Clinical trial results:
A randomized, controlled, long-term safety study evaluating the effect of repeated applications of Qutenza (Capsaicin (8%) high-concentration patch) plus Standard of Care versus Standard of Care Alone in participants with Painful Diabetic Peripheral Neuropathy (PDPN).

Summary

EudraCT number	2009-016458-42
Trial protocol	DE BE GB CZ NL ES IT PL
Global end of trial date	27 February 2014

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	05 June 2015
Version creation reason	• Correction of full data set Correction of full data set = Revisions to the data made and clarification of previously reported data provided.

Trial information

Trial identification

Sponsor protocol code	E05-CL-3002/PACE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01478607
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V.
Sponsor organisation address	Sylviusweg 62, 2333 BE Leiden, Netherlands,
Public contact	Medical Science Director, Global Medical Science Astellas Pharma Global Development, Astellas Pharma Europe B.V., Astellas.resultsdisclosure@astellas.com
Scientific contact	Medical Science Director, Global Medical Science Astellas Pharma Global Development, Astellas Pharma Europe B.V., 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	27 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2014
Global end of trial reached?	Yes
Global end of trial date	27 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess safety and efficacy of repeat applications of Qutenza (Capsaicin (8%) high-concentration patch) administered over a period of 12 months in subjects with Painful Diabetic Peripheral Neuropathy (PDPN).

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, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

Participants received topical anaesthetic, Eutectic Mixture of Local Anesthetics (EMLA), on their painful affected area(s) prior to placement of Qutenza patches (Capsaicin (8%) high-concentration patch). A short-acting analgesic (including short-acting opioid if required) could be administered to relieve treatment-associated discomfort during treatment procedure and up to 5 consecutive days post-treatment. Any pain medications used as Standard of Care (SOC) in Painful Diabetic Peripheral Neuropathy (PDPN) were used as per the investigator’s discretion. Furthermore participants were allowed to take aspirin up to 325 mg/day for the prevention of ischemia as well as any anti-diabetic medication (including insulin and OHA) and any other medical therapy not specifically prohibited (e.g., statins, fibric acid derivatives etc.). Participants could receive oral and transdermal opioid medication if it did not exceed a total oral daily dose of morphine of 80 mg or the equivalent, which was to be calculated using the Opioid Dose Worksheet. Any changes, additions or discontinuations to medications were assessed and recorded at every study visit. Cooling measures, such as cool packs, a light wrapping of gauze misted with cool water or a fan were permitted only after patch removal.

Evidence for comparator: -

Actual start date of recruitment	10 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 81
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czech Republic: 100
Country: Number of subjects enrolled	France: 11

Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Russian Federation: 92
Country: Number of subjects enrolled	Ukraine: 111
Worldwide total number of subjects	468
EEA total number of subjects	265

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)	308
From 65 to 84 years	160
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This randomized, controlled, long-term safety study was conducted at 71 centers in a total of 11 countries. If the results of the screening assessments did not reveal any conditions inconsistent with the inclusion and exclusion criteria, the patient qualified for enrollment.

Pre-assignment

Screening details:

After obtaining written informed consent, screening assessments were performed including the collection of demographics,medical history,physical examination,vital signs, electrocardiogram (ECG), pregnancy test,identification and assessment of painful areas, and questions of the Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DN).

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Patients and investigators were not blinded but physicians assessing neurological function were blinded to treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC

Arm description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 30 minutes.The efficacy of a single 30-minute treatment has been demonstrated in patients with HIV-Associated Neuropathy (HIV-AN). The rationale for the 30-minute application time was to keep the mode of administration of the investigational medicinal product (Qutenza) in full accordance with the approved Summary of Product Characteristics(SmPC) for application time to the feet.

Arm type	Experimental
Investigational medicinal product name	Qutenza (Capsaicin (8%) high-concentration patch)
Investigational medicinal product code	A0805/NGX-4010
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical use

Dosage and administration details:

Each patch contained a total of 179 mg capsaicin or 640 µg of capsaicin per 1 cm2 of patch (8% w/w). Up to 4 patches (1120 cm2) could be applied at each application. Qutenza is a topical capsaicin delivery system in the form of a patch which had to be applied to intact, nonirritated dry skin. The patches were applied for 30 minutes (arm 1) or 60 minutes (arm 2) to painful areas.

Arm title	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC

Arm description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 60 minutes. The efficacy of a single 60 minute treatment has been demonstrated in Postherpetic Neuralgia (PHN).The rationale for studying the effects of a 60-minute application time in this study was to cover the contingency that this may ultimately prove to be the optimal application time for efficacy in patients with Painful Diabetic Peripheral Neuropathy (PDPN).

Arm type	Experimental

Investigational medicinal product name	Qutenza (Capsaicin (8%) high-concentration patch)
Investigational medicinal product code	A0805/NGX-4010
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical use

Dosage and administration details:

Each patch contained a total of 179 mg capsaicin or 640 µg of capsaicin per 1 cm^2 of patch (8% w/w). Up to 4 patches (1120 cm^2) could be applied at each application. Qutenza is a topical Capsaicin patch which had to be applied to intact, non-irritated, dry skin. The patches were applied for 30 minutes (arm 1) or 60 minutes (arm 2) to painful areas.

Arm title	SOC (Standard of Care)

Arm description:

Control Group-Standard of Care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Patients and investigators were not blinded but physicians assessing neurological function were blinded to treatment.

Number of subjects in period 1	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)
Started	156	157	155
Completed	132	128	128
Not completed	24	29	27
Protocol deviation	1	3	3
Lack of efficacy	3	1	-
Due to personal problems can't attend study visits	1	1	1
Adverse event, non-fatal	7	8	3
Consent withdrawn by subject	10	15	19
Lost to follow-up	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC

Reporting group description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 30 minutes.The efficacy of a single 30-minute treatment has been demonstrated in patients with HIV-Associated Neuropathy (HIV-AN). The rationale for the 30-minute application time was to keep the mode of administration of the investigational medicinal product (Qutenza) in full accordance with the approved Summary of Product Characteristics(SmPC) for application time to the feet.

Reporting group title	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC

Reporting group description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 60 minutes. The efficacy of a single 60 minute treatment has been demonstrated in Postherpetic Neuralgia (PHN).The rationale for studying the effects of a 60-minute application time in this study was to cover the contingency that this may ultimately prove to be the optimal application time for efficacy in patients with Painful Diabetic Peripheral Neuropathy (PDPN).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Control Group-Standard of Care

Reporting group values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)
Number of subjects	156	157	155
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	98	100	110
From 65-84 years	58	57	45
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	60.9	61	59.1
standard deviation	± 10.88	± 10.3	± 10.32
Gender categorical			
Units: Subjects			
Female	82	78	84
Male	74	79	71
Race			
Units: Subjects			
White	154	155	154
Other	2	2	1
Age group summary by treatment group			

Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	98	100	110
From 65-84 years	58	57	45
85 years and over	0	0	0
Country summary by treatment group Units: Subjects			
Belgium	2	3	2
Czech Republic	32	33	35
France	5	4	2
Germany	16	9	14
Italy	2	2	1
Netherlands	4	6	5
Poland	27	29	25
Russian Federation	29	31	32
Spain	0	0	1
Ukraine	36	39	36
United Kingdom	3	1	2
Duration of PDPN (years) Units: year			
arithmetic mean	4.1	4.4	4.4
standard deviation	± 3.68	± 3.86	± 3.61
HbA1c (mmol/mol) (Screening) Units: (mmol/mol)			
arithmetic mean	56.561	57.497	57.575
standard deviation	± 10.7651	± 10.7887	± 11.3553
Screening BPI-DN Scores, Pain on the Average (Question 5) Units: Number			
arithmetic mean	5.6	5.6	5.7
standard deviation	± 1.27	± 1.4	± 1.3

Reporting group values	Total		
Number of subjects	468		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	308		
From 65-84 years	160		

85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	244		
Male	224		
Race Units: Subjects			
White	463		
Other	5		
Age group summary by treatment group Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	308		
From 65-84 years	160		
85 years and over	0		
Country summary by treatment group Units: Subjects			
Belgium	7		
Czech Republic	100		
France	11		
Germany	39		
Italy	5		
Netherlands	15		
Poland	81		
Russian Federation	92		
Spain	1		
Ukraine	111		
United Kingdom	6		
Duration of PDPN (years) Units: year arithmetic mean standard deviation	- -		
HbA1c (mmol/mol) (Screening) Units: (mmol/mol) arithmetic mean standard deviation	- -		
Screening BPI-DN Scores, Pain on the Average (Question 5) Units: Number			

arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC

Reporting group description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 30 minutes.The efficacy of a single 30-minute treatment has been demonstrated in patients with HIV-Associated Neuropathy (HIV-AN). The rationale for the 30-minute application time was to keep the mode of administration of the investigational medicinal product (Qutenza) in full accordance with the approved Summary of Product Characteristics(SmPC) for application time to the feet.

Reporting group title	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC

Reporting group description:

Qutenza is a high-concentration (8%) capsaicin patch applied for 60 minutes. The efficacy of a single 60 minute treatment has been demonstrated in Postherpetic Neuralgia (PHN).The rationale for studying the effects of a 60-minute application time in this study was to cover the contingency that this may ultimately prove to be the optimal application time for efficacy in patients with Painful Diabetic Peripheral Neuropathy (PDPN).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Control Group-Standard of Care

Primary: Norfolk Quality-of-Life Questionnaire for Diabetic Neuropathy (QOL-DN) from Baseline to End of Study (EOS)(SAF)

End point title	Norfolk Quality-of-Life Questionnaire for Diabetic Neuropathy (QOL-DN) from Baseline to End of Study (EOS)(SAF)

End point description:

The endpoint assessed percentage change from baseline to end of study (EOS) in Norfolk Quality of Life (QOL)-Diabetic Neuropathy (DN) total score. The Norfolk (QOL-DN) is a self-administered questionnaire, designed to capture and quantify the impact of DN on the quality of life of individual participants. In general, items 1 to 7 (Part I) are a simple inventory of neuropathy symptoms. The presence of the symptom is checked and an absence of a symptom is checked under "none." Positive responses are scored as 1 and negative responses as 0. Reduction in score means improvement in QOL. Items 8 to 35 (Part II) pertain to Activities of Daily Life, and most of these are scored on a 5-point Likert scale ranging from 0 ("Not a problem" or "Not at all") to 4 ("Severe problem" or "Severely"). The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Primary

End point timeframe:

Baseline to End of Study (EOS)

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	139	123	
Units: Number of Participants				
arithmetic mean (standard deviation)	-27.6 (± 49.95)	-32.8 (± 53.21)	-6.7 (± 54.12)	

Statistical analyses

Statistical analysis title	Norfolk QOL-DN - Qutenza 30 min versus SOC
Statistical analysis description:	
Pairwise comparison with SOC alone using a one-way ANOVA with treatment group as fixed effect.	
Comparison groups	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC v SOC (Standard of Care)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	LS mean difference
Point estimate	-20.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-31.7
upper limit	-10.1

Notes:

[1] - One way ANOVA analysis was used with Last Observation Carried Forward (LOCF) imputation.

Statistical analysis title	Norfolk QOL-DN - Qutenza 60 min versus SOC
Statistical analysis description:	
Pairwise comparison with SOC alone using a one-way ANOVA with treatment group as fixed effect.	
Comparison groups	SOC (Standard of Care) v Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	LS mean difference
Point estimate	-26.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-36.8
upper limit	-15.4

Notes:

[2] - One way ANOVA analysis was used with Last Observation Carried Forward (LOCF) imputation.

Secondary: Utah Early Neuropathy Scale (UENS) used to detect and quantify early neuropathy and changes in sensory severity (SAF)

End point title	Utah Early Neuropathy Scale (UENS) used to detect and quantify early neuropathy and changes in sensory severity (SAF)

End point description:

The Utah Early Neuropathy Scale (UENS) is a sensitive clinical examination scale which was specifically developed to detect changes or progression in the severity and anatomical distribution of sensory

neuropathy. The UENS places most emphasis on the severity and anatomical distribution of sharp sensation in the lower limbs. A reduction in the UENS score indicates a lack of deterioration in neurological function including no increase in small-fiber sensory loss. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary
End point timeframe:	
Baseline to End of Study (EOS)	

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	153	142	
Units: Number of Participants				
arithmetic mean (standard deviation)	-2.1 (± 5.03)	-3 (± 5.05)	-1.2 (± 4.22)	

Statistical analyses

Statistical analysis title	UENS Qutenza 30 minutes versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in UENS Total Score. Statistical analysis was done with one-way ANOVA and Last Observation Carried Forward (LOCF) imputation.	
Comparison groups	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC v SOC (Standard of Care)
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.8
upper limit	0.1

Statistical analysis title	UENS Qutenza 60 minutes versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in UENS total score. Statistical analysis was done with one-way ANOVA and Last Observation Carried Forward (LOCF) imputation.	
Comparison groups	SOC (Standard of Care) v Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	other

Parameter estimate	LS mean difference
Point estimate	-1.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.7
upper limit	-0.8

Secondary: Tolerability of patch application by dermal assessment (SAF)

End point title	Tolerability of patch application by dermal assessment (SAF)[3]

End point description:

Dermal assessment at patch applications was assessed 15 and 60 minutes after the patch removal and according to categories, Category=0 (No evidence of irritation), Category=1 (Minimal erythema barely perceptive), Category=2(Definite erythema, readily visible; minimal edema or minimal papular response), Category=3 (Erythema and papules), Category=4 (Definite edema), Category=5 (Erythema, edema, and papules), Category=6 (Vesicular eruption), Category=7 (Strong reaction spreading beyond test site) and combined category >= 4 (Definite edema or higher).Dermal assessments were performed on a 0 to 7 point severity scale at screening, and before and after patch application. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)

Notes:

[3] - 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: Data for Standard of Care (SOC) arm was not reported in the Clinical Study Report.

