consequences.		
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex regional pain syndrome			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Application site burn			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Swollen tongue			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 282 (0.35%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pregabalin [oral hard 75 mg capsules]	Qutenza [Capsaicin (8%) high-concentration patch]	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	176 / 277 (63.54%)	208 / 282 (73.76%)	
Investigations			
Weight increased			
subjects affected / exposed	17 / 277 (6.14%)	0 / 282 (0.00%)	
occurrences (all)	17	0	
Nervous system disorders			
Headache			
subjects affected / exposed	51 / 277 (18.41%)	37 / 282 (13.12%)	
occurrences (all)	85	66	
Dizziness			
subjects affected / exposed	54 / 277 (19.49%)	7 / 282 (2.48%)	
occurrences (all)	108	7	
Burning sensation			
subjects affected / exposed	1 / 277 (0.36%)	45 / 282 (15.96%)	
occurrences (all)	1	50	
Somnolence			
subjects affected / exposed	43 / 277 (15.52%)	2 / 282 (0.71%)	
occurrences (all)	67	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	14 / 277 (5.05%)	1 / 282 (0.35%)	
occurrences (all)	16	1	
General disorders and administration site conditions			

Application site pain			
subjects affected / exposed	0 / 277 (0.00%)	67 / 282 (23.76%)	
occurrences (all)	0	71	
Pain			
subjects affected / exposed	7 / 277 (2.53%)	18 / 282 (6.38%)	
occurrences (all)	8	28	
Application site erythema			
subjects affected / exposed	0 / 277 (0.00%)	25 / 282 (8.87%)	
occurrences (all)	0	25	
Oedema peripheral			
subjects affected / exposed	17 / 277 (6.14%)	3 / 282 (1.06%)	
occurrences (all)	32	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	35 / 277 (12.64%)	14 / 282 (4.96%)	
occurrences (all)	48	20	
Abdominal pain upper			
subjects affected / exposed	15 / 277 (5.42%)	9 / 282 (3.19%)	
occurrences (all)	26	10	
Constipation			
subjects affected / exposed	14 / 277 (5.05%)	2 / 282 (0.71%)	
occurrences (all)	19	2	
Dry mouth			
subjects affected / exposed	14 / 277 (5.05%)	0 / 282 (0.00%)	
occurrences (all)	15	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 277 (0.36%)	59 / 282 (20.92%)	
occurrences (all)	1	60	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 277 (3.25%)	15 / 282 (5.32%)	
occurrences (all)	10	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2012	The first amendment was the only substantial amendment, prior to the study initiation date, which detailed: ● Revision of the primary endpoint ● Introduction of an Independent Data Review Board (IDRB) ● Definition of clinically significant change in pregabalin dosing between Week 5 and Week 8 ● Definition of clinically significant change in QUTENZA dosing ● Assessment of allodynia at the Screening Visit ● Addition of an "Identification of Painful Area(s)" at Visit 5 (Week 8/EoS Visit) ● Permitted concomitant medications ● A clarification within the AE section that detailed that "Lack of efficacy" was not to be recorded as an AE ● A change to the pregabalin capsule count (to be collected on paper diary rather than electronic diary) ● The discontinuation of pregabalin ● A correction of the MOS Cog Scale, MOS Sleep Scale and NPRS versions ● A correction of NPRS pain score recording time for patients within the QUTENZA arm ● Minor administrative changes and change of study manager.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported