A Randomized, Controlled, Long-term Safety Study Evaluating the Effect of Repeated Applications of QUTENZA plus Standard of Care versus Standard of Care alone in Subjects with Painful Diabetic Peripheral Neuropathy

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Primary objective:To assess the safety of repeat applications of QUTENZA administered over a period of 12 months in subjects with PDPN.Secondary objectives:To assess the efficacy of repeat applications of QUTENZA administered over a period of 12...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON39911

Source
ToetsingOnline

Brief title
PACE

Condition

- Diabetic complications
- Glucose metabolism disorders (incl diabetes mellitus)
- Peripheral neuropathies

Synonym
Painful diabetic peripheral neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma
Source(s) of monetary or material Support: Astellas Pharma

Intervention

Keyword: Painful Diabetic Peripheral Neuropathy, Randomized, Repeated Applications of QUTENZA

Outcome measures

Primary outcome

To assess the safety of repeat applications of QUTENZA administered over a

period of 12 months in subjects with PDPN.

Secondary outcome

To assess the efficacy of repeat applications of QUTENZA administered over a

period of 12 months in subjects with PDPN

Study description

Background summary

Background (p27 of the protocol)
Neuropathy is one of the most common long-term complications of diabetes mellitus (DM) and successful treatment offers a challenging task. About 60% of diabetic patients have some form of peripheral neuropathy, with the highest prevalence among people who have had the disease for longer durations. Diabetic neuropathy is relatively more common in older patients and patients with sub-optimal glycemic control [Spruce et al, 2002]. Approximately 20%- 24% of patients experience onset of insidious pain (or dysesthesias) and present with varying degrees of numbness, tingling, burning pain, loss of sensations or strange sensations (paresthesias), and loss of balance or coordination. Of the 60% of diabetic patients who develop neuropathy, about 30%-40% present with no symptoms. Painful diabetic peripheral neuropathy (PDPN) results from damage to the sensory nerves due to metabolic insult of high circulating levels of

glucose and glucose metabolites, as well as inadequate oxygenation of peripheral areas due to neuro-vascular damage. As the sensory nerves get affected, there is a gradual loss of cutaneous innervation [Kennedy et al, 1996]. The surviving cutaneous nociceptors provide a constant afferent barrage which, at least in part, drives the pain syndrome [Michaelis, 2002]. Attempts to treat PDPN can be divided into those directed at modification of the underlying disease process and those directed toward symptom suppression [Backonja, 1998]. Management relies mainly on the pharmacological treatment of overt symptoms, namely severe pain [Spruce et al, 2002]. No consensus on the optimal management of neuropathic pain exists and consequently the treatment of neuropathic pain is largely empirical and diverse, relying primarily on antidepressants (duloxetine, tricyclics, MAOI), anticonvulsants (gabapentin, carbamazepine, phenytoin, lamotrigine, topiramate, pregabalin), and narcotic analgesics (tramadol, codeine, oxycodone, methadone) [Koltzenburg, 1999]. The only currently approved by the European Medicines Agency (EMEA) and Food and Drug Administration (FDA) drugs for treatment of PDPN are Lyrica® (pregabalin) [Pfizer,Inc.; NY, NY] and Cymbalta® (duloxetine hydrochloride) [Eli Lilly and Company, Inc.; Indianapolis, IN]. Other pharmacological therapies attempted include N-methyl-D-Aspartate (NMDA) antagonists (dextromethorphan) and antiarrhythmics (lignocaine, mexiletine); while non pharmacological approaches have included nerve stimulating therapies (Transcutaneous Electrical Nerve Stimulation [TENS], Percutaneous Electrical Nerve Stimulation [PENS], electrical spinal cord stimulation, acupuncture) and invasive therapies (nerve blocks, ablative surgery) [Spruce et al, 2002]. However, the use of many of these treatments is often limited by poor tolerability, the need for titration, drug-drug interactions and administration of multiple daily doses or invasive nature of the procedure. In addition, many patients continue to experience significant pain while taking these treatments [Baron et al, 2006; Sindrup et al, 1999]. It is believed that exaggerated activity of capsaicin-sensitive nerve fibers is involved in mediating the pain of peripheral neuropathies. Capsaicin, or 6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl, (6E), the pungent ingredient in chili peppers, is a highly selective activating ligand for transient receptor potential vanilloid 1 (TRPV1), which is a ligand-gated non-selective cation channel highly expressed in small diameter primary afferent neurons (C-fibers and Aδ-fibers), especially those nerve fibers that specialize in the detection of painful or noxious sensations [Caterina et al, 1997; Szallasi et al, 1999; Tominaga et al, 1998]. Activation of this receptor by capsaicin results in a burning sensation, hyperalgesia, allodynia, and erythema. The erythema produced by capsaicin originates from the release of vasoactive neuropeptides from small-diameter sensory axons. This phenomenon is termed *neurogenic inflammation* [Szallasi et al, 1999]. After prolonged exposure to capsaicin, the small diameter sensory axons become less sensitive to a variety of stimuli, including
capsaicin itself or thermal stimuli, resulting in a reduced pain response [Caterina et al, 1997]. These later stage effects of capsaicin are frequently referred to as *defunctionalization* and serve as the rationale for the development of capsaicin formulations for the treatment of neuropathic pain