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	157		
Units: Number				
number (not applicable)				
1st before EMLA Category=0[N=156;N=157]	148	149		
1st before EMLA Category=1[N=156;N=157]	7	6		
1st before EMLA Category=2[N=156;N=157]	1	2		
1st before EMLA Category=3[N=156;N=157]	0	0		
1st before EMLA Category=4[N=156;N=157]	0	0		
1st before EMLA Category=5[N=156;N=157]	0	0		
1st before EMLA Category=6[N=156;N=157]	0	0		
1st before EMLA Category=7[N=156;N=157]	0	0		
1st before EMLA CombinedCategory[N=156;N;157]	0	0		

1st 15 min after patch Category=0[N=156;N=157]	106	88		
1st 15 min after patch Category=1 [N=156;N=157]	45	53		
1st 15 min after patch Category=2 [N=156;N=157]	5	13		
1st 15 min after patch Category=3 [N=156;N=157]	0	3		
1st 15 min after patch Category=4 [N=156;N=157]	0	0		
1st 15 min after patch Category=5 [N=156;N=157]	0	0		
1st 15 min after patch Category=6 [N=156;N=157]	0	0		
1st 15 min after patch Category=7 [N=156;N=157]	0	0		
1st15 min after patch CombineCategory[N=156;N=157]	0	0		
1st 60min after patch Category=0[N=156;N=157]	112	95		
1st 60min after patch Category=1[N=156;N=157]	39	47		
1st 60min after patch Category=2[N=156;N=157]	4	14		
1st 60min after patch Category=3[N=156;N=157]	1	1		
1st 60min after patch Category=4[N=156;N=157]	0	0		
1st 60min after patch Category=5[N=156;N=157]	0	0		
1st 60min after patch Category=6[N=156;N=157]	0	0		
1st 60min after patch Category=7[N=156;N=157]	0	0		
1st 60min after patch CombineCategory[N=156;N=157]	0	0		
2nd before EMLA Category=0[N=148;151]	144	145		
2nd before EMLA Category=1[N=148;151]	4	5		
2nd before EMLA Category=2[N=148;151]	0	1		
2nd before EMLA Category=3[N=148;151]	0	0		
2nd before EMLA Category=4[N=148;151]	0	0		
2nd before EMLA Category=5[N=148;151]	0	0		
2nd before EMLA Category=6[N=148;151]	0	0		
2nd before EMLA Category=7[N=148;151]	0	0		
2nd before EMLA CombinedCategory[N=148;151]	0	0		
2nd 15min after patch Category=0[N=149;N=151]	105	88		
2nd 15min after patch Category=1[N=149;N=151]	41	53		
2nd 15min after patch Category=2[N=156;N=157]	3	10		
2nd 15min after patch Category=3[N=149;N=151]	0	0		

2nd 15min after patch Category=4[N=149;N=151]	0	0		
2nd 15min after patch Category=5[N=149;N=151]	0	0		
2nd 15min after patch Category=6[N=149;N=151]	0	0		
2nd 15min after patch Category=7[N=149;N=151]	0	0		
2nd 15min after patch CombineCategory[N=149;N=151]	0	0		
2nd 60min after patch Category=0[N=149;N=151]	114	104		
2nd 60min after patch Category=1[N=149;N=151]	30	38		
2nd 60min after patch Category=2[N=149;N=151]	5	9		
2nd 60min after patch Category=3[N=149;N=151]	0	0		
2nd 60min after patch Category=4[N=149;N=151]	0	0		
2nd 60min after patch Category=5[N=149;N=151]	0	0		
2nd 60min after patch Category=6[N=149;N=151]	0	0		
2nd 60min after patch Category=7[N=149;N=151]	0	0		
2nd 60min after patch CombineCategory[N=149;N=151]	0	0		
3rd before EMLA Category=0[N=144;N=138]	139	136		
3rd before EMLA Category=1[N=144;N=138]	5	2		
3rd before EMLA Category=2[N=144;N=138]	0	0		
3rd before EMLA Category=3[N=144;N=138]	0	0		
3rd before EMLA Category=4[N=144;N=138]	0	0		
3rd before EMLA Category=5[N=144;N=138]	0	0		
3rd before EMLA Category=6[N=144;N=138]	0	0		
3rd before EMLA Category=7[N=144;N=138]	0	0		
3rd before EMLA CombinedCategory[N=144;N=138]	0	0		
3rd 15min after patch Category=0[N=144;N=139]	97	91		
3rd 15min after patch Category=1[N=144;N=139]	45	41		
3rd 15min after patch Category=2[N=144;N=139]	2	7		
3rd 15min after patch Category=3[N=144;N=139]	0	0		
3rd 15min after patch Category=4[N=144;N=139]	0	0		
3rd 15min after patch Category=5[N=144;N=139]	0	0		
3rd 15min after patch Category=6[N=144;N=139]	0	0		
3rd 15min after patch Category=7[N=144;N=139]	0	0		

3rd 15min after patch CombineCategory[N=144;N=139]	0	0		
3rd 60min after patch Category=0[N=144;N=138]	118	101		
3rd 60min after patch Category=1[N=144;N=138]	24	33		
3rd 60min after patch Category=2[N=144;N=138]	2	4		
3rd 60min after patch Category=3[N=144;N=138]	0	0		
3rd 60min after patch Category=4[N=144;N=138]	0	0		
3rd 60min after patch Category=5[N=144;N=138]	0	0		
3rd 60min after patch Category=6[N=144;N=138]	0	0		
3rd 60min after patch Category=7[N=144;N=138]	0	0		
3rd 60min after patch CombineCategory[N=144;N=138]	0	0		
4th before EMLA Category=0[N=129;N=130]	126	127		
4th before EMLA Category=1[N=129;N=130]	3	3		
4th before EMLA Category=2[N=129;N=130]	0	0		
4th before EMLA Category=3[N=129;N=130]	0	0		
4th before EMLA Category=4[N=129;N=130]	0	0		
4th before EMLA Category=5[N=129;N=130]	0	0		
4th before EMLA Category=6[N=129;N=130]	0	0		
4th before EMLA Category=7[N=129;N=130]	0	0		
4th before EMLA CombinedCategory[N=129;N=130]	0	0		
4th 15min after patch Category=0[N=129;N=131]	89	90		
4th 15min after patch Category=1[N=129;N=131]	35	33		
4th 15min after patch Category=2[N=129;N=131]	5	8		
4th 15min after patch Category=3[N=129;N=131]	0	0		
4th 15min after patch Category=4[N=129;N=131]	0	0		
4th 15min after patch Category=5[N=129;N=131]	0	0		
4th 15min after patch Category=6[N=129;N=131]	0	0		
4th 15min after patch Category=7[N=129;N=131]	0	0		
4th 15min after patch CombineCategory[N=129;N=131]	0	0		
4th 60min after patch Category=0[N=129;N=131]	104	99		
4th 60min after patch Category=1[N=129;N=131]	22	25		
4th 60min after patch Category=2[N=129;N=131]	3	7		

4th 60min after patch Category=3[N=129;N=131]	0	0		
4th 60min after patch Category=4[N=129;N=131]	0	0		
4th 60min after patch Category=5[N=129;N=131]	0	0		
4th 60min after patch Category=6[N=129;N=131]	0	0		
4th 60min after patch Category=7[N=129;N=131]	0	0		
4th 60min after patch CombineCategory[N=129;N=131]	0	0		
5th before EMLA Category=0[N=122;N=120]	118	118		
5th before EMLA Category=1[N=122;N=120]	4	2		
5th before EMLA Category=2[N=122;N=120]	0	0		
5th before EMLA Category=3[N=122;N=120]	0	0		
5th before EMLA Category=4[N=122;N=120]	0	0		
5th before EMLA Category=5[N=122;N=120]	0	0		
5th before EMLA Category=6[N=122;N=120]	0	0		
5th before EMLA CombinedCategory[N=122;N=120]	0	0		
5th 15min after patch Category=0[N=122;N=119]	91	81		
5th 15min after patch Category=1[N=122;N=119]	26	32		
5th 15min after patch Category=2[N=122;N=119]	5	6		
5th 15min after patch Category=3[N=122;N=119]	0	0		
5th 15min after patch Category=4[N=122;N=119]	0	0		
5th 15min after patch Category=5[N=122;N=119]	0	0		
5th 15min after patch Category=6[N=122;N=119]	0	0		
5th 15min after patch Category=7[N=122;N=119]	0	0		
5th 15min after patch CombineCategory[N=122;N=119]	0	0		
5th 60min after patch Category=0[N=122;N=120]	102	95		
5th 60min after patch Category=1[N=122;N=120]	17	18		
5th 60min after patch Category=2[N=122;N=120]	3	7		
5th 60min after patch Category=3[N=122;N=120]	0	0		
5th 60min after patch Category=4[N=122;N=120]	0	0		
5th 60min after patch Category=5[N=122;N=120]	0	0		
5th 60min after patch Category=6[N=122;N=120]	0	0		
5th 60min after patch Category=7[N=122;N=120]	0	0		

5th 60min after patch CombineCategory[N=122;N=120]	0	0		
6th before EMLA Category=0[N=108;N=109]	108	107		
6th before EMLA Category=1[N=108;N=109]	0	2		
6th before EMLA Category=2[N=108;N=109]	0	0		
6th before EMLA Category=3[N=108;N=109]	0	0		
6th before EMLA Category=4[N=108;N=109]	0	0		
6th before EMLA Category=5[N=108;N=109]	0	0		
6th before EMLA Category=6[N=108;N=109]	0	0		
6th before EMLA Category=7[N=108;N=109]	0	0		
6th before EMLA CombinedCategory[N=108;N=109]	0	0		
6th 15min after patch Category=0[N=108;N=109]	84	78		
6th 15min after patch Category=1[N=108;N=109]	20	28		
6th 15min after patch Category=2[N=108;N=109]	4	3		
6th 15min after patch Category=3[N=108;N=109]	0	0		
6th 15min after patch Category=4[N=108;N=109]	0	0		
6th 15min after patch Category=5[N=108;N=109]	0	0		
6th 15min after patch Category=6[N=108;N=109]	0	0		
6th 15min after patch Category=7[N=108;N=109]	0	0		
6th 15min after patch CombineCategory[N=108;N=109]	0	0		
6th 60min after patch Category=0[N=108;N=109]	89	86		
6th 60min after patch Category=1[N=108;N=109]	17	20		
6th 60min after patch Category=2[N=108;N=109]	2	3		
6th 60min after patch Category=3[N=108;N=109]	0	0		
6th 60min after patch Category=4[N=108;N=109]	0	0		
6th 60min after patch Category=5[N=108;N=109]	0	0		
6th 60min after patch Category=6[N=108;N=109]	0	0		
6th 60min after patch Category=7[N=108;N=109]	0	0		
6th 60min after patch CombineCategory[N=108;N=109]	0	0		
7th before EMLA Category=0[N=84;N=83]	84	83		
7th before EMLA Category=1[N=84;N=83]	0	0		
7th before EMLA Category=2[N=84;N=83]	0	0		

7th before EMLA Category=3[N=84;N=83]	0	0		
7th before EMLA Category=4[N=84;N=83]	0	0		
7th before EMLA Category=5[N=84;N=83]	0	0		
7th before EMLA Category=6[N=84;N=83]	0	0		
7th before EMLA Category=7[N=84;N=83]	0	0		
7th before EMLA CombinedCategory[N=84;N=83]	0	0		
7th 15min after patch Category=0[N=84;N=82]	66	58		
7th 15min after patch Category=1[N=84;N=82]	15	22		
7th 15min after patch Category=2[N=84;N=82]	3	1		
7th 15min after patch Category=3[N=84;N=82]	0	1		
7th 15min after patch Category=4[N=84;N=82]	0	0		
7th 15min after patch Category=5[N=84;N=82]	0	0		
7th 15min after patch Category=6[N=84;N=82]	0	0		
7th 15min after patch Category=7[N=84;N=82]	0	0		
7th 15min after patch CombinedCategory[N=84;N=82]	0	0		
7th 60min after patch Category=0[N=84;N=83]	68	65		
7th 60min after patch Category=1[N=84;N=83]	14	15		
7th 60min after patch Category=2[N=84;N=83]	2	3		
7th 60min after patch Category=3[N=84;N=83]	0	0		
7th 60min after patch Category=4[N=84;N=83]	0	0		
7th 60min after patch Category=5[N=84;N=83]	0	0		
7th 60min after patch Category=6[N=84;N=83]	0	0		
7th 60min after patch Category=7[N=84;N=83]	0	0		
7th 60min after patch CombinedCategory[N=84;N=83]	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of patch application by "pain now" Numeric Pain Rating Scale (NPRS) scores after patch application (SAF)

End point title	Tolerability of patch application by "pain now" Numeric Pain Rating Scale (NPRS) scores after patch application (SAF)[4]

End point description:

The "pain now" NPRS uses a 0 to 10 scale to rate discomfort associated with patch application. The "pain now" endpoint of interest was the absolute value of the score within 15 minutes and 60 minutes after patch removal. Results are represented as mean values scores. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (15 and 60 minutes after patch removal)

Notes:

[4] - 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: Data for Standard of Care (SOC) arm was not reported in the Clinical Study Report.

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	157		
Units: Number of Participants				
arithmetic mean (standard deviation)				
15 minutes after patch removal	2.6 (± 1.93)	2.7 (± 2.03)		
60 minutes after patch removal	2.5 (± 1.99)	2.4 (± 1.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of patch application by rescue medication (SAF)

End point title	Tolerability of patch application by rescue medication (SAF)

End point description:

Rescue medication was used for pain associated with patch application and it was used on Days 1 to 5 after patch application only.

End point type	Secondary

End point timeframe:

Days 1 through 5 after each patch application

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: Number of Participants				
number (not applicable)				
Analgesics	25	39	0	
Antiepileptics	1	0	0	

Antihistamines for systemic use	1	0	0	
Antiinflammatory and antirheumatic products	13	17	0	
Antipruritics,inc antihistamines,anesthetics etc	1	0	0	
Antithrombic agents	1	1	0	
Cardiac Therapy	6	7	0	
Cough and Cold Preparations	0	1	0	
Drugs for functional gastrointestinal disorders	0	1	0	
Muscle Relaxants	0	1	0	
Nasal Preparations	0	1	0	
Ophthalmologicals	4	5	0	
Other dermatological preparations	4	5	0	
Other gynecologicals	6	7	0	
Preparations for treatment of wounds and ulcers	0	1	0	
Psychoanaleptics	1	0	0	
Psycholeptics	1	1	0	
Stomatological Preparations	7	8	0	
Topical Products for joint and muscular pain	14	17	0	
Vitamins	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs Associated with Patch Applications (heart rate and blood pressure) Absolute Value (SAF)

End point title	Vital Signs Associated with Patch Applications (heart rate and blood pressure) Absolute Value (SAF)[5]

End point description:

The End of Study (EOS) visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Screening to End of Study (EOS)

Notes:

[5] - 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: Data for Standard of Care (SOC) arm was not reported in the Clinical Study Report.