syndromes. Application of low-concentration capsaicin creams (0.025% and 0.075%) have demonstrated efficacy in the treatment of PDPN [Tandan et al, 1992; Mason et al, 2004] but these low-concentration capsaicin creams require continued, multiple daily applications and are associated with repeated burning sensations at the application site and the risk of contamination of sensitive areas, which may lead to poor patient compliance. QUTENZA is a high-concentration capsaicin dermal patch (capsaicin, 8% w/w) developed to rapidly deliver a therapeutic dose of capsaicin into the skin. Prolonged pain reduction following QUTENZA application was observed in patients with Postherpetic Neuralgia (PHN) and painful HIV-AN in Phase II and III studies [Backonja et al, 2008; Simpson et al, 2008]. It has been granted marketing authorization in the EU for *the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal product for pain*.

Study objective

Primary objective:
To assess the safety of repeat applications of QUTENZA administered over a period of 12 months in subjects with PDPN.
Secondary objectives:
To assess the efficacy of repeat applications of QUTENZA administered over a period of 12 months in subjects with PDPN

Study design

Multicenter, randomized (3 arms), open-label, phase 3 study

Intervention

3 treatment arms
1) Active arm: QUTENZA patch (30 minutes) plus standard of care
2) Active arm: QUTENZA patch (60 minutes) plus standard of care
3) Control arm: standard of care only

Study burden and risks

Capsaicin Risks: As a consequence of the defunctionalization of epidermal and dermal nociceptors, a reduction in the ability to detect heat stimuli in the treated skin areas could be expected. Based on previous experience with topical capsaicin application, impairment of sensory function is expected to be subtle, limited to warmth or heat detection, and transient. In fact, temporary, minor changes in heat detection (1oC to 2oC) were detected at the QUTENZA application site in healthy volunteer studies, although no such changes have been noted during clinical studies in patients with PNP. Transient local erythema is expected from the capsaicin treatment procedure. Mild and in some cases,

moderate to severe treatment associated discomfort including warmth, stinging, burning sensation, or pain is expected at treatment areas. Treatment-associated discomfort or pain usually subsides after patch removal and is expected to resolve by the end of the treatment day. Some subjects may experience severe pain during patch application, which begins to decrease after patch removal. Accidental contact of other skin and particularly mucous membrane areas with capsaicin may also cause such symptoms. Aerosolization of capsaicin, (e.g., during the removal of the patches) may evoke coughing. AEs that have been reported in clinical trials of QUTENZA as possibly or probably related include bruising, burning, dermatitis, discoloration, dryness, erythema, excoriation, hyperesthesia, edema, pain, papules, paresthesia, pruritus, reaction, swelling, urticaria, vesicles, fatigue, oedema peripheral, pain not otherwise specified (NOS), and pain exacerbated. Most of the related AEs listed above were of mild to moderate intensity and were noted to resolve within one week of their onset.

The cleansing gel for QUTENZA contains butylhydroxyanisole, which may cause local skin reactions (e.g., contact dermatitis) or irritation of the eyes and mucous membranes.

As a result of treatment-related increases in pain, transient increases in blood pressure (on average < 8.0 mmHg) may occur during and shortly after the QUTENZA treatment. Blood pressure should be monitored during the treatment procedure. Patients experiencing increased pain will be provided with supportive treatment such as local cooling or oral analgesics (i.e., short acting opioids). For patients with unstable or poorly controlled hypertension or a recent history of cardiovascular events, the risk of adverse cardiovascular reactions due to the potential stress of the procedure should be considered prior to initiating QUTENZA treatment. Enrolment of patients with cardiovascular risk factors into the current study will be left to the decision of the investigator.

Opioid-based oral pain medications, such as oxycodone hydrochloride oral solution 1 mg/ml concentration or hydrocodone/acetaminophen tablets, pose the following risks: lightheadedness, dizziness, sedation, nausea, vomiting, constipation, headache, respiratory depression, pruritus, rash, euphoria and dysphoria. Light-headedness, dizziness, sedation, nausea and vomiting may be more prominent in ambulatory than in non-ambulatory patients and some of these side effects may be alleviated if the patient lies down.

Topical anesthetics (e.g., lidocaine) pose the following risks: skin irritation, redness, itching, rash, erythema, edema and abnormal sensation at the site of treatment. Less common side effects include blurred vision, dizziness, drowsiness, difficulty breathing, trembling, chest pain, irregular heartbeat and allergic or anaphylactoid reactions characterized by urticaria, angioedema, bronchospasm and shock). Should any of these less common side effects develop, emergency medical attention should be sought immediately. The EMLA topical anesthetic contains lidocaine and prilocain. Contact of EMLA with

eyes may cause eye irritation and potential abrasion. EMLA should not be used in patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia as they are more susceptible to drug induced methemoglobinemia. Caution should also be exercised in patients with anemia.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable)
2. Male or female >18 years of age
3. Diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy which is due to