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	157		
Units: Number of Participants				
arithmetic mean (standard deviation)				

Screening	136.1 (± 14.79)	136.1 (± 15.13)		
Before 1st Application	133.7 (± 14.92)	135.5 (± 12.87)		
After 1st Application	134.7 (± 16.49)	137.7 (± 16.05)		
Before 2nd Application	131.7 (± 12.32)	132.9 (± 12.34)		
After 2nd Application	133.5 (± 12.1)	135.9 (± 13.63)		
Before 3rd Application	132.5 (± 11.59)	131.6 (± 11.4)		
After 3rd Application	134 (± 13.7)	135.1 (± 12.91)		
Before 4th Application	131.6 (± 12.95)	131.9 (± 12.69)		
After 4th Application	133.1 (± 13.73)	135.9 (± 15.09)		
Before 5th Application	131.1 (± 11.22)	134.6 (± 12.03)		
After 5th Application	132.2 (± 12.69)	136.5 (± 12.87)		
Before 6th Application	130.8 (± 10.85)	134.7 (± 12.53)		
After 6th Application	133.8 (± 12.4)	136.2 (± 13.62)		
Before 7th Application	130.4 (± 11.64)	132 (± 12.4)		
After 7th Application	131.9 (± 12.19)	135 (± 12.75)		
Before Last Application	131.7 (± 13.05)	132.4 (± 13.31)		
After Last Application	132.9 (± 14.11)	135.1 (± 14.11)		
Before Subject Mean (all Applications)	132.5 (± 10.3)	133.7 (± 10.13)		
After Subject Mean (all Applications)	133.9 (± 11.55)	136.3 (± 11.68)		
EOT- End of Treatment	132.5 (± 10.96)	133.8 (± 12.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Laboratory Assessments (assessments of HbA1c and lipids profiles) Change from Baseline (SAF)

End point title	Clinical Laboratory Assessments (assessments of HbA1c and lipids profiles) Change from Baseline (SAF)

End point description:

Laboratory assessments of HbA1c (mmol/mol) and lipids profiles [total cholesterol (mmol/L), low-density lipoprotein [LDL]-cholesterol (mmol/L), high-density lipoprotein [HDL]-cholesterol (mmol/L) and triglycerides (mmol/L)] were collected at screening and bimonthly visits. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: mmol				
arithmetic mean (standard deviation)				
HbA1c Month 2 [N=141;N=146;N=136]	1.003 (± 7.4575)	0.908 (± 8.5429)	1.15 (± 10.0739)	
HbA1c Month 4 [N=137;N=138;N=137]	1.711 (± 12.3447)	1.178 (± 10.5664)	1.463 (± 10.4435)	
HbA1c Month 6 [N=128;N=131;N=127]	1.839 (± 10.8738)	1.026 (± 11.1515)	2.143 (± 10.8025)	
HbA1c Month 8 [N=122;N=130;N=125]	1.502 (± 11.6611)	1.406 (± 11.2172)	3.148 (± 11.3131)	
HbA1c Month 10 [N=124;N=122;N=124]	0.58 (± 10.4266)	0.868 (± 11.1243)	2.453 (± 11.7181)	
HbA1c Month 12 [N=122;N=122;N=116]	0.552 (± 10.9702)	0.733 (± 10.685)	3.602 (± 9.9211)	
HbA1c EOT (LOCF) [N=144;N=149;N=141]	0.665 (± 9.8461)	0.625 (± 10.5329)	2.575 (± 10.2414)	
Cholesterol Month 2 [N=134;N=139;N=132]	0.043 (± 1.0555)	0.075 (± 1.1545)	-0.069 (± 0.8523)	
Cholesterol Month 4 [N=136;N=140;N=135]	-0.006 (± 0.9418)	0.072 (± 1.0549)	0.019 (± 1.054)	
Cholesterol Month 6 [N=129;N=133;N=129]	-0.037 (± 1.0284)	-0.036 (± 1.1769)	0.026 (± 0.8913)	
Cholesterol Month 8 [N=123;N=130;N=125]	-0.081 (± 1.0322)	0.113 (± 1.1901)	0.048 (± 1.0848)	
Cholesterol Month 10 [N=125;N=122;N=124]	0.05 (± 1.2105)	0.092 (± 1.2344)	-0.059 (± 1.1542)	
Cholesterol Month 12 [N=122;N=122;N=118]	-0.087 (± 1.0267)	0.274 (± 1.3192)	0.021 (± 1.0095)	
Cholesterol EOT(LOCF) [N=143;N=147;N=142]	-0.104 (± 0.9949)	0.113 (± 1.0187)	0.042 (± 1.0075)	
HDL Cholesterol Month 2[N=133;N=138 N=132]	-0.02 (± 0.2808)	0.025 (± 0.3577)	-0.008 (± 0.3142)	
HDL Cholesterol Month 4[N=136;N=139; N=135]	-0.058 (± 0.4536)	-0.017 (± 0.3606)	-0.002 (± 0.3205)	
HDL Cholesterol Month 6[N=129;N=132; N=130]	-0.037 (± 0.464)	-0.007 (± 0.3921)	-0.008 (± 0.4564)	
HDL Cholesterol Month 8[N=123;N=128; N=124]	-0.013 (± 0.5047)	0.016 (± 0.3474)	0.015 (± 0.3655)	
HDL Cholesterol Month 10[N=125;N=120; N=122]	-0.001 (± 0.4641)	0.005 (± 0.3331)	0.005 (± 0.3242)	
HDL Cholesterol Month 12[N=122;N=121; N=118]	-0.078 (± 0.4306)	0.028 (± 0.2922)	0.028 (± 0.3943)	
HDL Cholesterol EOT(LOCF)[N=143;N=146;N=142]	-0.077 (± 0.3858)	0.094 (± 1.1099)	0.018 (± 0.3873)	
LDL Cholesterol Month 2[N=131;N=136;N=130]	-0.039 (± 0.9793)	-0.079 (± 0.9017)	-0.008 (± 0.8726)	
LDL Cholesterol Month 4[N=133;N=137;N=133]	-0.014 (± 0.8795)	-0.001 (± 0.9254)	-0.082 (± 0.8474)	

LDL Cholesterol Month 6[N=127;N=131;N=129]	-0.131 (± 1.0019)	-0.116 (± 0.9709)	-0.006 (± 0.9436)	
LDL Cholesterol Month 8[N=119;N=127;N=123]	-0.179 (± 1.1248)	-0.04 (± 1.0938)	-0.018 (± 0.9809)	
LDL Cholesterol Month 10[N=124;N=118;N=121]	-0.018 (± 1.1264)	-0.016 (± 0.9429)	-0.006 (± 1.065)	
LDL Cholesterol Month 12[N=120;N=120;N=117]	-0.176 (± 0.9779)	0.05 (± 1.0922)	0.03 (± 0.9678)	
LDL Cholesterol EOT(LOCF) [N=141;N=144;N=141]	-0.117 (± 0.9599)	0.008 (± 0.9434)	0.022 (± 0.937)	
Triglycerides Month 2[N=134;N=139;N=133]	0.068 (± 1.5088)	0.121 (± 1.5031)	-0.057 (± 1.0087)	
Triglycerides Month 4[N=134;N=140;N=136]	-0.071 (± 1.5373)	0.033 (± 1.1793)	0.089 (± 1.0323)	
Triglycerides Month 6[N=129;N=133;N=130]	-0.022 (± 1.6021)	-0.066 (± 1.1939)	0.128 (± 1.0188)	
Triglycerides Month 8[N=123;N=130;N=126]	-0.173 (± 1.4995)	0.021 (± 1.3225)	0.104 (± 1.1094)	
Triglycerides Month 10[N=125;N=122;N=124]	-0.123 (± 1.4794)	0.113 (± 1.8644)	-0.13 (± 1.0656)	
Triglycerides Month 12[N=122;N=122;N=118]	-0.027 (± 1.572)	0.219 (± 2.2574)	-0.033 (± 1.0027)	
Triglycerides EOT(LOCF) [N=143;N=147;N=142]	0.035 (± 1.498)	-0.042 (± 1.4191)	0.072 (± 0.9336)	

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory -Diabetic Peripheral Neuropathy Question 5 Mean Change from Baseline (Average Pain) (SAF)

End point title	Brief Pain Inventory -Diabetic Peripheral Neuropathy Question 5 Mean Change from Baseline (Average Pain) (SAF)

End point description:

The BPI is a widely used and validated, patient completed, numeric rating scale (NRS) that measures severity of pain and its interference with daily function. A major benefit of the BPI is its numeric rating scale format, which has been recommended for research on neuropathic pain. The BPI-DN is a modified version of the BPI that has been developed specifically for use in patients with PDPN and includes the 4-item pain Severity scale(Worst Pain, Least Pain, Average Pain, and Pain Now)and the 7-item pain Interference scale (General Activity,Mood, Walking Ability, Normal Work, Relations With Others, Sleep, Enjoyment of Life).The Pain Severity Index is obtained by taking the average of the 4 Pain Severity items and the Pain Interference Index is obtained by taking the average of the 7 Interference Items. Last observation carried forward (LOCF)was imputed and Safety Analysis Set (SAF) was used for analysis. The EOS visit for 30 &60 min was between 8 & 12 weeks after patch and SOC 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	155	148	
Units: Number of participants				
arithmetic mean (standard deviation)	-2 (± 1.82)	-2.3 (± 2.11)	-1.1 (± 2.01)	

Statistical analyses

Statistical analysis title	BPI-Mean change Q5 Qutenza 30 min versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in average pain based on the Brief Pain Inventory question 5.	
Comparison groups	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC v SOC (Standard of Care)
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.4
upper limit	-0.6

Statistical analysis title	BPI-Mean change Q5 Qutenza 60 min versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in average pain based on the Brief Pain Inventory question 5.	
Comparison groups	SOC (Standard of Care) v Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	-0.9

Secondary: Brief Pain Inventory-Diabetic Neuropathy (Pain Severity Index) (SAF)	
End point title	Brief Pain Inventory-Diabetic Neuropathy (Pain Severity Index) (SAF)

End point description:

Data presented represents mean change from Baseline to EOS in Pain Severity Index (Safety Analysis Set). The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	155	148	
Units: Number of participants				
arithmetic mean (standard deviation)	-1.9 (± 1.8)	-2.2 (± 1.89)	-0.9 (± 1.71)	

Statistical analyses

Statistical analysis title	BPI-Pain Severity Qutenza 30 min versus SOC

Statistical analysis description:

Mean change from baseline to End of Study (EOS) in Pain Severity Index.

Comparison groups	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC v SOC (Standard of Care)
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.3
upper limit	-0.6

Statistical analysis title	BPI-Pain Severity Qutenza 60 min versus SOC

Statistical analysis description:

Mean change from baseline to End of Study (EOS) in Pain Severity Index.

Comparison groups	SOC (Standard of Care) v Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC
Number of subjects included in analysis	303

Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	-0.9

Secondary: Patient Global Impression of Change (SAF)

End point title	Patient Global Impression of Change (SAF)

End point description:

The PGIC is a patient-rated instrument that measures change in patients' overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Counts by combined categories [Very Much + Much Improved][Very Much + Much + Minimally Improved] and [No change + Minimally Worse + Much Worse] are reported for this endpoint. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS).

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	155	148	
Units: number of participants				
number (not applicable)				
Very much improved + much improved	37	38	14	
Very much impr + much impr +min improved	103	110	57	
No change + min worse+much worse+very much worse	50	45	91	

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D (European Quality of Life Questionnaire in 5 Dimensions) Questionnaire Change from Baseline (SAF)

End point title	EQ-5D (European Quality of Life Questionnaire in 5 Dimensions) Questionnaire Change from Baseline (SAF)

End point description:

The EQ-5D is used to assess patients health-related quality of life (HRQoL). The EQ-5D self-reported questionnaire includes a visual analog scale (VAS), which records the patient's self-rated health status on a graduated (0 to 100) scale, with higher scores for higher HRQoL. It also includes the EQ-5D descriptive system, which comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: Number of participants				
arithmetic mean (standard deviation)				
Month 2 [N=145;N=149;N=141]	2.7 (± 15.5)	2 (± 17.57)	3 (± 17.58)	
Month 4 [N=137;N=135;N=136]	5.5 (± 16.75)	5.8 (± 17.32)	2.9 (± 18.6)	
Month 6 [N=130;N=133;N=130]	7.2 (± 16.92)	8.4 (± 18.39)	3.7 (± 17.62)	
Month 8 [N=125;N=130;N=125]	11.1 (± 18.95)	10.2 (± 19.12)	3.6 (± 17.95)	
Month 10 [N=125;N=121;N=127]	8.3 (± 19.24)	12.3 (± 18.51)	4.9 (± 16.78)	
Month 12 [N=121;N=120;N=122]	10.5 (± 17.34)	12.2 (± 20.11)	6.2 (± 19.23)	
Month 13 [N=26;N=27;N=81]	9.3 (± 21.89)	9.2 (± 17.02)	5.6 (± 16.76)	
Month 14 [N=87;N=83;N=5]	12.8 (± 17.05)	14.3 (± 21.02)	-5.4 (± 12.78)	
Month 15 [N=14;N=13;N=0]	10.6 (± 20.09)	2.8 (± 22.73)	0 (± 0)	
EOT (LOCF)[N=149;N=151;N=145]	10.4 (± 18.52)	11.2 (± 21.42)	5.5 (± 18.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment satisfaction using the Self-Assessment of Treatment (SAT) questionnaire (SAF)

End point title	Treatment satisfaction using the Self-Assessment of Treatment (SAT) questionnaire (SAF)

End point description:

The Self-Assessment of Treatment (SAT) assessed treatment satisfaction by using a 5-point Likert-type scale ranging from -2 (a strong negative response) to 2 (a strong positive response) and zero indicating a neutral response. The questionnaire contains each of the following questions, How do you assess your pain level after treatment in this study?How do you assess your activity level after treatment in this study? How has your quality of life changed after treatment in this study?; Would you undergo this treatment again?; How do you compare the treatment you received in this study to previous medication or therapies for your pain?. The SAT variables of interest were counts by category, counts by combined categories (Worse: (-2) + (-1), Not Better or Worse: (-2) + (-1) + (0), Better: (1) + (2). The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary
End point timeframe:	
Baseline to End of Study (EOS)	

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: Number of participants				
number (not applicable)				
Pain level better[N=145;N=144;N=139]	94	103	45	
Pain level worse[N=145;N=144;N=139]	13	10	26	
Activity level better[N=145;N=144;N=139]	73	78	31	
Activity level worse[N=145;N=144;N=139]	18	12	16	
Quality of life better[N=145;N=144;N=139]	78	93	44	
Quality of life worse[N=145;N=144;N=139]	12	8	21	

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Concomitant Medications (SAF)

End point title	Use of Concomitant Medications (SAF)

End point description:

Use of medications of interest at baseline and at the end of the treatment. The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary
End point timeframe:	
Baseline and End of Study (EOS)	

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: Number of participants				
number (not applicable)				
Baseline Antidepressants[N=156 N=157 N=155]	17	8	12	
Baseline Antiepileptic drugs [N=156 N=157 N=155]	44	49	50	
Baseline Opioids[N=156 N=157 N=155]	17	9	13	
EOT Antidepressants[N=146 N=147 N=146]	16	10	22	
EOT Antiepileptic drugs[N=146 N=147 N=146]	43	53	63	
EOT Opioids[N=146 N=147 N=146]	16	12	17	

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Pain Inventory Diabetic Neuropathy (Pain Interference)(SAF)

End point title	Brief Pain Inventory Diabetic Neuropathy (Pain Interference)(SAF)

End point description:

Data represents mean change from Baseline to End of Treatment in Pain Interference (Safety Analysis Set). The EOS visit for Qutenza 30 min (arm I) & 60 min (arm II) took place between 8 and 12 weeks after last patch application and for SOC (arm III) between week 52-56.

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	154	148	
Units: Number of participants				
arithmetic mean (standard deviation)	-1.9 (± 2.09)	-2 (± 2.28)	-0.8 (± 1.85)	

Statistical analyses

Statistical analysis title	BPI-Pain Interference Qutenza (30 min) versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in Pain Interference.	
Comparison groups	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC v SOC (Standard of Care)
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.4
upper limit	-0.6

Statistical analysis title	BPI-Pain Interference Qutenza (60 min) versus SOC
Statistical analysis description:	
Mean change from baseline to End of Study (EOS) in Pain Interference.	
Comparison groups	SOC (Standard of Care) v Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	-0.8

Secondary: Average Sensory Testing Score per Modality (SAF)

End point title	Average Sensory Testing Score per Modality (SAF)

End point description:

Sensory testing involved ratings of evoked sensations and pain by recording reduced or increased stimulus perception. It involved the assessment of 5 modalities: vibration, heat, cold and sharp sensations and the assessment of deep tendon reflexes. The left and right sides were assessed separately as; [Vibration sensation: not felt (= 0), < 6 sec (= 1), 6 to 10 sec (= 2), > 10 sec (= 3, normal)] [Reflexes: no response (= 0), hypoactive (= 1), normal (= 2),hyperactive (= 3), clonus (= 4)],[Heat at each of ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus: not warm (= 0), slightly warm (= 1), warm or hot (= 2, normal), painfully hot (= 3)], [Cold at each of ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus: not cold (= 0), slightly cold (= 1), cold (= 2, normal), painfully cold (= 3)] [Sharp at each ball of foot, mid-plantar, dorsal first toe, dorsal foot, medial malleolus not felt(=0),dull(=1),sharp (= 2, normal), painfully sharp (= 3)]

End point type	Secondary

End point timeframe:

Baseline to End of Study (EOS)[EOS defined for arms Qutenza 30 min & 60 min between 8 and 12 weeks after last patch application and SOC between week 52-56]

End point values	Qutenza (Capsaicin (8%) high-concentration patch) 30 min & SOC	Qutenza (Capsaicin (8%) high-concentration patch) 60 min & SOC	SOC (Standard of Care)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	157	155	
Units: Number				
arithmetic mean (standard deviation)				
Baseline Vibration [N=153;148;150]	0.9 (± 0.79)	0.9 (± 0.75)	1 (± 0.71)	
Month 2 Vibration [N=150;153;145]	0.9 (± 0.79)	0.9 (± 0.76)	1 (± 0.75)	
Month 4 Vibration [N=141;142;140]	1 (± 0.86)	1.1 (± 0.83)	1 (± 0.78)	
Month 6 Vibration [N=132;135;133]	1 (± 0.78)	1.1 (± 0.8)	1 (± 0.75)	
Month 8 Vibration [N=128;133;127]	1.1 (± 0.78)	1.2 (± 0.85)	1.1 (± 0.68)	
Month 10 Vibration [N=128;125;129]	1.1 (± 0.8)	1.1 (± 0.8)	1.1 (± 0.74)	
Month 12 Vibration [N=126;124;126]	1.2 (± 0.79)	1.2 (± 0.8)	1.1 (± 0.74)	
Month 13 Vibration [N=26;29;82]	1 (± 0.87)	1.2 (± 0.82)	1.1 (± 0.75)	
Month 14 Vibration [N=90;84;5]	1.1 (± 0.75)	1.1 (± 0.86)	1 (± 0.71)	
Month 15 Vibration [N=14;13;0]	1.4 (± 0.77)	1.3 (± 0.83)	0 (± 0)	
EOT(LOCF) Vibration[N=153;155;147]	1 (± 0.79)	1.1 (± 0.81)	1.1 (± 0.78)	
Baseline Reflexes [N=153;148;150]	0.5 (± 0.66)	0.6 (± 0.72)	0.6 (± 0.64)	
Month 2 Reflexes [N=150;153;145]	0.5 (± 0.65)	0.5 (± 0.69)	0.6 (± 0.7)	
Month 4 Reflexes [N=141;142;140]	0.5 (± 0.62)	0.5 (± 0.68)	0.5 (± 0.62)	
Month 6 Reflexes [N=132;135;133]	0.5 (± 0.63)	0.6 (± 0.71)	0.5 (± 0.63)	
Month 8 Reflexes [N=128;133;127]	0.5 (± 0.63)	0.6 (± 0.68)	0.5 (± 0.64)	
Month 10 Reflexes [N=128;125;129]	0.6 (± 0.69)	0.6 (± 0.73)	0.6 (± 0.65)	
Month 12 Reflexes [N=126;124;126]	0.6 (± 0.74)	0.6 (± 0.7)	0.6 (± 0.69)	
Month 13 Reflexes [N=26;29;82]	0.7 (± 0.75)	0.7 (± 0.68)	0.8 (± 0.69)	
Month 14 Reflexes [N=90;84;5]	0.5 (± 0.64)	0.5 (± 0.67)	0.4 (± 0.55)	
Month 15 Reflexes [N=14;13;0]	0.9 (± 0.95)	0.7 (± 0.67)	0 (± 0)	
EOT(LOCF) Reflexes[N=153;155;147]	0.6 (± 0.72)	0.6 (± 0.7)	0.6 (± 0.69)	
Baseline Heat[N=153;148;150]	0.8 (± 0.56)	0.8 (± 0.51)	0.8 (± 0.52)	
Month 2 Heat[N=150;153;145]	0.8 (± 0.52)	0.9 (± 0.54)	0.8 (± 0.55)	
Month 4 Heat[N=141;142;140]	0.9 (± 0.53)	1 (± 0.54)	0.8 (± 0.5)	
Month 6 Heat[N=132;135;133]	0.9 (± 0.54)	1 (± 0.55)	0.9 (± 0.52)	
Month 8 Heat[N=128;133;127]	0.9 (± 0.55)	1.1 (± 0.54)	0.9 (± 0.56)	
Month 10 Heat[N=128;125;129]	1 (± 0.56)	1.1 (± 0.58)	0.9 (± 0.56)	
Month 12 Heat[N=126;124;126]	1 (± 0.6)	1.2 (± 0.57)	1 (± 0.58)	
Month 13 Heat[N=26;29;82]	1.2 (± 0.72)	1.2 (± 0.59)	1 (± 0.57)	
Month 14 Heat[N=90;84;5]	1 (± 0.57)	1.2 (± 0.62)	1.2 (± 0.69)	
Month 15 Heat[N=14;13;0]	1.2 (± 0.58)	1 (± 0.52)	0 (± 0)	
EOT (LOCF) Heat[N=153;155;147]	1 (± 0.62)	1.1 (± 0.59)	0.9 (± 0.59)	
Baseline Cold[N=153;148;150]	1 (± 0.58)	1.1 (± 0.59)	1.1 (± 0.61)	
Month 2 Cold [N=150;153;145]	1.1 (± 0.57)	1.2 (± 0.55)	1.1 (± 0.59)	
Month 4 Cold [N=141;142;140]	1.1 (± 0.56)	1.2 (± 0.61)	1.1 (± 0.57)	
Month 6 Cold [N=132;135;133]	1.2 (± 0.56)	1.2 (± 0.56)	1.2 (± 0.57)	
Month 8 Cold [N=128;133;127]	1.2 (± 0.57)	1.2 (± 0.58)	1.2 (± 0.56)	
Month 10 Cold [N=128;125;129]	1.2 (± 0.58)	1.4 (± 0.59)	1.2 (± 0.57)	