diabetes, for at least 1 year prior to screening visit
4. Diagnosis of PDPN confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI)
5. At least one medical record of glycosylated hemoglobin (HbA1c) of <9% at 3-6 months before screening visit and an HbA1c of <9% at screening visit. A subject who has an HbA1c of >9% at the screening visit, for whom the pre-screening value was <9%, may undergo a more intensive period of diabetes treatment for 3 months and be re-screened. Upon re-screening, the subject may be enrolled if the HbA1c is <9% or if the investigator attests that Diabetes Mellitus (DM) is appropriately optimized for that subject
6. Stable glycemic control for at least 6 months prior to screening visit, i.e., on antidiabetic drugs (including insulin and/or oral hypoglycemic agents [OHA])
7. Average Numeric Pain Rating Scale (NPRS) score over the last 24 hours of >4 at the screening and the baseline visit

Exclusion criteria

1. Primary pain associated with PDPN in the ankles or above
2. Pain that could not be clearly differentiated from, or conditions that might interfere with, the assessment of PDPN, such as plantar fasciitis, heel spurs, tibial neuropathy, Morton*s neuroma, bunions, metatarsalgia, arthritis in feet, peripheral vascular disease (ischemic pain), neurological disorders unrelated to diabetic neuropathy (e.g., phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation (e.g., plantar ulcer)
3. Significant pain (moderate or above) of an etiology other than PDPN (e.g., compression-related neuropathies [e.g., spinal stenosis, fibromyalgia or arthritis]), that may interfere with judging PDPN-related pain
4. Current or previous foot ulcer as determined by medical history and medical examination
5. Any amputation of lower extremity
6. Severe renal disease as defined by a creatinine clearance of <30 ml/min calculated according to the Cockcroft-Gault formula
7. Clinically significant cardiovascular disease within 6 months prior to screening visit defined as cerebrovascular accident, unstable or poorly controlled hypertension, transient ischemic attack, myocardial infarction, unstable angina, current arrhythmia, any heart surgery including coronary artery bypass graft surgery, percutaneous coronary angioplasty/stent placement, or valvular heart disease
8. Significant peripheral vascular disease (intermittent claudication or lack of pulsation of either the dorsalis pedis or posterior tibial artery, or ankle-brachial systolic blood pressure index of <0.80)
9. Clinically significant foot deformities, including hallux rigidus, hallux valgus, or rigid toe as determined by physical examination as judged by the investigator
10. Clinically significant ongoing, uncontrolled or untreated abnormalities in cardiac, renal, hepatic, or pulmonary function that may interfere either with the ability to complete the study or the evaluation of adverse events
11. Any active signs of skin inflammation around onychomycosis sites such as pain, redness, swelling or drainage

12. Subject is unwilling to implement proper foot care methods
13. Clinically significant abnormal ECG at screening
14. Impaired glucose tolerance (IGT) only - without DM
15. Body mass index (BMI) of >=40 kg/m2
16. Diagnosis of any poorly controlled major psychiatric disorder
17. Evidence of cognitive impairment including dementia that may interfere with subject*s ability to complete pain assessments requiring subject*s recall of average pain level in the past 24 hours
18. Active substance abuse or history of chronic substance abuse within 1 year prior to Screening visit or any prior chronic substance abuse (including alcoholism) likely to re-occur during the study period as judged by the investigator
19. Participation in any other clinical trial for an investigational drug within 30 days prior to screening visit
20. Previous treatment with QUTENZA
21. Female subjects of childbearing potential must have a negative serum or urine pregnancy test at enrollment and must agree to maintain highly effective birth control during the study. A highly effective method of birth control is defined as those which result in a low failure rate (CPMP/ICH/286/95 modified) of less than 1% per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized
partner.
22. Hypersensitivity to capsaicin (i.e., chili peppers or over-the-counter [OTC] capsaicin products), any QUTENZA excipients, EMLA ingredients or adhesives
23. Use of any topical pain medication, such as non-steroidal anti-inflammatory drugs, menthol, methyl salicylate, local anesthetics, steroids or capsaicin products on the painful areas within 7 days preceding the first patch application at the baseline visit
24. Use of oral or transdermal opioids exceeding a total daily dose of morphine of 80 mg/day, or equivalent; or any parenteral opioids, regardless of dose, within 7 days preceding the first patch application at the baseline visit
25. Lack of an effective pain medication strategy for the subject, such as unwillingness to use opioid analgesics during study treatment, or high tolerance to opioids precluding the ability to relieve treatment-associated discomfort with oxycodone or other analgesic, as judged by the investigator
26. Skin areas to be treated with QUTENZA showing changes such as crusting or ulcers.
27. Active malignancy or history of malignancy during the past 5 years prior to screening visit (a history of squamous cell carcinoma or a basal cell carcinoma not involving the area to be treated is allowed)
28. Planned elective surgery during the trial
29. Subject, who in the opinion of the investigator, is not likely to complete the study for any reason
30. Subject is an employee of the Astellas Group, third parties associated with the study or the clinical study site team.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-06-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	QUTENZA
Generic name:	capsaicin dermal patch
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-08-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-04-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-016458-42-NL
CCMO	NL37292.041.11