Month 12 Cold [N=126;124;126]	1.2 (± 0.62)	1.3 (± 0.58)	1.2 (± 0.57)	
Month 13 Cold [N=26;29;82]	1.2 (± 0.72)	1.4 (± 0.6)	1.2 (± 0.58)	
Month 14 Cold [N=90;84;5]	1.2 (± 0.59)	1.4 (± 0.62)	1.2 (± 0.69)	
Month 15 Cold [N=14;13;0]	1.6 (± 0.66)	1.4 (± 0.46)	0 (± 0)	
EOT(LOCF) [N=153;155;147]	1.2 (± 0.63)	1.3 (± 0.58)	1.1 (± 0.61)	
Baseline Sharp [N=153;148;150]	1 (± 0.59)	1 (± 0.58)	1.1 (± 0.55)	
Month 2 Sharp [N=150;153;145]	1 (± 0.54)	1.1 (± 0.54)	1.1 (± 0.53)	
Month 4 Sharp [N=141;142;139]	1.1 (± 0.57)	1.2 (± 0.56)	1.1 (± 0.54)	
Month 6 Sharp [N=132;135;133]	1.1 (± 0.53)	1.2 (± 0.54)	1.2 (± 0.51)	
Month 8 Sharp [N=128;133;127]	1.1 (± 0.56)	1.2 (± 0.54)	1.2 (± 0.51)	
Month 10 Sharp [N=128;125;129]	1.2 (± 0.51)	1.3 (± 0.53)	1.2 (± 0.51)	
Month 12 Sharp [N=126;124;126]	1.2 (± 0.58)	1.3 (± 0.56)	1.1 (± 0.55)	
Month 13 Sharp [N=26;29;82]	1.2 (± 0.73)	1.3 (± 0.5)	1.3 (± 0.55)	
Month 14 Sharp [N=90;84;5]	1.2 (± 0.58)	1.3 (± 0.61)	1.2 (± 0.32)	
Month 15 Sharp [N=14;13;0]	1.4 (± 0.61)	1.3 (± 0.56)	0 (± 0)	
EOT(LOCF) Sharp [N=153;155;147]	1.2 (± 0.61)	1.2 (± 0.6)	1.2 (± 0.54)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to End of Treatment (EOT).

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was an AE observed after starting administration of the test drug thus, there were no TEAEs in the SOC alone arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Qutenza (30 min) + SOC

Reporting group description: -

Reporting group title	Qutenza (60 min) + SOC

Reporting group description: -

Serious adverse events	Qutenza (30 min) + SOC	Qutenza (60 min) + SOC	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 156 (12.82%)	13 / 157 (8.28%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			

subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (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			
Ankle fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 156 (1.28%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery diseases			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic coma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hypotension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyopathy			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 156 (1.28%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 156 (1.92%)	0 / 157 (0.00%)	
occurrences causally related to treatment / all	0 / 5	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	Qutenza (30 min) + SOC	Qutenza (60 min) + SOC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 156 (49.36%)	84 / 157 (53.50%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 156 (1.92%)	10 / 157 (6.37%)	
occurrences (all)	3	11	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	8 / 156 (5.13%)	3 / 157 (1.91%)	
occurrences (all)	9	3	
Glycosylated haemoglobin increased			
subjects affected / exposed	9 / 156 (5.77%)	5 / 157 (3.18%)	
occurrences (all)	9	8	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	15 / 156 (9.62%)	15 / 157 (9.55%)	
occurrences (all)	22	39	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	12 / 156 (7.69%)	14 / 157 (8.92%)	
occurrences (all)	32	36	
Application site pain			
subjects affected / exposed	44 / 156 (28.21%)	46 / 157 (29.30%)	
occurrences (all)	129	122	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 156 (5.13%)	5 / 157 (3.18%)	
occurrences (all)	10	5	
Pain in extremity			
subjects affected / exposed	8 / 156 (5.13%)	14 / 157 (8.92%)	
occurrences (all)	18	31	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 156 (0.00%)	8 / 157 (5.10%)	
occurrences (all)	0	9	
Nasopharyngitis			
subjects affected / exposed	4 / 156 (2.56%)	9 / 157 (5.73%)	
occurrences (all)	6	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2011	The original study protocol dated 11 April 2011 was amended (prior to study enrolment) via substantial amendment 1 on 11 July 2011. Amendment 1 included removal of an exclusion criterion for diabetic retinopathy (exclusion criterion 6), an amendment to exclusion criterion 2 to provide a more precise definition of onychomycosis and to clarify that questionnaires were to be completed on paper.
17 April 2013	Amendment 3 dated 17 April 2013 described comprehensive foot examinations which should have been conducted at every scheduled visit, to identify high risk foot conditions. In this amendment previously mandatory comprehensive diabetes foot exam was made optional.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported