Trial code:	AV001
Title of trial:	An interventional, Phase III, double-blind, randomized, controlled, parallel-group, multi-site, clinical trial evaluating the efficacy and safety of Qutenza® in subjects with post-surgical neuropathic pain
Brief title:	Comparison of Qutenza (8% capsaicin topical system) with a low-dose capsaicin topical system for treatment of nerve pain after surgery
Indication:	Post-surgical neuropathic pain (PSNP)
International coordinating investigator: [a]	Prof. John Douglas Markman, MD, Department of Neurosurgery, University of Rochester Medical Center, 2180 S Clinton Ave, Rochester, NY 14618, USA
Trial sites:	Multi-site trial (approximately 100 sites worldwide). Documentation of the involved trial sites will be maintained.
Trial sponsor:	Averitas Pharma, Inc. [b]
Sponsor's signatory:	Lizandra Marcondes, MD, PhD Head of Medical Affairs and Clinical Development, GRT US Holding, Inc.

a) Contact detail changes during the course of the trial will be documented and do not require a protocol amendment.

b) Averitas Pharma, Inc. is part of the Grünenthal US Holding.

Version	**Date**	**DMS version number**	**Valid for**
Original:	26 Apr 2021	2.0	All countries
Amendment 01:	07 Dec 2021	3.0	All countries

IND number:	063354
EudraCT number:	2021-001409-64
Universal Trial Number:	U1111-1272-1340

CONFIDENTIAL

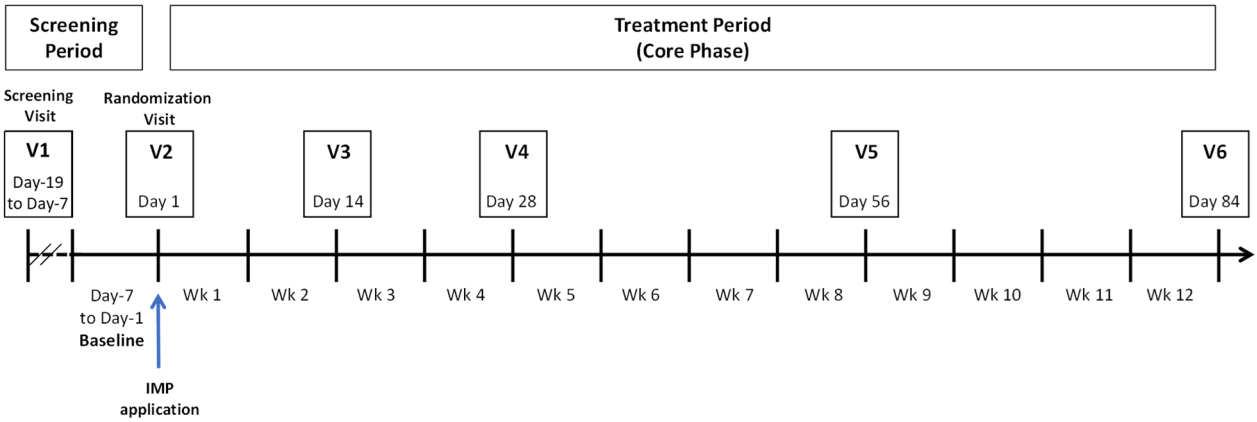
The contents of this document may not be disclosed to any other person without written permission from the sponsor, unless required by good clinical practice or applicable regulatory requirements. Any supplemental documentation for the clinical trial is also covered by this provision.

1 PROTOCOL SYNOPSIS

1.1 Trial design

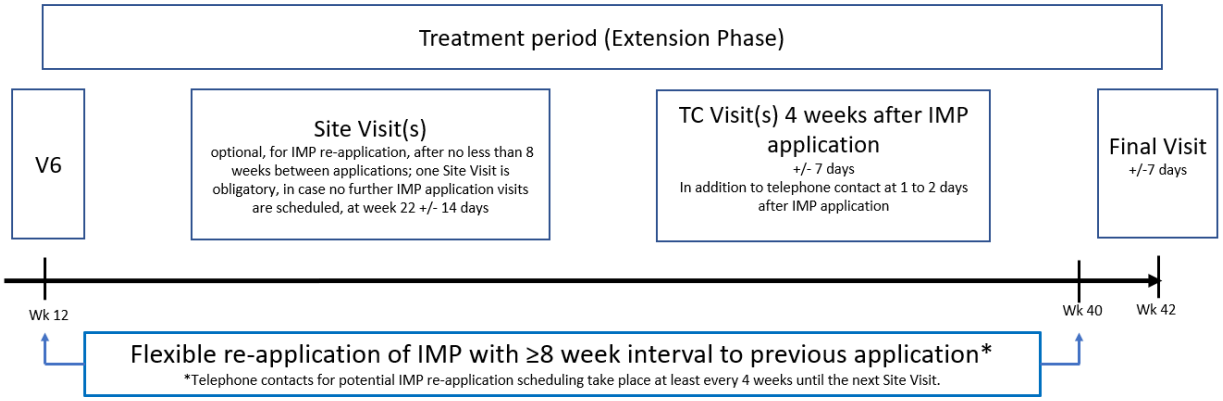
This is an interventional, Phase III, double-blind, randomized, controlled, parallel-group, multi-site, clinical trial to confirm the efficacy and safety of repeated topical application of Qutenza (capsaicin 8% topical system) versus low-dose capsaicin control (capsaicin 0.04% topical system) in subjects with moderate to severe PSNP.

1.1.1 Flow diagram summary of the trial



IMP = Investigational Medicinal Product; V = Visit; Wk = Week

Figure 1: Flow diagram of the Screening Period (Day -19 to Day -1) and the Core Phase of the Treatment Period (Day 1 to Week 12)



After Visit 6, additional site visits are performed for application of IMP as needed. If the last IMP application is at week 39 or later, the TC 4 weeks after IMP application can be replaced by the final visit.

FU = Follow-Up Phase; IMP = Investigational Medicinal Product; TC = Telephone Contact; V = Visit; Wk = Week

Figure 2: Flow diagram of the Extension Phase of the Treatment Period including Follow-up Phase (Week 13 to Week 42)

1.1.2 Brief description of the sequence and duration of all trial periods

After a Screening Period of up to 19 days, including the Baseline Phase from Day -7 to Day -1, subjects will be allocated to Qutenza or to low-dose capsaicin control topical system (capsaicin 0.04%) at the Randomization Visit. The blinded Treatment Period consists of a Core Phase (Day 1 to Week 12, see Figure 1) and an Extension Phase (Week 13 to Week 42), which includes a Follow-up of 14 days (see Figure 2).

See Section 1.1.1 for a summary of the trial in flow diagrams and Section 1.7 for a tabular schedule of events.

Each subject is expected to be in the trial for up to 44 weeks.

1.2 Trial objectives and endpoints

Core Phase		
Objective	**Endpoint/Outcome**	**Measure description and timeframe**
Primary	**Primary**	
To demonstrate superiority of Qutenza over low-dose capsaicin control in change from baseline to Week 12 in the 24-hr average pain intensity in subjects with PSNP.	For the US: Change from baseline to the weekly average score of Week 12 in the 24-hr average pain intensity. For non-US countries/regions: Change from baseline to the average score of the entire period between Week 2 and Week 12 in the 24-hr average pain intensity.	The 24-hr average pain intensity will be assessed and reported in the electronic diary (e-diary) once daily in the evening, using an 11-point numeric pain rating scale (NPRS, from 0 = no pain to 10 = pain as bad as you can imagine). Timeframe for the assessment: from the Baseline Phase (Day -7 to Day -1) to Visit 6 (Week 12/Day 84).
Secondary	**Secondary**	
To demonstrate superiority of Qutenza over low-dose capsaicin control in change from baseline to Week 12 in treatment area size in subjects with PSNP.	Change from baseline to Week 12 in the treatment area size.	The treatment area size [cm^2] (the treatment area will be comprised of the area identified by the subject as the usually most painful area(s) and/or the area characterized by dynamic mechanical allodynia [DMA] and/or the area of pinprick hyperalgesia) at Visit 2 (Day 1) before investigational medicinal product (IMP) application and at Visit 6 before IMP application (Week 12/Day 84).
To assess the safety and tolerability of Qutenza in subjects with PSNP.	Incidence of treatment-emergent adverse events (TEAEs). Incidence of TEAEs leading to discontinuation in the Core Phase.	Documentation of TEAEs from the start of treatment at Visit 2 (Day 1) up to the time of the last scheduled contact in the Core Phase of the Treatment Period, i.e., Visit 6 before IMP application (Week 12/Day 84).

Extension Phase		
Objective	**Endpoint/Outcome**	**Measure description and timeframe**
Secondary	**Secondary**	
To confirm the long-term efficacy of Qutenza in subjects with PSNP.	Change from baseline to the weekly average score of Week 42 in the 24-hr average pain intensity.	The 24-hr average pain intensity will be assessed and reported in the e-diary once daily in the evening using an 11-point NPRS (from 0 = no pain to 10 = pain as bad as you can imagine). Timeframe for the assessment: from the Baseline Phase (Day -7 to Day -1) to Final Visit (Week 42/Day 294).
	Change from baseline to Week 42 in the treatment area size.	The treatment area size [cm^2] (the treatment area will be comprised of the area identified by the subject as the usually most painful area(s) and/or the area characterized by DMA and/or the area of pinprick hyperalgesia) at Visit 2 (Day 1) before investigational medicinal product (IMP) application and at Visit 6 before IMP application (Week 12/Day 84).
	Change from baseline to the average score of the entire period between Week 2 and Week 42 in the 24-hr average pain intensity.	The 24-hr average pain intensity will be assessed and reported in the e-diary once daily in the evening, using an 11-point NPRS (from 0 = no pain to 10 = pain as bad as you can imagine). Timeframe for the assessment: from the Baseline Phase (Day -7 to Day -1) to the Final Visit (Week 42/Day 294). The average score over the entire period between Week 2 and Week 42 will be calculated per subject as the mean of all available post-baseline weekly average values of the 24-hr average pain intensity excluding pain measurements at the day of and during the first 5 consecutive days after any IMP application.
To assess the long-term safety and tolerability of Qutenza in subjects with PSNP.	Incidence of TEAEs. Incidence of TEAEs leading to discontinuation in the Extension Phase.	Documentation of TEAEs from start of treatment at Visit 2 (Day 1) up to the time of the last scheduled contact in the Extension Phase of the Treatment Period, i.e., Final Visit (Week 42/Day 294).

Other data to be collected that are not directly attributed to an endpoint
General note: All other data not directly attributed to an endpoint will be collected at the applicable time points given in the schedule of events (Section 1.7).
To describe the trial population and to evaluate subject eligibility • Demographic data, relevant medical history and details of the surgery leading to PSNP, prior and concomitant medications, physical examination, neurological/sensory examination status, DN4i (Douleur Neuropathique 4 interview) status, urine pregnancy test, urine drugs of abuse test.
To assess the efficacy • 24-hr average pain intensity: relative change from baseline (percent change). • Response to treatment (response defined as ≥30% decrease from baseline in 24-hr average pain intensity). • Time to onset of response to treatment (response defined as ≥30% decrease from baseline in 24-hr average pain intensity). • Relevant response to treatment (relevant response defined as reduction by ≥2 points on the NPRS in 24-hr average pain intensity). • Interval length between IMP applications based on time points of IMP application (trial day) for all applications and for all subjects. • DMA intensity: change from baseline. • DMA area size [cm^2]: change from baseline. • MOS Sleep Scale: change from baseline for single items and the sleep problem index. • Intake of concomitant analgesic medication for treatment of PSNP. • PGIC at V6, subsequent IMP application Visits, and at the Final Visit. • Neuropathic Pain Symptom Inventory (NPSI) total score: change from baseline. • BPI Interference Scale score (Question 9A to 9G): change from baseline. • Short Form 36 Health Survey® (SF-36) physical component summary and mental component summary: change from baseline. • Treatment Satisfaction Questionnaire for Medication (TSQM) scores. • Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscale scores: change from baseline. • Work Productivity Activity Impairment assessment (WPAI, neuropathic pain version): change from baseline. • Physical activity as measured by an actigraphy device in selected centers. • Sleep efficiency as measured by an actigraphy device in selected centers.
To assess the safety • Incidence of TEAEs. • Vital signs. • Physical examination. • Dermal assessment score: change from baseline. • Neurological/sensory examination. • “Pain now” (current pain intensity) related to the IMP application site. • Occupational exposure in trial personnel administering Qutenza.

1.3 Trial subjects – the population to be studied

1.3.1 Inclusion criteria

Subjects are eligible for the trial if all the inclusion criteria are met. Subjects will only receive IMP if documentation is available showing that they do meet all inclusion criteria.

General

1. The subject has given written informed consent to participate.
2. Female or male subjects aged 18 years or older.
3. For women of childbearing potential: negative pregnancy tests at Screening Visit (Visit 1), the Randomization Visit (Visit 2), and prior to each reapplication of the IMP, and must have agreed to practice medically acceptable methods of birth control.

Confirmation of diagnosis of chronic moderate to severe PSNP (see also Table 1 "Non-exhaustive list of examples of types of surgeries with resulting PSNP")

4. Documented diagnosis of PSNP by the following criteria:
   a. A history of post-surgical pain with a duration of at least 6 months to maximally 60 months that is plausibly related to the surgical intervention as documented on a body map.
   b. DN4i of at least 3 out of 7 points at Visit 1.
   c. The pain must extend beyond the scar area to neuroanatomically adjacent skin areas and be related to the site of the surgery.
5. Documented diagnosis of probable or definite PSNP according to the following criteria (Finnerup et al. 2016):
   a. The pain must be associated with sensory signs in the same neuroanatomically plausible distribution. The area of sensory changes may extend beyond, be within, or overlap with the area of pain (criterion for probable neuropathic pain), or
   b. In addition to 5a: Direct surgical evidence (e.g., surgeon's clear verification of an intraoperative nerve lesion) (criterion for definite neuropathic pain).
6. The subject has moderate to severe pain with a baseline value for 24-hr average pain intensity of at least 4 points on the NPRS. The baseline value is calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1). At least 5 (out of the last 7 days) pain ratings should be available during the Baseline Phase. If less than 5 pain ratings are available in the last 7 days, the subject may be rescheduled for Visit 2 (1 time only) after having received appropriate re-training in the use of the e-diary to ensure compliance.

Suitability for treatment with IMP

7. The size of the affected painful intact skin area is not larger than the size of 4 standard Qutenza topical systems (1120 cm^2).
8. The skin in the area where the IMP will be applied, and that may also contain the scar tissue, is intact, dry, and non-irritated (i.e., there are no signs and symptoms of skin disease, skin irritation, inflammation or injury, such as active herpes zoster lesions, atopic dermatitis, ulceration, wounds). This is reflected by a dermal assessment score of 0 = "no evidence of irritation" or 1 = "minimal erythema, barely perceptible".

Eligibility with regard to protocol adherence, to allowed pre-treatments and concomitant treatments

9. The subject is willing to adhere to the restricted use of concomitant treatments (see concomitant treatments in Section 1.4.2).
10. The subject experiencing pain is:
    a. currently not receiving treatment for PSNP or
    b. receives a stable systemic treatment for PSNP that started more than 30 days prior to the Randomization Visit (Visit 2).

Table 1: Non-exhaustive list of examples of types of surgeries with resulting PSNP

Examples of surgeries suitable for eligibility:
Thoracic surgery
Breast surgery
Abdominal surgery (cholecystectomy, appendectomy)
Donor nephrectomy
Gynecologic surgery (hysterectomy, C-section)
Varicose vein surgery
Inguinal herniotomy
Lipoma removal
Knee surgery
Knee arthroplasty
Ankle surgery

1.3.2 Exclusion criteria

Subjects will not be eligible for the trial if any of the exclusion criteria are met. Subjects will only receive IMP if documentation is available showing that they do not meet any of these exclusion criteria.

General or previous treatments

1. The subject received Qutenza before the Randomization Visit (Visit 2) or received a medical device in another clinical trial within 7 days before the Randomization Visit (Visit 2), or
    a. Any former use of topical capsaicin in the area of the PSNP before Visit 2, except for the use of a low-dose (<1%) capsaicin product – but not within 7 days before Visit 2.
    b. The subject participated previously in this clinical trial or participated in another clinical trial for the treatment of PSNP completing less than 3 months ago.
2. A score of 0 out of 5 in all 3 categories of the neurological/sensory examinations, i.e., for warm sensation, pinprick and cold sensation at the Screening Visit (Visit 1).

Confounding factors

3. The subject reported a 24-hr average pain intensity score of 10 on the NPRS for at least 4 days during the Baseline Phase.
4. Any painful procedure planned during the course of the trial that may, in the opinion of the investigator, affect the efficacy or safety assessments.

5. Subjects with PSNP related to a surgery/condition with a high potential for confounding symptoms, e.g., the pain is at least partially due to pain in deeper structures such as muscles or bones (including referred pain from deeper structures) as listed in examples in Table 2.
6. Other painful conditions in the body area that is affected by PSNP and may affect efficacy or safety assessments and cannot be discriminated from the target pain by the subject, including infectious, non-infectious, inflammatory or neuropathic conditions which could also be complications related to the previous surgical procedure.

Table 2: Non-exhaustive list of examples of types of surgeries/conditions not suitable for eligibility

Examples of excluded surgeries/conditions:
Any surgery performed due to suspected neoplasia: suspected residual neoplasia or metastases Conditions where nociceptive or neuropathic pain has been the reason for the surgery, e.g., failed back surgery, carpal tunnel syndrome or other nerve compression syndromes leading to neuropathic pain, (e.g., meralgia paresthetica)
Conditions of projected neuropathic pain (i.e., from inguinal hernia repair) with painful symptoms in the genital region, e.g., the scrotum or vagina
Amputations
Radicular pain and nerve trunk lesions
Scar pain neuroma
Complex Regional Pain Syndrome (Type I or Type II)

Contraindications to IMP

7. Neuropathic pain areas located only on the face, above the hairline of the scalp, and/or in proximity to mucous membranes.
8. Hypersensitivity to capsaicin (i.e., chili peppers or over-the-counter [OTC] capsaicin products), or to any excipients of the IMP or to excipients of the cleansing gel in use and their components, or to topical anesthetics in use and their components.

Medical history/concurrent condition(s)/other factors

9. Pending litigation due to chronic pain or disability.
10. The subject has a history of alcohol or drug abuse or is actively abusing drugs (including alcohol, medication) during the 1 year prior to the Screening Visit (Visit 1) as judged by the investigator.
11. Evidence or history of severe psychiatric illness/disorder during the 3 years prior to the Screening Visit (Visit 1) that, in the investigator's opinion, may affect efficacy or safety assessments or may compromise the subject's safety during trial participation, e.g., major depression, major anxiety disorder, psychosis, severe personality disorders.
12. Evidence of cognitive impairment including dementia that may interfere with the subject's ability to complete pain assessments requiring recall of the average pain level in the past 24 hrs.

13. Surgical intervention in the last 3 months preceding the Screening Visit (Visit 1) if it is affecting the efficacy or safety assessments, or any scheduled or planned surgery during the trial, with the exception of the Extension Phase if the planned surgery is not expected to affect the efficacy or safety assessments.
14. Patients with current clinically significant disease(s) or condition(s) (including clinically significant cardiovascular disease and/or significant pain in other areas) that may affect efficacy or safety assessments, or any other reason which, in the investigator's opinion, may preclude the subject's participation in the full duration of the trial. Patients with current signs and symptoms consistent with Coronavirus disease 2019 (COVID-19) (e.g., dry cough, dyspnea, sore throat, fatigue, fever) or patients who had those symptoms within the last 14 days prior to screening and had a positive SARS-CoV2 PCR test result.
15. Unstable or poorly controlled blood pressure which, in the opinion of the investigator, would put the subject at risk of severe adverse blood pressure increases upon IMP application.
16. Known or suspected of not being able to comply with the requirements of the trial protocol or the instructions of the trial site staff.
17. Not able to communicate meaningfully with the trial site staff.
18. The subject is an employee of the investigator or trial site, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial site, or is a family member of the employees or the investigator.

1.4 Trial treatments

1.4.1 Investigational medicinal products

Subjects who fulfil all inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to 1 of the 2 treatments in a 1:1 ratio:

- Qutenza (capsaicin 8% topical system, containing capsaicin 179 mg or capsaicin 640 µg/cm^2 of topical system).
- Low-dose capsaicin control (capsaicin 0.04% topical system, containing capsaicin 0.9 mg or capsaicin 3.2 µg/cm^2 of topical system).

The appearance of Qutenza and low-dose control topical systems will not be distinguishable. The size of each IMP topical system is 14 cm by 20 cm (280 cm^2). Up to 4 topical systems (1120 cm^2), depending on the size of the painful affected area, will be applied topically for 60 mins to the treatment area. Prior to the IMP application, the treatment area will be pre-treated with a topical anesthetic.

The initial IMP application will occur at the Randomization Visit (Visit 2/Day 1).

Re-application of the IMP is dependent on: the investigator's judgment that the subject's pain level is appropriate (e.g., pain levels >4 during the last week preceding the re-application), and the subject's wish to receive another treatment based on their pain assessment. Re-application is not allowed if the subject did not tolerate previous IMP application(s) as judged by the investigator, developed hypersensitivity to the IMP, or if the subject is pregnant.

The first re-application of the IMP can take place at the earliest 12 weeks after the first application (i.e., at Visit 6, after the Core Phase of the Treatment Period). During the Extension Phase of the

trial, the minimum time interval between applications should be 8 weeks. The last IMP application can occur no later than 40 weeks after the first IMP application (if an application occurs at Week 40, the Final Visit has to take place at the earliest 14 days later).

1.4.2 Prior and concomitant medications or therapies

1.4.2.1 Forbidden prior medications

- Newly started or when dosage adjustment was required within 30 days prior to randomization: oral tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or anticonvulsants.
- Within 7 days prior to randomization: topically applied gabapentin, amitriptyline, baclofen, capsaicin, and/or lidocaine.
- Within 7 days prior to randomization: opioids.

1.4.2.2 Forbidden concomitant medications or therapies

- All opioids are forbidden during the course of the trial, unless medically indicated for short-term treatment (not more than 3 consecutive days and not more than 7 days in total in between two successive IMP applications) for non-PSNP-related pain. Opioids are not allowed for treatment of acute pain due to the IMP application.
- Any local/topical pain therapy or systemic non-pharmacologic treatment of pain, e.g., nerve block, nerve ablation, acupuncture, magnets, and transcutaneous electrical nerve stimulation, unless these are occasional treatments for non-PSNP-related pain (i.e., acupuncture for headache or nerve stimulation for back pain).
- Oral drugs for the treatment of sleep disorders are forbidden during the first 12 weeks of the trial unless their dose has been stable for more than 30 days before the Randomization Visit and is expected to remain stable over the first 12 weeks (i.e., at least to Visit 6).
- Regular use of oral and injectable steroids.
- Any change in stable pre-trial analgesic therapy or start of new analgesic therapy for the treatment of PSNP is forbidden during the first 12 weeks of the trial.

1.4.2.3 Allowed analgesic concomitant medications to address application site pain and during first 12 weeks

- At each IMP application, subjects will be pre-treated with a topical anesthetic according to local practice (e.g., lidocaine 4%, lidocaine 2.5%/prilocaine 2.5%) on their treatment area prior to placement of the IMP.
- Short-acting analgesics other than opioids to relieve treatment-associated pain or discomfort during the application procedure and up to 5 days after the IMP application.
- Other oral analgesic drugs for the treatment of PSNP (e.g., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants) are only allowed if their dose has been stable for more than 30 days before the Randomization Visit. Changes in the stable analgesic medication and doses are not permitted during the first 12 weeks of the trial (i.e., at least to Visit 6).
- Oral drugs for the treatment of sleep disorders are only allowed if their dose has been stable for more than 30 days before the Randomization Visit and is expected to remain stable over the first 12 weeks of the trial (i.e., at least to Visit 6).

- Other medical pain therapy (including OTC pain medication) not specifically prohibited is allowed. This applies for conditions other than PSNP or medications taken occasionally due to unforeseen circumstances or transient adverse events (such as headaches, toothache, acute low back pain, and dysmenorrhea). However, all such therapy or medications must be documented.

1.4.2.4 Allowed analgesic medication for treatment of PSNP after the first 12 weeks (rescue medication):

- After the first 12 weeks any additional intake of analgesic medications is allowed - except for the analgesics mentioned as forbidden for the entire trial in Section 1.4.2.2 - and must be documented on the Rescue Medication case report form (CRF) page:
  - either newly taken analgesic medication, if no stable concomitant medication is used,
  - or any dose increase in ongoing stable concomitant analgesic medication for the treatment of PSNP and that is not for application site pain,
  - or analgesic medication taken on top of stable concomitant analgesic medication for PSNP.

1.5 Statistical analyses

The final analysis of this trial, including the Extension Phase, will be performed after the last subject has completed the trial and the complete database has been locked.

1.5.1 Sample size rationale

Effect size estimates were based on previous pivotal studies with Qutenza, utilizing the percent change from baseline to Week 12 endpoint. A total number of 408 subjects (204 subjects per treatment group) is required to achieve an overall power of at least 90% to reject the null hypothesis of no treatment difference in treatment group means between Qutenza and low-dose capsaicin control (1-sided t-test, type I error of $\alpha = 0.025$), assuming an expected treatment difference of at least 9.8% (relative change from baseline in the 24-hr average pain intensity) on the primary efficacy endpoint and a relative change from baseline of 30.5% as standard deviation in both treatment groups.

A blinded interim analysis will be conducted when at least 265 subjects (i.e., approximately 65% of 408 subjects) have completed Visit 6 or discontinued from the trial, to re-estimate and increase the sample size up to a maximum of 500 subjects if the standard deviation is >30.5%. This approach can preserve the power of at least 90% for an observed standard deviation of ≤33.75%.

Assuming a screening failure rate of about 20%, approximately 510 subjects are planned to be screened in order to randomize 408 subjects for the primary analysis (204 evaluable subjects per treatment group, 1:1 randomization).

To avoid excessive variation in the numbers of subjects per trial site, the number of randomly assigned subjects planned for each trial site is recommended to not exceed 45 subjects. A decision to exceed the number of randomized subjects per trial site must consider the quality of the data and the potential impact on the planned analyses.

Sample size calculations were performed with nQuery Advisor 7.0.

1.5.2 Analysis populations

Safety Set (SAF)

All subjects with at least 1 IMP application (including incomplete applications of less than 60 mins).

Analyses on the SAF will be conducted based on actual treatment received.

Full Analysis Set (FAS)

All randomly assigned subjects with at least 1 IMP application (including incomplete applications of less than 60 mins).

Analyses on the FAS will be conducted based on the treatment as randomized, i.e., based on planned treatment.

1.5.3 Statistical methods and analysis

The planned analysis of the primary efficacy endpoint is described in Section 1.5.3.1. The planned analysis of secondary endpoints, including the multiple testing procedure used to control the family-wise type I error rate, is provided in Section 14 of the protocol.

All efficacy endpoints will be summarized descriptively for the FAS.

Details of the statistical methods and analysis will be specified in the statistical analysis plan.

Subject disposition as well as demographic and baseline data and other subject characteristics, e.g., medical history and prior and concomitant medications, will be summarized descriptively for the FAS and the SAF. Adverse events, vital signs, and further safety parameters will be summarized descriptively for the SAF. Further details on the planned secondary and exploratory analyses will be provided in the statistical analysis plan.

1.5.3.1 Analysis of the primary endpoint

The primary endpoint for the US and non-US countries/regions are defined in Section 1.2.

The 24-hr average pain intensity will be assessed once daily in the evening using an 11-point NPRS. The baseline pain will be calculated from the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of the last 7 days must be available. Each trial week is defined as a sequential 7-day interval subsequent to the Randomization Visit (Visit 2). The weekly average pain of a trial week is defined as the average of non-missing 24-hr average pain assessments for the respective trial week.

The estimand of interest for the primary efficacy analysis is the difference in treatment group means in the primary efficacy endpoint in all subjects in the FAS attributable to the randomized treatment regimen.

The primary efficacy analysis will be performed using a mixed-effects model for repeated measures (MMRM). The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for the treatment of PSNP, and baseline pain intensity and an unstructured covariance matrix to model the covariance structure of the repeated measures.

This analysis will be performed based on all available post-baseline weekly average values of the 24-hr average pain intensity, excluding pain measurements at the day of and during the first 5 consecutive days after any IMP application, because of the potential for treatment-associated pain during the application procedure and the permitted use of short-acting (non-opioid) analgesics.

Sensitivity analyses will be conducted to assess the robustness of the primary analysis results with respect to the missingness assumption missing at random (MAR).

The primary efficacy endpoint will be investigated by applying an analysis of covariance (ANCOVA) model with the same covariates as the primary analysis model to multiple imputation datasets:

- Imputed with the MAR assumption.
- Imputed with the MAR assumption and incorporating a penalty delta in the Qutenza group only, with delta = 15%. The penalty of 15% was chosen to correspond to an absolute change from baseline of 1 point on the NPRS, assuming an average baseline measurement of approximately 6.5 points on the NPRS.
- A tipping point analysis to identify the highest delta penalty that would still result in a statistically significant difference between treatment groups (Permutt 2016).

1.5.3.2 Missing data handling

Subject discontinuation from the trial will be handled as an intercurrent event. Unobserved assessments after discontinuation will be handled by the primary analysis (MMRM) as MAR due to the long-lasting pharmacodynamic effect of the IMP.

The start of intake of forbidden concomitant medication for pain related to PSNP will also be handled as an intercurrent event. All pain assessments collected after the start of intake of forbidden concomitant medication for pain due to PSNP during Weeks 2 through 12 will be ignored and the ignored assessments will be imputed by the subject's baseline pain score.

1.5.4 Interim analysis

A blinded interim analysis will be conducted when at least 265 subjects (i.e., approximately 65% of 408 subjects) have completed Visit 6 or discontinued from the trial, to re-estimate and increase the sample size up to a maximum of 500 subjects if the standard deviation is >30.5%. This approach can preserve the power of at least 90% for an observed standard deviation of ≤33.75%.

1.6 References cited in the protocol synopsis

Permutt T. Sensitivity analysis for missing data in regulatory submissions. Stat Med 2016; 35(17): 2876-9.

Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016; 157(8): 1599-606.

1.7 Schedule of events

Trial Period	**Screening Period**		**Treatment Phase**							**Follow-up**
			Core Phase					**Extension Phase** [b]		
Visit	**V1**		**V2**	**V3**	**V4 (TC)**	**V5 (TC)**	**V6**	**TC Visits 4 weeks after each IMP application** [l]	**Site Visits**	**Final Visit or Early Termination Visit**
	Screening Visit	Baseline Phase	Random-ization Visit	+/- 3 days	+/- 3 days	+/- 3 days	+ 3 days	+/- 7 days	Interval ≥8 weeks	Final Visit [a, l] +/- 7 days
Day	**-19 to -7**	**-7 to -1**	**1**	**14**	**28**	**56**	**84**			**294**
Week			**-**	**2**	**4**	**8**	**12**			**42**
Obtain informed consent	X									
Collect demographic data	X									
Record medical history [c]	X									
Record previous medications/therapies	X									
Record concomitant medications/therapies	X		X [g]	X	X	X	X [g]	X	X [g]	X
Perform physical exam [d]	X		X				X		X	X
Perform neurological / sensory exam [d]	X		X				X		X	X
Record vital signs	X		X [f]				X [f,n]		X [f,n]	
Mapping of treatment area	X		X				X		X [n]	X
Perform dermal assessment	X		X [h]				X [h,n]		X [h,n]	

Trial Period	**Screening Period**		**Treatment Phase**							**Follow-up**
			Core Phase					**Extension Phase** [b]		
Visit	**V1**		**V2**	**V3**	**V4 (TC)**	**V5 (TC)**	**V6**	**TC Visits 4 weeks after each IMP application** [l]	**Site Visits**	**Final Visit or Early Termination Visit**
	Screening Visit	Baseline Phase	Random-ization Visit	+/- 3 days	+/- 3 days	+/- 3 days	+ 3 days	+/- 7 days	Interval ≥8 weeks	Final Visit [a, l] +/- 7 days
Day	**-19 to -7**	**-7 to -1**	**1**	**14**	**28**	**56**	**84**			**294**
Week			**-**	**2**	**4**	**8**	**12**			**42**
Perform DMA [e] and pinprick hyperalgesia testing	X		X				X		X [n]	X
Collect urine and perform pregnancy [m] and drugs of abuse testing	X		X				X		X [n]	X
Check inclusion/exclusion criteria	X		X							
Train subjects on e-diaries	X									
Dispense e-diary	X									
Ask subject to record 24-hr average pain intensity score in their e-diaries [i]. Check e-diary compliance [j]	X	X	X	X	X	X	X	X	X	
Dispense subject trial card	X									

Trial Period	**Screening Period**		**Treatment Phase**							**Follow-up**
			Core Phase					**Extension Phase** [b]		
Visit	**V1**		**V2**	**V3**	**V4 (TC)**	**V5 (TC)**	**V6**	**TC Visits 4 weeks after each IMP application** [l]	**Site Visits**	**Final Visit or Early Termination Visit**
	Screening Visit	Baseline Phase	Random-ization Visit	+/- 3 days	+/- 3 days	+/- 3 days	+ 3 days	+/- 7 days	Interval ≥8 weeks	Final Visit [a, l] +/- 7 days
Day	**-19 to -7**	**-7 to -1**	**1**	**14**	**28**	**56**	**84**			**294**
Week			**-**	**2**	**4**	**8**	**12**			**42**
Ask subject to complete questionnaires on tablet computer at site										
DN4i	X									
Actigraphy device [o]	X		X							X
TSQM							X			X
PGIC							X		X	X
BPI, SF-36, HADS, NPSI, MOS Sleep Scale			X				X		X	X
WPAI			X							X
Randomization to treatment			X							
Pre-treatment with topical anesthetic			X				X		X	
Apply IMP [k]			X				X [n]		X [n]	
Ask subjects to rate their “pain now” [p]			X				X [n]		X [n]	

Trial Period	**Screening Period**		**Treatment Phase**							**Follow-up**
			Core Phase					**Extension Phase** [b]		
Visit	**V1**		**V2**	**V3**	**V4 (TC)**	**V5 (TC)**	**V6**	**TC Visits 4 weeks after each IMP application** [l]	**Site Visits**	**Final Visit or Early Termination Visit**
	Screening Visit	Baseline Phase	Random-ization Visit	+/- 3 days	+/- 3 days	+/- 3 days	+ 3 days	+/- 7 days	Interval ≥8 weeks	Final Visit [a, l] +/- 7 days
Day	**-19 to -7**	**-7 to -1**	**1**	**14**	**28**	**56**	**84**			**294**
Week			**-**	**2**	**4**	**8**	**12**			**42**
Evaluate the need for IMP re-application; apply IMP if applicable							X		X [b]	
Record adverse events	X		X [g]	X	X	X	X [g]	X	X [g]	X
Check discontinuation criteria			X	X	X	X	X	X	X	
Collect e-diary										X
Collect subject trial card										X

a) Subjects who discontinue or are discontinued earlier from the trial will perform the Final Visit/Early Termination Visit as a last trial visit, if possible.

b) Site visits in the Extension Phase are only needed in case of IMP application. The minimum interval between IMP applications during the Extension Phase (starting at Visit 6) is 8 weeks. In case no further Site Visits for IMP applications take place after V6, an obligatory Interim Site Visit is scheduled in week 22 +/-14 days. In that case, the following will be performed: Record concomitant medications/therapies; Ask subject to record 24-hr average pain intensity score in their e-diaries; Check e-diary compliance; Ask subject to complete questionnaires on tablet computer at site: PGIC, BPI, SF-36, HADS, NPSI, MOS Sleep Scale; Evaluate the need for IMP re-application; Apply IMP if applicable.

c) Including relevant surgical history (date of surgery, location and type of surgery leading to PSNP, and indication for the surgery) and date of onset of pain after surgery.

d) For visits with IMP application, perform neurological/sensory examinations before IMP application.

e) Measurement of the area and intensity of DMA (pain intensity in response to the cotton swab stroke assessed on an 11-point NPRS).

f) At IMP application visits, vital signs will be recorded 15 mins before local anesthetic application, and at 55 mins after IMP application.

g) At IMP application visits, record adverse events at any time before, during, and after IMP application. In addition to the recording at the visit, the subject will be contacted by telephone 1 to 2 days after the visit (in case IMP was applied) and be asked about adverse events using non-leading questions, any use of measures for treatment-associated discomfort after IMP application, and about their use of concomitant medication/therapies.

h) Dermal assessment scores - only in case of IMP application - will be recorded: 15 mins before local anesthetic application, and immediately after IMP removal.

i) Subjects will record data in the e-diary once daily in the evening from Visit 1 to the evening before the Final Visit.

j) Starting after Visit 1, until the Final Visit the e-diary will be reviewed for completeness prior to initiating any treatment-associated procedures; the subject will be re-trained if needed.

k) The IMP will be applied for 60 mins. Starting from V6, the minimum time between 2 IMP applications is 8 weeks.

l) This TC visit after 4 weeks following IMP application is scheduled for data collection as indicated. Further telephone contacts for potential IMP application scheduling without data collection take place at least every 4 weeks until the next Site Visit. If the last IMP application is at week 39 or later, the next visit has to take place not earlier than 14 days later and can be replaced by the Final Visit.

m) Only for women of childbearing potential and from V2 onward only at Visits with IMP application.

n) If the visit includes an IMP application.

o) Actigraphy will be done at some selected sites only.

p) Subjects will be asked to rate their “pain now” (current pain intensity on the NPRS) using the tablet computer at the site at the following time points: 15 mins before local anesthetic application and at 55 mins after IMP application.

BPI = Brief Pain Inventory; DMA = Dynamic Mechanical Allodynia; DN4i = Douleur Neuropathique 4 interview of the patient (Question 1 and Question 2); e-diary = electronic diary; exam = examination; HADS = Hospital Anxiety and Depression Scale; IMP = Investigational Medicinal Product; MOS = Medical Outcomes Study; NPRS=Numeric Pain Rating Scale; NPSI = Neuropathic Pain Symptom Inventory; PGIC = Patient Global Impression of Change; SF-36 = Short Form-36 Health Survey; TC = Telephone Contact; TSQM = Treatment Satisfaction Questionnaire for Medication; V = Visit; WPAI = Work Productivity and Activity Impairment.

2 TABLE OF CONTENTS

1	PROTOCOL SYNOPSIS	2
1.1	Trial design	2
1.1.1	Flow diagram summary of the trial	2
1.1.2	Brief description of the sequence and duration of all trial periods	3
1.2	Trial objectives and endpoints	3
1.3	Trial subjects – the population to be studied	6
1.3.1	Inclusion criteria	6
1.3.2	Exclusion criteria	7
1.4	Trial treatments	9
1.4.1	Investigational medicinal products	9
1.4.2	Prior and concomitant medications or therapies	10
1.5	Statistical analyses	11
1.5.1	Sample size rationale	11
1.5.2	Analysis populations	12
1.5.3	Statistical methods and analysis	12
1.5.4	Interim analysis	13
1.6	References cited in the protocol synopsis	13
1.7	Schedule of events	14
2	TABLE OF CONTENTS	19
2.1	LIST OF IN-TEXT TABLES	24
2.2	LIST OF IN-TEXT FIGURES	24
3	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	25
3.1	Abbreviations	25
3.2	Definition of terms	26
4	ETHICS	28
4.1	Independent ethics committees and institutional review boards	28
4.2	Subject information and informed consent	28
4.3	Informing the subject’s healthcare provider	28
5	INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE	29
5.1	Investigators and trial site personnel	29
5.1.1	Investigators	29
5.1.2	Trial site personnel assigned trial-related duties	29
5.2	Contract research organizations	29
5.3	The sponsor and sponsor’s personnel	30

6	INTRODUCTION AND TRIAL BACKGROUND	30
6.1	Introduction	30
6.2	Background to the IMP	30
6.3	Relevant non-clinical and clinical data	31
6.4	Trial rationale	31
6.5	Special agreements with regulatory authorities	31
7	TRIAL OBJECTIVES AND ENDPOINTS	31
8	TRIAL DESIGN	32
8.1	Discussion of the trial design	32
8.1.1	Rationale for the IMPs and the selected trial treatments	32
8.1.2	Rationale for the number and the frequency of visits/assessments	33
8.2	Benefit/risk analysis	34
9	SUBJECT SCREENING AND TRIAL DISCONTINUATION	36
9.1	Subject screening procedure	36
9.1.1	Handling of low recruitment	36
9.2	Inclusion/exclusion criteria	37
9.3	Subject discontinuation from the trial or from repeated IMP application	37
9.3.1	Subject discontinuation from the trial	37
9.3.2	Subject discontinuation from repeated IMP application	38
9.3.3	Procedure for the handling of discontinued subjects	38
9.3.4	Premature termination or suspension of the trial	39
10	TRIAL TREATMENTS	39
10.1	Investigational medicinal products	39
10.1.1	Identity and composition – Qutenza	39
10.1.2	Identity and composition – Low-dose capsaicin control	40
10.1.3	Preparation of IMP and precautions for IMP application	40
10.1.4	Cleansing gel to be used after IMP removal	41
10.1.5	Packaging and labeling	41
10.1.6	Delivery, storage, and disposal	41
10.2	Administration of IMPs	42
10.2.1	Mapping of the treatment area	42
10.2.2	Dosing (duration of application) and time of administration	42
10.3	Method of assigning subjects to treatment groups (randomization)	43
10.4	Blinding and unblinding	43
10.4.1	Methods of blinding	43

10.4.2 Methods of unblinding 44
10.4.3 Identification of IMP in emergency situations 44
10.5 Allowed and forbidden prior and concomitant medications or therapies 44
10.6 Documentation of drug accountability 45
11 COURSE OF THE TRIAL AND CONDITIONS 45
11.1 Course of the trial 45
11.1.1 Screening Period 45
11.1.2 Treatment Period (Core Phase) 46
11.1.3 Treatment Period (Extension Phase including Follow-up) 50
11.2 Examination hierarchy and time windows 52
11.3 Conditions during the trial 52
11.3.1 Medical care 52
11.3.2 Counseling of women of reproductive age and breast-feeding women 52
11.4 Subject trial cards 53
11.5 Provisions of any additional care of subject after trial termination 53
12 TRIAL ASSESSMENTS 53
12.1 Collection of demographic data and other baseline characteristics 53
12.1.1 Demographic data 53
12.1.2 Relevant medical history and details of the surgery leading to PSNP 54
12.1.3 Prior and concomitant medication or therapies 54
12.1.4 Physical examination 54
12.1.5 Neurological/sensory examination 54
12.1.6 Douleur Neuropathique 4 assessment 55
12.1.7 Urine beta-human chorionic gonadotropin pregnancy test 55
12.1.8 Urine drugs of abuse test 55
12.2 Collection of efficacy data 56
12.2.1 Pain intensity (11-point NPRS) 56
12.2.2 Dynamic mechanical allodynia 56
12.2.3 Treatment area size 57
12.2.4 Medical Outcomes Study Sleep Scale 58
12.2.5 Patient Global Impression of Change 58
12.2.6 Neuropathic Pain Symptom Inventory 58
12.2.7 Brief Pain Inventory Question 9A to 9G 59
12.2.8 Short Form-36® Health Survey 59
12.2.9 Treatment Satisfaction Questionnaire for Medication 59
12.2.10 Hospital Anxiety and Depression Scale 59

12.2.11 Work Productivity and Activity Impairment questionnaire 60
12.2.12 Actigraphy Device 60
12.3 Collection of safety data 60
12.3.1 Adverse events 60
12.3.2 Vital signs 65
12.3.3 Physical examinations 65
12.3.4 Dermal assessments 65
12.3.5 Neurological/sensory examinations 65
12.3.6 "Pain now" (current pain intensity on the NPRS) related to the IMP application site 66
12.3.7 Data on occupational exposure 66
12.4 Appropriateness of measurements 66
12.5 Compliance 67
13 DOCUMENTATION OF TRIAL DATA 67
13.1 Case report forms 67
13.2 Subject-reported outcomes 68
13.3 Data management 68
13.4 Source data 68
13.5 Investigator's site file and the TMF 69
14 QUANTITATIVE ANALYSES 69
14.1 Sample size rationale 69
14.2 General description of statistical analyses 70
14.3 Analysis populations (analysis sets) 70
14.4 Analysis of subject disposition 70
14.5 Analysis of demographic data and other baseline characteristics 70
14.6 Analysis of efficacy data 70
14.6.1 Multiple testing strategy 70
14.6.2 Analysis of the primary endpoint 72
14.6.3 Analysis of the secondary endpoints 74
14.6.4 Handling of intercurrent events and missing data 77
14.6.5 Subgroup analyses 78
14.7 Analysis of safety data 78
14.7.1 Analysis of adverse events 78
14.7.2 Analysis of vital signs 79
14.7.3 Analysis of dermal assessment 79
14.7.4 Analysis of neurological/sensory examination 79
14.7.5 Analysis of "pain now" related to the IMP application site 79

14.8	Interim analysis	79
15	QUALITY SYSTEM, AUDIT, AND INSPECTION	80
15.1	Quality system	80
15.2	Data quality assurance	80
15.3	Inspections	80
16	GENERAL CONDITIONS AND AGREEMENTS	80
16.1	Insurance	80
16.2	Legal regulations	81
16.3	Contracts	81
16.4	Subject data and data protection	81
16.5	Public disclosure	82
16.6	Trial results reporting	82
16.7	Approval	83
16.7.1	Sponsor	83
16.7.2	Coordinating investigator	83
17	REFERENCES	83
18	APPENDIX	87
18.1	List of potentially important medical concepts – classified by System Organ Class	87
18.2	Other assessment tools	89
18.2.1	Douleur Neuropathique 4 interview	90
18.2.2	Medical Outcomes Study Sleep Scale	91
18.2.3	Patient Global Impression of Change	95
18.2.4	Neuropathic Pain Symptom Inventory	96
18.2.5	Brief Pain Inventory Questions 9A to 9G	99
18.2.6	Short Form-36 Health Survey	101
18.2.7	Treatment Satisfaction Questionnaire for Medication	106
18.2.8	Hospital Anxiety and Depression Scale	110
18.2.9	Neurological/sensory examination	111
18.2.10	Work Productivity and Activity Impairment questionnaire - for neuropathic pain	114
19	PROTOCOL AMENDMENTS	116
19.1	Protocol Amendment 01	116

2.1 LIST OF IN-TEXT TABLES

Table 1: Non-exhaustive list of examples of types of surgeries with resulting PSNP 7

Table 2: Non-exhaustive list of examples of types of surgeries/conditions not suitable for eligibility 8

Table 3: Reasons for compulsory and optional discontinuation of subjects from the trial 37

2.2 LIST OF IN-TEXT FIGURES

Figure 1: Flow diagram of the Screening Period (Day -19 to Day -1) and the Core Phase of the Treatment Period (Day 1 to Week 12) 2

Figure 2: Flow diagram of the Extension Phase of the Treatment Period including Follow-up Phase (Week 13 to Week 42) 2

Figure 3: Graphical illustration of the planned testing procedure 72

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 Abbreviations

Abbreviation	Explanation
ANCOVA	Analysis of Covariance
BPI	Brief Pain Inventory
COVID-19	Coronavirus disease 2019
CRO(s)	Contract Research Organization(s)
CRF	Case Report Form
DMA	Dynamic Mechanical Allodynia
DN4i	Douleur Neuropathique 4 interview part
DPN	Diabetic Peripheral Neuropathy
EFNS	European Federation of Neurological Societies
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HIV-PN	Human Immunodeficiency Virus-Peripheral Neuropathy
hr(s)	Hour(s)
IASP	International Association for the Study of Pain
ICD	International Classification of Disease
IEC(s)	Independent Ethics Committee(s)
IMP	Investigational Medicinal Product
IRB(s)	Institutional Review Board(s)
IRT	Interactive Response Technology system
MAR	Missing At Random
min(s)	Minute(s)
MMRM	Mixed-effects Model for Repeated Measures
MOS	Medical Outcomes Study
NeuPSIG	Neuropathic Pain Special Interest Group
NPRS	Numeric Pain Rating Scale
NPSI	Neuropathic Pain Symptom Inventory
OTC	Over-the-counter
PB	Privacy Board
PGIC	Patient Global Impression of Change
PHI	Protected Health Information
PHN	Postherpetic Neuropathy

Abbreviation	Explanation
PNP	Peripheral Neuropathic Pain
PSNP	Post-Surgical Neuropathic Pain
SAE(s)	Serious Adverse Event(s)
SAF	Safety Set
SAP	Statistical Analysis Plan
SF-36	Short Form 36 Health Survey
SOP(s)	Standard Operating Procedure(s) (used as synonym for all procedural documents)
TC	Telephone Contact
TEAE(s)	Treatment-Emergent Adverse Event(s)
TMF	Trial Master File
TRPV-1	Transient Receptor Potential Vanilloid-1
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States (of America)
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Standard hematological and biochemical abbreviations are not listed.

3.2 Definition of terms

Term	Definition
Applicable regulatory requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials with IMPs applicable in the region where the trial is conducted.
End of the trial	The trial-related end of the trial is defined as the date of last subject out. The subject-related end of trial is defined as date of last contact with the subject according to the protocol.
First subject in	Date of first screened subject.
First subject randomized	First subject that was randomized to IMP.
Investigational medicinal product	A generic term describing the products under investigation in this trial, i.e., Qutenza and low-dose capsaicin control.
Last subject out	Date of last contact with the last subject according to the protocol.
Patient	Person under a physician's care for a particular disease or condition.
Screened subjects	Subjects who signed an informed consent form.
Screening failures	Screened subjects who were not allocated to IMP.
Subject	Individual who participates in a clinical trial (healthy person or patient), either as a recipient of an IMP or as a control.
Topical system	Name of the dosage form in the US and synonymous with `patch'.
Treated subjects	Subjects with at least 1 administration of IMP.

Use of the terms “must” and “should”

When “must” is used, the action/item is always mandatory. Non-compliance with this instruction constitutes a protocol deviation.

When “should” is used, the action/item is recommended but not mandatory. Non-compliance with this instruction does not constitute a protocol deviation.

4 ETHICS

This trial will be conducted according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

This trial will be registered in public registries according to the applicable laws and requirements.

4.1 Independent ethics committees and institutional review boards

The relevant independent ethics committees (IECs) and institutional review boards (IRBs) for this trial will be provided with all documents required to fulfill their responsibilities. Any updates thereof will be provided according to GCP and applicable regulatory requirements.

Trial activities will only start when approval from the relevant IECs or IRBs is available.

Documentation of all involved IECs and IRBs will be maintained according to GCP and applicable regulatory requirements.

4.2 Subject information and informed consent

Before any trial-related procedure will be performed, freely given informed consent must be obtained.

The informed consent discussion, the information sheet (if used), and the informed consent form provided to subjects, must adhere to GCP and applicable regulatory requirements. The informed consent discussion with the subject must be performed by the principal investigator or an appropriately trained delegate. The information sheet and informed consent form agreed with the sponsor must be used. Prior to use, these documents must be approved by the relevant IECs or IRBs.

Subjects must be informed as soon as possible if new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information must be documented.

4.3 Informing the subject’s healthcare provider

In countries where applicable, and only if the subject agrees in writing in the informed consent form and is treated by a healthcare provider, e.g., general practitioner, the subject’s healthcare provider should be informed about the subject’s participation in the trial at trial screening. The healthcare provider should be informed about the trial code, the principal investigator’s name, and a contact (telephone) number at the trial site.

Any communication with the healthcare provider must be documented in the subject’s medical records or the investigator’s site file.

5 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

5.1 Investigators and trial site personnel

5.1.1 Investigators

There must be an investigator at each trial site. In different countries, there may be country-specific terminology used for the investigator role.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator. All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with subject care. Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

If applicable, country-specific coordinating investigator(s) will be defined who are responsible for the coordination of principal investigators at multiple trial sites in 1 country.

An international coordinating investigator will be defined who is responsible for the coordination of principal investigators at multiple trial sites in multiple countries. Documentation of all responsibilities assigned to the international coordinating investigator must be maintained according to GCP and applicable regulatory requirements.

5.1.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

5.2 Contract research organizations

Contract research organizations (CROs; commercial, academic or other, e.g., central laboratory facilities, trial supply management provider, e-diary provider) may be contracted by the sponsor to perform trial-related duties and functions. Documentation of all involved CROs must be maintained according to GCP and applicable regulatory requirements. Documentation of any delegation of responsibilities to CROs must be maintained in the trial master file (TMF).

All involved CROs must have implemented quality control and quality assurance processes and support the sponsor's quality control and quality assurance measures.

5.3 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

If non-sponsor monitors are involved in the monitoring of this trial, a list of all non-sponsor monitors including their full names, addresses, and responsibilities, must be maintained.

6 INTRODUCTION AND TRIAL BACKGROUND

6.1 Introduction

Chronic post-surgical pain is a problem worldwide. It is often overlooked or minimized, poorly treated (Schug et al. 2019), causes disability, and is associated with reduced quality of life and increased use of health care resources (Lavand'homme 2017b). Given that 312 million major surgeries are performed annually worldwide, the magnitude of the problem becomes obvious (Katz et al. 2019), and despite advances in surgical techniques the prevalence of chronic post-surgical pain is still high (Lavand'homme 2017b). Chronic post-surgical pain has become a health priority and has been included in the upcoming version of the International Classification of Disease, ICD-11 (Schug et al. 2019). Certain frequently performed surgical procedures have inherent risks of developing chronic post-surgical pain. These operations often involve damage to large peripheral nerves (Kehlet et al. 2006, Durkin et al. 2010). Neuropathic features occur in approximately 35% to 57% of patients with chronic post-surgical pain (Lavand'homme 2017a), a prevalence that varies according to the type of operation, e.g., post-thoracotomy (29%), post-mastectomy (31%), cesarean section (21.4%), saphenectomy (15.7%), inguinal hernia repair (11.4%), cholecystectomy (6.1%) (Dualé et al. 2011, Haroutiunian et al. 2013, Pickering et al. 2017).

PNP such as PSNP presents in a defined localized area of the body, with an area of pain usually related to the primary lesion. It is a type of neuropathic pain that is characterized by a temporal relationship to a known nerve injury (Freeman et al. 2019).

PSNP has consistent and circumscribed area(s) of maximum pain, associated with negative or positive signs of sensory disturbance in the innervation of the injured nerve, and/or spontaneous symptoms characteristic of neuropathic pain (Freeman et al. 2019, Mick et al. 2012).

6.2 Background to the IMP

Capsaicin is a highly selective agonist of transient receptor potential vanilloid-1 (TRPV-1). The TRPV-1 receptor is an ion channel-receptor complex expressed on small-diameter sensory neurons

(C- and Aδ-fibers), e.g., nociceptors in the skin which are specialized in the detection of painful or noxious stimuli.

Qutenza is an adhesive capsaicin dermal topical system that delivers a high concentration of synthetic capsaicin directly to the site of pain, where it induces reversible dermo-epidermal denervation and depletion of capsaicin-sensitive nociceptors (Lo Vecchio et al. 2018), and enables the effective treatment of PNP conditions.

6.3 Relevant non-clinical and clinical data

For a detailed summary of relevant non-clinical and clinical experience, see the current edition of the Qutenza investigator's brochure.

6.4 Trial rationale

Qutenza has been proposed as a treatment for PNP in patients with a localized painful neuropathy (Treede et al. 2013).

In the regions where the trial is planned to be performed, Qutenza is authorized for the following indications:

EU + UK: treatment of PNP in adults either alone or in combination with other medicinal products for the treatment of pain.
US: in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet.

South Africa: the treatment of PNP associated with PHN in adults and human immunodeficiency virus (HIV) associated neuropathy in adults.

Qutenza has been shown to decrease pain and to be safe in approximately 1800 subjects with post-surgical and post-traumatic neuropathic pain (mostly clustered as post-traumatic nerve injury), who were included in Phase IV interventional trials and non-interventional studies (e.g., Maihöfner and Heskamp 2014, Haanpää et al. 2016, Gálvez et al. 2017, Mankowski et al. 2017, Lantéri-Minet and Perrot 2019, Hansson et al. 2018; for details on effectiveness and safety results, see the current version of the Qutenza investigator's brochure).

The purpose of this Phase III trial is to confirm the efficacy and safety of Qutenza, applied once or repeatedly within a time period of up to 10 months, for 60 mins, in subjects with moderate to severe PSNP. Moreover, the purpose of the trial is to explore a flexible dosing scheme with a minimum interval of 8 weeks between Qutenza applications after the second application.

6.5 Special agreements with regulatory authorities

None.

7 TRIAL OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are given in Section 1.2.

8 TRIAL DESIGN

8.1 Discussion of the trial design

PSNP, a subtype of chronic post-surgical pain that is caused by damage to one or more nerves usually during surgery or in the peri-surgical period, is as such reflected in the recent International Association for the Study of Pain (IASP) recommendations and World Health Organization's (WHO) ICD-11 (Scholz et al. 2019; Schug et al. 2019). Inclusion Criteria 4, 5, and 6, and the use of the DN4i as a screening tool will support the identification of eligible subjects suffering from probable or definite moderate to severe PSNP.

The eligible population will include both treatment-naïve subjects, and subjects who continue to suffer from moderate to severe pain while on a stable analgesic treatment for their PSNP. This population represents the population in scope for this medication.

The dose selection is expected to be effective based on previous trials in other PNP conditions such as PHN, HIV peripheral neuropathy (HIV-PN), and DPN (see Section 8.2). The frequency of administration is 12 weeks after the first administration to allow for consistent assessment of the primary endpoint across all subjects. Thereafter, additional applications can occur as pain re-occurs, but not more frequently than every 8 weeks. Experience with an 8-week Qutenza treatment interval has been gained previously in the PACE trial (Vinik et al. 2016). This treatment interval was found to be effective and well tolerated.

A low-dose capsaicin topical system was selected as a control treatment because it is expected to cause a perceptible local sensation; thereby preserving the trial blind (see Section 8.1.1).

To ensure that the trial fulfils regulatory requirements of an adequate and well-controlled trial, a double-blind, randomized, controlled, parallel-group design was chosen to avoid bias in parameter assessment.

A 12-week Core Phase was chosen for the evaluation of the primary efficacy endpoint (i.e., the change from baseline to the weekly average score of Week 12 in the 24-hr average pain intensity) as well as for the evaluation of the effect of Qutenza on PSNP and/or functional symptoms, and safety and tolerability, in line with current regulatory guidance for pivotal trials and other pivotal trials conducted to date in PSNP indications. The Core Phase will be followed by a blinded Extension Phase (Week 13 to Week 42) designed to confirm the long-term efficacy and safety of Qutenza in subjects with PSNP.

It is hypothesized that the severity of neuropathic pain symptoms is directly linked to the degree of impairment experienced, and therefore, the assessment and analysis of data from concepts like pain quality (as measured by assessment of size and intensity of DMA), sleep (MOS Sleep Scale) and the PGIC are important. Moreover, data from patient-related outcomes on physical functioning, mood, health-related quality of life, and work productivity, will be collected.

8.1.1 Rationale for the IMPs and the selected trial treatments

In the US, the currently approved dosing regimen for subjects with PHN is a single, 60-min application of up to 4 topical systems. Treatment with Qutenza may be repeated every 3 months or as warranted by the return of pain (not more frequently than every 3 months).

In this trial, up to 4 topical systems of IMP will be applied in one application (i.e., one treatment) for 60 mins to the treatment area. The IMP will remain on the skin for 60 mins irrespective of the body area treated. A period of 60 mins was found to be effective and safe on feet (HIV-PN, DPN) and other body areas (PHN) and was found to be well tolerated in randomized controlled trials (Backonja et al. 2008, Simpson et al. 2017, Vinik et al. 2016). To ensure consistency of application duration in the trial, all treated body areas will therefore be treated with IMP for 60 mins. Prior to the initial IMP application, the treatment area will be pre-treated with a topical anesthetic. The second application will be at least 12 weeks after the first application. Subsequent IMP applications will be at least 8 weeks after the previous application. These intervals were chosen because repeated application of Qutenza based on the clinical need and the recurrence of pain was well tolerated in reported trials with repeated application of Qutenza using intervals between applications of 6 weeks to 9 weeks for periods of up to 1 year (Backonja et al. 2010, Vinik et al. 2016, Gálvez et al. 2017).

Qutenza is a matrix topical system that contains a lipogel with highly concentrated capsaicin dissolved in glycol ether. Using a silicon adhesive, the topical system brings capsaicin into contact with the skin surface (Babbar et al. 2009). While altering the conditions for skin penetration, use of this adhesive ensures reliable skin contact during the application period and confines capsaicin penetration to the application site. The high initial capsaicin concentration in the lipogel (640 µg/cm^2) causes a distinct concentration difference between donor (topical system) and acceptor (stratum corneum) and ensures the formation of a reservoir in the stratum corneum (Wohlrab et al. 2015). After 30 mins, a depot of the active substance was detected in the stratum corneum, which remained fairly constant in all settings even after longer application times. Over time, the penetration rate increases slightly. Under physiological *in vitro* conditions (32°C), thick skin develops a larger reservoir in the stratum corneum and slightly higher concentrations in the vital epidermis than thin skin (Wohlrab et al. 2015).

The low-dose capsaicin topical system (capsaicin 0.04%, 3.2 µg/cm^2) was selected as control treatment, because it is expected to cause a perceptible local sensation, thereby preserving the blind, without producing demonstrable changes in nerve fiber density or sensory function (Backonja et al. 2008, Irving et al. 2011).

8.1.2 Rationale for the number and the frequency of visits/assessments

Depending on the need and time-interval for re-treatment of the subject (see Section 1.4.1), the trial comprises between a total of at least 8 scheduled visits (6 site visits and 2 telephone call visits) in the case of no retreatment, and a total of 14 scheduled visits (8 site visits and 6 telephone call visits) in the case of assumed 8-week re-treatment intervals.

There will be a Screening Visit (Visit 1) to ensure eligibility of the subject. Following the Baseline Phase (Day -7 to Day -1), eligible subjects will be randomly allocated to treatment at the Randomization Visit (Visit 2) and baseline values for the efficacy and safety parameters to be examined in the trial will be recorded. To monitor efficacy, safety and tolerability aspects of the treatment, data will be collected at IMP application visits and at Telephone Contact (TC) Visits during the first 4 weeks after IMP application. Further TCs without data collection for potential scheduling of IMP application take place at least every 4 weeks until the next Site Visit. In case no further IMP applications take place after V6, an obligatory Interim Site Visit is scheduled in week 22 +/-14 days for data collection. There will be shorter intervals for TC visits to monitor efficacy,

safety and tolerability aspects of the treatment (2 weeks and 4 weeks) in the Core Phase up to Week 12 (data relevant for the primary endpoint) and an interval of 4 weeks during the Extension Phase ending at the Final Visit. Visits in the Extension Phase are scheduled to be flexible depending on subjects´ preferences for re-treatment at 8- or 12-week intervals. The last application must take place at the latest at Week 40 and the next visit has to take place not earlier than 14 days later. The trial will end with the Final Visit at Week 42 to conclude data collection and adverse event reporting.

A combination of visits at site and as telephone calls is considered appropriate to collect trial data, monitor subjects' safety and to support subjects' compliance with the use of the e-diary.

8.2 Benefit/risk analysis

Benefits

A positive evaluation of the efficacy of Qutenza has resulted in marketing authorizations being granted for its use "in adults for the treatment of neuropathic pain associated with PHN and for neuropathic pain associated with DPN of the feet" in the US and for "treatment of PNP in adults either alone or in combination with other medicinal products for the treatment of pain" in the EU.

Treatment with Qutenza has resulted in significant pain relief in subjects with different PNP conditions (e.g., Backonja et al. 2008, Simpson et al. 2017, Vinik et al. 2016). In addition, open-label trials of Qutenza (e.g., Maihöfner and Heskamp 2014, Haanpää et al. 2016, Mankowski et al. 2017, Gálvez et al. 2017, Hansson et al. 2018, Lantéri-Minet and Perrot 2019) including approximately 1800 subjects with post-surgical and post-traumatic neuropathic pain (mostly clustered as post-traumatic nerve injury) indicated that the safety and pain relief profiles in this patient population were comparable to those seen in double-blind controlled trials. These data are suggestive of the efficacy of Qutenza for PSNP, an indication for which there is currently an unmet medical need for additional treatments. Based on the available data, Qutenza is expected to show good safety and tolerability in this trial in subjects with PSNP.

Risks

In subjects and patients with PNP exposed to Qutenza, beyond transient application site reactions (e.g., erythema, pain) which may affect up to 60% of the treated population, no further common adverse reactions are expected. The reported adverse reactions were mostly transient, self-limiting, and usually mild to moderate in intensity. This safety profile reflects the limited and transient systemic capsaicin exposure which occurs with Qutenza application.

Across all trials and all indications, blood pressure increased on the day of treatment during topical system application to the skin, with larger increases seen in the Qutenza group compared to the control group. Blood pressure in both Qutenza and control groups gradually decreased after topical system removal. The highest increases in blood pressure were seen towards the end of the topical system application period; the average maximum change in systolic and diastolic blood pressure did not exceed +18 mmHg and +11 mmHg, respectively, in any treatment group. Considering that these observed increases in blood pressure might be linked to pain caused by the application and that the subjects' susceptibility to pain may vary significantly, these increases are hard to predict. Therefore, blood pressure will be monitored during and after application of Qutenza in this trial.

For subjects with unstable or poorly controlled hypertension or a history of cardiovascular disease, the risk of adverse cardiovascular events due to the potential stress of the procedure should be considered prior to initiating Qutenza treatment.

Temporary reduction of neurosensory function (e.g., temperature sensation) may occur after treatment with Qutenza. Although a theoretical risk of a persistent reduction or loss of neurosensory function following repeated Qutenza treatment cannot be excluded, currently available data show limited evidence for persistent neurological impairment.

Throughout all clinical trials, exposure to Qutenza was not associated with meaningful changes in clinical chemistry and hematology values, which is consistent with the limited and transient systemic capsaicin exposure which occurs with Qutenza application.

Accidental exposure to capsaicin (manifesting as skin, respiratory tract, and/or eye irritation) was observed infrequently in subjects during the trials. During the post-marketing period, healthcare professionals applying the topical system were more commonly affected by accidental exposure than the patients. The majority of exposed individuals experienced short-term symptoms that fully recovered, with respiratory symptoms reported most commonly. Protective measures (mask, nitrile gloves, protective glasses, ventilation of the treatment room) and appropriate handling are deemed sufficient to minimize accidental exposure (see Section 10.1.3 for detailed instructions). Trial site staff will be trained on the handling of IMP to minimize the risk of accidental exposure.

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

Topical anesthetics (e.g., lidocaine 4%, lidocaine 2.5%/prilocaine 2.5%) pose the following risks: irritation, redness, itching, rash, burning sensation, pruritus, erythema, edema, warmth, pallor and abnormal sensation at the site of treatment, corneal irritation, and potential abrasion after accidental eye exposure. Less common side effects may include blurred vision, dizziness or drowsiness, difficulty breathing, trembling, chest pain, irregular heartbeat, or an allergic or anaphylactoid reaction (characterized by urticaria, angioedema, bronchospasm, and shock). Should any of these less common side effects develop, emergency medical attention should be sought immediately.

The topical anesthetic lidocaine 2.5%/prilocaine 2.5% should not be used in subjects 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 subjects with anemia (see e.g., EMLA® FDA prescribing information, last updated on Nov 13, 2019).

Additional information may be obtained from the product information sheets accompanying each local anesthetic and medication.

Beyond the risks described above, there are no other trial-related risks, e.g., due to the use of invasive or non-standard procedures.

Risks relating to the COVID-19 pandemic

Based on the clinical experience with Qutenza, which is applied topically, it is not considered to affect the patient's health status in such a way that the susceptibility to COVID-19 disease would be increased beyond the basic susceptibility of the individual patient based on the prevailing medical condition and comorbidities.

Before patients are enrolled into the trial, a proper eligibility assessment is performed including assessment of their general health status. Patients will be excluded if they meet any criteria that could affect their underlying condition and susceptibility to COVID-19 (see Exclusion Criteria 10 to 14).

The patient's personal visits to the sites are reduced to a minimum to ensure scientific validity of the trial by adhering to the essential endpoint assessments. Frequent telephone contacts or more extensive telephone visits are implemented to lower the burden of the patients and to avoid unnecessary travel. During the Extension Phase of the trial, the patient returns to the site only for re-application of the IMP, or, in case no further IMP applications take place, one time at the midpoint of the Extension Phase to keep the patient in the trial and thus to support scientific validity of the outcome of the trial.

Benefits/risks conclusion

Overall, Qutenza has been shown to be safe and effective across different PNP conditions. Qutenza was also shown to be effective and safe in approximately 1800 subjects with post-surgical and post-traumatic neuropathic pain (mostly clustered as post-traumatic nerve injury). Based on the available data, Qutenza is expected to show similar safety and efficacy in confirmatory trials in subjects with PSNP.

The risks related to participation in this trial are considered acceptable given the opportunity to develop an effective treatment for PSNP, where there is an unmet medical need for reliable treatment.

The risk for SARS-Cov-2 exposure and COVID-19 disease is unlikely impacted or increased by participation in this clinical trial.

9 SUBJECT SCREENING AND TRIAL DISCONTINUATION

9.1 Subject screening procedure

Subjects will be pre-screened to identify those who could potentially be included in the trial. Potentially eligible subjects will be asked to provide written informed consent.

The selection of trial subjects will be monitored closely by the sponsor to ensure a balanced representation of different type of surgeries in the trial. The subjects' eligibility review by the investigator will be supported by an external adjudication committee consisting of independent clinical expert(s) to ensure that only suitable subjects are included in the trial based on inclusion and exclusion criteria. Specifications about the setup and operational details of the adjudication committee will be described in a separate document.

If required by applicable regulatory requirements, the principal investigator must keep suitable logs of the subject pre-screening procedure.

9.1.1 Handling of low recruitment

Trial sites with a low recruitment rate and/or which persistently deviate from the protocol may be required by the sponsor/coordinating investigator/sponsor's authorized delegate to stop further recruitment at once or to cease participation in the trial.

An activated site will be considered to have a low recruitment rate if it has not randomized a subject to treatment within 12 weeks after medication availability at site.

9.2 Inclusion/exclusion criteria

The trial population must comply with the inclusion/exclusion criteria given in Section 1.3. Subjects will only receive IMP if documentation is available showing that they comply with these criteria.

9.3 Subject discontinuation from the trial or from repeated IMP application

9.3.1 Subject discontinuation from the trial

Once a subject is screened in this trial, whilst protecting subject safety, the trial site should make every effort to retain the subject for the planned duration of the trial. If subjects are not eligible for randomization to IMP, they must be classified as screening failures and be discontinued from the trial.

Reasons for compulsory and optional discontinuation of subjects from the trial are given in Table 3.

Table 3: Reasons for compulsory and optional discontinuation of subjects from the trial

	Discontinuation from trial	
	Compulsory	**Optional**
Screening failure (i.e., subject was not randomized to treatment due to failure to meet inclusion or exclusion criteria and did not receive IMP).	X	
Subject withdrawal of consent (the reason for withdrawal must be specified).	X	
Subject's death.	X	
Subject lost to follow-up (i.e., no further contact with the subject is possible).	X	
Sponsor decision to discontinue the subject.	X	
Sponsor and/or regulatory/ethical body decision to terminate the trial.	X	
Sponsor and/or principal investigator decision to terminate the trial at an individual trial site.	X	
Adverse events.		X
Lack of efficacy.		X
Technical reasons (e.g., site is no longer able to function or participate in the trial, and the subject is too remote from other site locations).		X
Other reasons.		X

The principal investigator may decide to discontinue a subject from the trial if, in their opinion, the discontinuation is justified in the interest of subject safety or due to a change in the benefit/risk assessment for the subject.

A subject may withdraw consent at any time.

In case subjects wish to discontinue from the trial during the double-blind Treatment Period, the investigator should encourage subjects to stay in the trial and to continue their pain assessments at least until the end of Week 12 (Visit 6, Day 84). All planned procedures for the end of treatment should be performed (i.e., a final visit as described in Section 1.7 for Final Visit).

9.3.2 Subject discontinuation from repeated IMP application

The principal investigator may decide against repeated IMP application if it is considered to pose an undue risk to the subject, e.g., due to adverse events, vital signs.

Repeated application is not allowed if any of the following criteria are met:

- Pregnancy.
- Development of hypersensitivity to the IMP.
- Lack of tolerance to the IMP application, as assessed by the investigator.

9.3.3 Procedure for the handling of discontinued subjects

9.3.3.1 Handling of subjects who discontinued from the trial

The principal investigator must document any discontinuation of a subject and inform the sponsor. Where applicable and according to regulations, the relevant IECs or IRBs must be informed with a detailed written explanation.

The following must be done for all discontinued subjects, including screen failure subjects and subjects who withdrew consent:

- Document all demographic data including the date of signing the informed consent form.
- Document all new, and update documentation of ongoing, adverse events (both serious and non-serious).
- Document the date and main reason for discontinuation from the trial (including all inclusion/exclusion criteria not met for screen failure subjects).
- For subjects withdrawing consent, document the date and time of withdrawal.

For discontinued subjects who received IMP, the following should also be done:

- Ensure that all data collected until the time of discontinuation are transferred to the CRF.
- Final drug accountability must be performed.
- Ensure that any dispensed e-diaries are returned.
- If possible and the subject agrees (documented in writing), perform all tests as defined for the end of treatment (i.e., the final visit as described in Section 1.7 for Final Visit).
- Complete any other trial-related formalities, e.g., those related to discharge from the trial site.

9.3.3.2 Handling of subjects discontinued from repeat application of IMP but not from the trial

For subjects who do not receive repeat application of IMP, all other procedures and scheduled visits described in the protocol should be completed for their own safety and to preserve the integrity of the trial.

9.3.3.3 Replacement of subjects

Subjects will not be replaced.

9.3.4 Premature termination or suspension of the trial

The trial will be prematurely terminated or suspended in the event of any of the following:

- IRB or IEC decision.
- Regulatory authority decision.
- Sponsor decision, based on a change in the benefit/risk ratio of the trial.

The relevant IECs or IRBs, the regulatory authorities, or the sponsor alone or in conjunction, have the power to make a binding decision to prematurely terminate or suspend the trial at any or all trial sites. In addition, for an individual trial site, this decision can be made by the principal investigator.

The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigator(s), the relevant IECs or IRBs, the relevant regulatory authorities, or the sponsor/the sponsor's authorized delegate, as applicable).

In addition, if the principal investigator decides to terminate or suspend the trial at the trial site, they must promptly inform the subjects, ensure appropriate follow-up for any screened or randomized subjects, and provide the relevant IECs or IRBs and the sponsor or the sponsor's authorized delegate, as applicable, with a written explanation of the termination or suspension.

The coordinating investigator must be informed immediately if the trial is prematurely terminated or suspended.

10 TRIAL TREATMENTS

10.1 Investigational medicinal products

10.1.1 Identity and composition – Qutenza

Name:	Qutenza
International non-proprietary name:	Capsaicin
Active substance:	Capsaicin
Dose (strength):	Capsaicin 179 mg or capsaicin 640 µg/cm^2 of topical system (8% w/w). Each topical system is 14 cm by 20 cm (280 cm^2)
Supplier:	Averitas Pharma, Inc.

For further information about the identity and composition of the IMP, see the Qutenza investigator's brochure.

10.1.2 Identity and composition – Low-dose capsaicin control

Name:	Low-dose capsaicin control
International non-proprietary name:	Capsaicin
Active substance:	Capsaicin
Dose (strength):	Capsaicin 0.9 mg or capsaicin 3.2 µg/cm^2 of topical system (0.04% w/w). Each topical system is 14 cm by 20 cm (280 cm^2)
Supplier:	Averitas Pharma, Inc.

10.1.3 Preparation of IMP and precautions for IMP application

The following precautions, including those described in the Qutenza investigator's brochure, should be followed to minimize accidental exposure to capsaicin when handling the IMP, i.e., Qutenza and low-dose capsaicin control topical systems.

- Only physicians or qualified healthcare professionals under the close supervision of a physician should administer the topical systems.
- Topical systems should be applied in a well-ventilated area.
- Nitrile gloves should be worn at all times while handling the topical systems and cleaning the treatment area. Latex gloves should NOT be worn as they do not provide adequate protection.
- The use of a mask and protective glasses is recommended, particularly during application and removal of the topical system. These precautions should be taken to avoid unintentional contact with the topical systems or other materials that have come in contact with the treated areas. This may result in transient erythema and burning sensation (with mucous membranes being particularly susceptible), eye pain, eye and throat irritation, and coughing.
- Topical systems should not be held near eyes or mucous membranes.
- If necessary, hairs in the affected area should be clipped to promote topical system adherence (do not shave).
- The treatment area should be washed gently with soap and water. Following hair removal and washing, the skin should be dried thoroughly.
- Prior to IMP application, the treatment area will be pre-treated with a topical anesthetic according to local practice (e.g., for 60 mins with topical lidocaine 4% or lidocaine 2.5%/prilocaine 2.5% cream). Following pre-treatment, the skin should be washed and dried thoroughly.
- The topical systems can be cut to match the size and shape of the treatment area. The topical systems should be cut prior to removal of the release liner.
- The release liner should NOT be removed until just prior to application. There is a diagonal cut in the release liner to aid in its removal. A section of the release liner should be peeled and folded, and the adhesive side of the printed topical system placed on the treatment area.

The topical system should be held in place. The release liner should be slowly and carefully peeled from underneath with one hand while the topical system should simultaneously be smoothed onto the skin with the other, to ensure that there is complete contact between the topical system and the skin, with no air bubbles and no moisture.

- To ensure the topical system maintains contact with the treatment area, stretchable socks or rolled gauze may be used.
- The topical systems should be removed gently and slowly by rolling them inward to minimize the risk of aerosolization of capsaicin. For disposal, see Section 10.1.6.
- After topical system removal, cleansing gel should be applied liberally to the treatment area and left on for at least 1 min. Thereafter, cleansing gel should be wiped off with dry gauze to remove any remaining capsaicin from the skin, before the treated skin is washed gently with soap and water.

10.1.4 Cleansing gel to be used after IMP removal

Cleansing gel must only be used after the removal of IMP (i.e., not before IMP application). The cleansing gel is composed of macrogol 300, carbomer, purified water, sodium hydroxide (E524), disodium edetate, and butylhydroxyanisole (E320).

10.1.5 Packaging and labeling

The IMP will be supplied as a topical system stored in a paper-coated aluminum foil sachet with an acrylnitrile-acrylic acid copolymer heat seal layer. The IMP packs will contain 1 topical system of IMP. A 50 g-tube of cleansing gel will be provided to the sites in each kit along with the topical systems.

For detailed information about packaging and labeling, see the specific documents (available on request).

10.1.6 Delivery, storage, and disposal

Storage conditions will be specified on the labels of the IMP. The IMP must be stored flat in the original sachet below 25ºC. The cleansing gel must be stored below 25ºC. The IMP must be stored in a secure place with restricted access and temperature monitoring according to local regulations.

Used and unused topical systems, and all other materials that have been in contact with the treated area, should be disposed of immediately after use by sealing them in a polyethylene medical waste bag and disposing them in accordance with local biomedical waste procedures.

Delivery (shipping), return, and disposal of the IMP must be performed in accordance with instructions provided by the sponsor, e.g., clinical distribution specifications (available on request).

Controls will be implemented at the trial site to ensure documented compliance with these requirements.

10.2 Administration of IMPs

10.2.1 Mapping of the treatment area

The treatment area will be mapped by the investigator or other trained personnel at the Screening Visit (Visit 1), the Randomization Visit (Visit 2), at Visit 6 and all other visits with IMP application, and at the Final Visit.

The treatment area will be comprised of the area identified by the subject as the usually most painful area(s) (Section 12.2.3.2) and/or the area characterized by DMA (pain in response to a cotton swab, Section 12.2.2) and/or the area of pinprick hyperalgesia (Section 12.2.3.3). Each area will be identified separately.

- If no DMA and/or pinprick hyperalgesia is observed, then the usually most painful area will be mapped and treated.
- If DMA and/or pinprick hyperalgesia is present, then the usually most painful area as indicated by the subject plus any additional area(s) of DMA and/or pinprick hyperalgesia beyond the usually most painful area will be treated, up to a maximum of 1120 cm^2.

Prior to marking the treatment area, the subject should be placed in a comfortable recumbent or semi-recumbent position, which will be the same position in which the subject is placed during the IMP application. The identified area will be marked with a solid line using a skin marking pen and traced onto plastic transparency sheet or tracing paper. Each subject's tracing of the treatment area will be labeled ("treatment area", visit number, subject number, tracer's initials, and date).

The treatment area tracing will be transferred onto the IMP topical systems for application to the subject's skin (Section 12.2.3.2). The size of the topical systems corresponds to the treatment area tracing at each application except for the second IMP application, when the size of the topical systems (application area) will correspond to the treatment area identified at the first IMP application (Visit 2). If the treatment area identified at the second IMP application is larger than the treatment area identified at Visit 2, then the larger treatment area will be used to determine the size of the topical systems for the second IMP application.

The detailed procedures at the application visit(s) are described in Section 11.1.2.1.3.

At the Screening Visit, the treatment area will be marked and assessed with regard to Inclusion Criterion 7; no transfer onto IMP topical systems will be performed at this visit.

10.2.2 Dosing (duration of application) and time of administration

The 2 IMPs (Qutenza and low-dose capsaicin control) and the timing of the initial IMP application and the re-application(s) during the course of the trial are described in Section 1.4.1.

At each application visit, the investigator (or delegate) will obtain a medication number via the interactive response technology system (IRT). The medication number will be used to select the correct package(s) of IMP to administer to the subject. Precautions in handling the IMP are described in Section 10.1.3. The detailed procedures at the application visit(s) are described in Section 11.1.2.1.3.

Up to 4 topical systems (1120 cm^2) of IMP will be applied for 60 mins to the treatment area.

10.3 Method of assigning subjects to treatment groups (randomization)

An IRT will assign a unique subject number to each subject at Visit 1.

Subjects who meet all inclusion criteria and who do not meet any of the exclusion criteria will be randomly assigned to 1 of the 2 treatment groups (Qutenza or low-dose capsaicin control) in a 1:1 ratio (Section 1.4.1).

Treatment assignment will be performed centrally at the Randomization Visit (Visit 2) via IRT prior to the first administration of IMP. A stratified block randomization will be performed by country/region with the stratification factors, intake of concomitant medication for treatment of PSNP (no/yes), and time since onset of pain after surgery (categories short duration [≤1 year] and long duration [>1 year]).

10.4 Blinding and unblinding

10.4.1 Methods of blinding

Randomization and blinding will be performed in accordance with the sponsor's (or authorized sponsor representative's) standard operating procedures (SOPs).

Qutenza and low-dose capsaicin control topical systems will not be distinguishable from each other in amount or shape of packaged IMP.

Given that the application of Qutenza or the low-dose capsaicin control often, but not invariably, results in pain and erythema, the following measures will be taken to maintain the blind:

- Instructions to the subject will stress that they may or may not experience pain during or after application of the topical system.
- The trial physician conducting the clinical assessments, and with access to the subjects' efficacy and safety data, will be independent of the physician or nurse responsible for IMP application and dermal assessment (e.g., trial nurse, subinvestigator).

Subjects and investigators will remain blinded until unblinding is performed after complete database lock at the end of the trial (after completion of the Extension Phase).

All persons involved in the conduct, data management, and analysis of the trial will be fully blinded to the subjects' treatments until database lock and unblinding of the 12-week data (Core Phase of the trial) have been completed.

Personnel at the sponsor and the CRO(s) who will have access to the unblinded data at subject level after completion of the Core Phase and before completion of the Extension Phase will be limited. Procedures will be implemented to guarantee the blinding of all personnel involved in the conduct of the Extension Phase. These procedures will be described in a Data Access Plan (see also Section 16.6).

Personnel in the clinical trial supply department of the sponsor (or authorized sponsor representative) will be unblinded during the trial according to the sponsor's SOPs.

Personnel in the responsible drug safety department of the sponsor (or authorized sponsor representative) will be unblinded according to the sponsor's SOPs, e.g., for regulatory requirements for the reporting of suspected unexpected serious adverse reactions.

10.4.2 Methods of unblinding

General unblinding will only take place after the trial has been completed and the complete database has been locked.

Except for single-subject unblinding in emergency situations, investigator unblinding will only be carried out after final database lock at the end of the trial.

Unblinding will be performed by the department of biostatistics at the sponsor (or authorized sponsor representative).

10.4.3 Identification of IMP in emergency situations

The investigator and the responsible drug safety department of the sponsor (or authorized sponsor representative) will receive appropriate methods for unblinding of single cases, i.e., IRT access to unblinding functionality.

The code may be broken when it is necessary and in that subject's interest in order to identify the IMPs given, e.g., if knowledge of the identity of the treatment group would lead to a different treatment by the investigator. In addition, within the responsible drug safety department of the sponsor (or authorized sponsor representative), the code may be broken for regulatory reporting, medico-scientific assessment of adverse events, or on request of the responsible qualified person for pharmacovigilance.

For every subject whose blind was broken, the following information must be documented on an "unblinding an individual subject form":

- The reason for, the date, and time of unblinding.
- The person(s) informed of the treatment randomization must be identified.

In order to maintain the double-blind nature of the trial, the randomization of IMPs for the subject must not be communicated further unless required for the surveillance of the subject or, if necessary, for urgent risk-to-benefit re-evaluation and/or measures for urgent risk minimization.

If required by local regulations, it may be that the IEC, IRB, or the coordinating investigator must be informed.

10.5 Allowed and forbidden prior and concomitant medications or therapies

A list of all allowed or forbidden prior or concomitant medications or therapies is provided in Section 1.4.2. The allowed and forbidden concomitant medications or therapies will be explained to the subject by the investigator.

In emergency situations, subjects should be treated according to standard medical practice (see Section 11.3.1).

For information about potential drug-drug interactions, see the Qutenza investigator's brochure.

10.6 Documentation of drug accountability

The principal investigator must ensure that documentation is maintained for the receipt, inventory, use, and destruction or return of unused, used, or partially used packages of IMPs. The documentation must include IMP name, dates, quantities, subject numbers, batch/serial numbers or other identification numbers, expiration dates, and the means to identify the subject to whom it was given.

Documentation must be maintained for the checking of drug accountability.

Before the unused IMPs supplied to the trial site are returned or destroyed, the principal investigator must allow sponsor representatives to perform drug reconciliation. The entries in the documentation will be compared with the returned and residual IMPs, and the administration/intake as documented in the CRF, with clarification of any discrepancies or inconsistencies.

11 COURSE OF THE TRIAL AND CONDITIONS

See Section 1.1.1 for flow diagram summaries of the trial and Section 1.7 for a schedule of events.

11.1 Course of the trial

11.1.1 Screening Period

The Screening Period consists of the Screening Visit and the Baseline Phase.

11.1.1.1 Screening Visit (Visit 1, Day -19 to Day -7)

The following evaluations will be performed:

- Obtain written informed consent before any trial-related procedures are performed.
- Record demographic data (for details, see Section 12.1.1).
- Record medical history (including relevant surgical history leading to PSNP, e.g., date of surgery, location and type of surgery, and indication for surgery) and date of onset of pain after surgery. The documentation must be adequate for the reconstruction of the surgery, the scar, and affected dermatomes, e.g., by using a body map.
- Record prior and concomitant medications and therapies (for forbidden medication, see Section 1.4.2).
- Perform and record results of DN4i (Section 12.1.6) on the tablet computer at the site.
- Perform and record physical examination outcome (for details, see Section 12.1.4).
- Perform and record neurological/sensory examination (for details, see Section 12.3.5).
- Record vital signs (for details, see Section 12.3.2).
- Perform DMA (Section 12.2.2). Map and trace the DMA area and record the pain intensity in response to the cotton swab stroke.
- Perform pinprick hyperalgesia assessment (Section 12.2.3.3).
- Map (mark and assess) the treatment area (Section 10.2.1) with regard to Inclusion Criterion 7; no transfer onto IMP topical systems will be performed at Visit 1.

- Perform dermal assessment (Section 12.3.4).
- From female subjects of childbearing potential, collect urine and perform a urine beta-human chorionic gonadotropin (ß-HCG) pregnancy test.
- Collect urine and perform the drug-of-abuse test.
- Check inclusion/exclusion criteria.
- Record adverse events.
- Perform training for the e-diary.
- Dispense the e-diary.
- Dispense the subject trial card.
- Ask subject to record 24-hr average pain intensity score in e-diary.
- Submit data to the adjudication committee for independent assessment of eligibility, as specified separately (Section 9.1).
- For selected sites only, hand-out the actigraphy device, as specified separately (Section 12.2.12).

11.1.1.2 Baseline Phase for pain assessment (Day -7 to Day -1)

During the Baseline Phase, subjects will record their average pain intensity for the previous 24 hrs (recall period) in the e-diary at home once daily in the evening (Section 12.2.1). According to Inclusion Criterion 6, at least 5 out of 7 pain ratings will be required to determine the baseline average pain score.

- After the Screening Visit and before Visit 2, check the subject's e-diary for compliance and, if necessary, remind the subject to perform and record daily pain intensity assessments.

11.1.2 Treatment Period (Core Phase)

The Core Phase (Day 1 to Week 12) of the Treatment Period includes Visit 2 (Randomization Visit) to Visit 6.

11.1.2.1 Randomization Visit (Visit 2)

11.1.2.1.1 Before randomization

- Record concomitant medications and therapies (for forbidden medication, see Section 1.4.2).
- Record adverse events.
- Perform physical examination, record changes to previous visit (for details, see Section 12.1.4).
- From female subjects of childbearing potential, collect urine and perform a urine ß-HCG pregnancy test.
- Collect urine and perform the drugs-of-abuse test.
- Perform and record neurological/sensory examination (for details, see Section 12.3.5).
- Perform DMA (Section 12.2.2). Map and trace the DMA area and record the pain intensity in response to the cotton swab stroke.

- Perform pinprick hyperalgesia assessment (Section 12.2.3.3).
- Mapping of the treatment area
  - Place the subject in the same position used during the marking of the treatment area at the Screening Visit. Verify the treatment area's location and size (Section 10.2.1).
  - The current boundaries of the treatment area must not be larger than a combined estimated total surface area of 1120 cm^2.
- Check inclusion and exclusion criteria, including assessment by independent adjudication committee (Section 9.1).
- Discontinue subjects from the trial, as screening failures, if they do not meet the eligibility criteria. If a subject is eligible except for Inclusion Criterion 6 (at least 5 pain ratings during the Baseline Phase), the subject may be rescheduled for Visit 2 (1 time only) after having received appropriate re-training in the use of the e-diary to ensure compliance.
- Ask the subjects who meet all eligibility criteria to complete the following questionnaires on the tablet computer at the site: NPSI, MOS Sleep Scale, BPI Question 9A to 9G, SF-36, HADS, and WPAI.
- For selected sites only, if subject is not eligible, collect the actigraphy device, as specified separately (Section 12.2.12).

11.1.2.1.2 Randomization

- If the subject is eligible, use the IRT to randomize the subject to IMP.

11.1.2.1.3 Procedures at IMP application

The IMP to be applied will be assigned via the IRT.

Record adverse events at any time before, during, and after IMP application.

Shortly before IMP application

Dermal assessment

- The physician or nurse responsible for IMP application and dermal assessment will examine the skin of the identified treatment area and determine the dermal assessment score 15 mins before application of the topical anesthetic. Skin integrity must be intact in order to proceed with treatment.

Clip hair, wash, dry treatment area

- If necessary, clip hairs in the affected area to promote topical system adherence (do not shave). Gently wash the treatment area with mild soap and water. Ensure that the skin is dried thoroughly following clipping and washing.

"Pain now" rating (current pain intensity on the NPRS)

- Ask the subject to rate the "pain now" related to the IMP application site 15 mins before local anesthetic application using the tablet computer at the site.

Vital signs

- Take blood pressure, heart rate, and respiratory rate 15 mins before IMP application.

Pre-treatment with topical anesthetic

- Prior to IMP application, pre-treat the treatment area with a topical anesthetic according to local practice (e.g., for 60 mins with topical lidocaine 4% or lidocaine 2.5%/prilocaine 2.5% cream). Following pre-treatment, gently wash the skin with mild soap and water, and ensure that the skin is thoroughly dried.

Preparation of topical systems

Important: Follow the precautions given in Section 10.1.3.

- There are 2 different sides to the topical system. The adhesive side of the topical system is covered by a diagonally-cut glossy release liner. The outer surface of the topical system is non-glossy. Therefore, take care to ensure the non-glossy side is up when laying out topical systems prior to trimming. Do not remove the release liner (glossy side) from topical systems until IMP application time.
- The topical systems can be cut to correspond to the size of the treatment area.

Application of IMP

Application of topical systems

Important: Follow the precautions given in Section 10.1.3.

- Place the subject in the same position used during the mapping of the treatment area at the Screening Visit.
- Only apply the topical systems to intact, unbroken skin.
- Remove the release liner and adhere the topical systems to the subject's treatment area. When treating feet, the topical systems can be wrapped around the whole circumference of the indicated area of the foot (i.e., top, side, and bottom), avoiding overlap of topical systems if possible.
- Once all topical systems are applied, record the application start time. The topical systems will be left on for 60 mins.
- If needed, a layer of dry conforming roll gauze may be wrapped over the area covered by the topical systems during treatment. If the treatment area is on the feet, it is recommended that a pair of lightweight stretchable socks are applied carefully over the topical systems on the soles of the subject's feet and worn through the IMP application period.

At 55 mins after the start of IMP application

- **Vital signs.** Take blood pressure, heart rate, and respiratory rate.
- Ask the subject to rate the "pain now" (current pain intensity on the NPRS) related to the IMP application site using the tablet computer at the site.

Measures for treatment-associated discomfort during IMP application

- If the subject reports more than mild pain during the topical system application (i.e., NPRS pain score ≥4), the application site will be cooled with a cool pack from the **refrigerator**, which should be replaced when the cooling effect dissipates, and a short-acting non-opioid analgesic may be administered to relieve treatment-associated pain/discomfort during the application procedure.

- If a subject cannot tolerate treatment-associated discomfort despite the use of pain medication and the use of cooling, the IMP will be removed, and the time of removal will be recorded in source notes and the CRF.

Removal of topical systems and cleansing of the treatment area

Important: Wear Nitrile gloves whenever handling topical systems. Follow instructions for protection in Section 10.1.3.

- After 60 mins, remove the topical systems slowly and gently. Roll the topical systems inward to minimize the risk of capsaicin contamination.
- When all topical systems have been removed, record the time of IMP removal.
- Apply cleansing gel to the treatment area (up to half a tube if the size of the treatment area is ≤560 cm^2, up to 1 tube if the size is >560 cm^2). Leave the cleansing gel on for at least 1 min, and then wipe it off with dry gauze or paper towels. Wash the area gently with soap and water and dry the skin.
- Immediately upon removal, dispose of all used topical systems, used gauze or paper towels, by sealing them in a medical waste bag and placing it in an appropriate medical waste container.

After IMP removal

Immediately after IMP removal

- **Dermal assessment**. The physician or nurse responsible for IMP application and dermal assessment will examine the skin of the treatment area and determine the dermal assessment score.

After IMP removal

- **Subject completion of the application visit**. Subjects will be discharged from the site when their condition is stable, as per clinical judgment. Subjects may remain under observation, if needed, until they are comfortable and ready for discharge.

Measures for treatment-associated discomfort after IMP removal

- After IMP removal, cool the application site with a cool pack from the **refrigerator** (not the freezer) and replace it when the cooling effect dissipates. Remove the cool pack 5 mins before the dermal assessments but continue to cool afterwards until the end of the visit. Cooling should be continued for at least 24 hrs after the IMP application.
- Short-acting (non-opioid) pain medication may be continued while the subject is in the clinic. Record medication name, time of usage, and total dose administered.
- Short-acting (non-opioid) pain medication is allowed for up to 5 consecutive days after the IMP application. Use has to be recorded in the CRF.

Telephone contact 1 day or 2 days after IMP application

- Check e-diary compliance before the telephone call and remind the subject to perform and record daily pain intensity assessments.
- Record concomitant medications and therapies.
- Record adverse events.

11.1.2.2 Visit 3, Visit 4 (telephone call), Visit 5 (telephone call)

- Check e-diary compliance and remind the subject to perform and record daily pain intensity assessments.
- Record concomitant medications and therapies. Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for PSNP separately.
- Record adverse events.
- Check the discontinuation criteria (Section 9.3.1).
- In case of trial discontinuation perform the Final Visit (see Section 11.1.3.3).

11.1.2.3 Visit 6 (End of Core Phase, Day 84)

Visit 6 must not occur before Day 84.

- Record concomitant medications and therapies (for forbidden medication, see Section 1.4.2). Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for PSNP separately.
- Record adverse events.
- Perform physical examination, record changes to previous visit (for details, see Section 12.1.4).
- Perform and record neurological/sensory examination (for details, see Section 12.3.5).
- Perform DMA (Section 12.2.2). Map and trace the DMA area and record the pain intensity in response to the cotton swab stroke.
- Perform pinprick hyperalgesia assessment (Section 12.2.3.3).
- Mapping of treatment area (Section 10.2.1).
- Ask the subjects to complete the following questionnaires on the tablet computer at the site: NPSI, PGIC, MOS Sleep Scale, BPI Question 9A to 9G, SF-36, TSQM, HADS.
- Check e-diary compliance and remind the subject to perform and record daily pain intensity assessments.
- Check the discontinuation criteria (Section 9.3.1).
- In case of trial discontinuation perform the Final Visit (see Section 11.1.3.3).
- Evaluate the need for IMP re-application (consider the criteria in Section 9.3.2).
- If the IMP is to be re-applied:
  - From female subjects of childbearing potential, collect urine and perform a urine ß-HCG pregnancy test.
  - Follow the procedures in Section 11.1.2.1.3.

11.1.3 Treatment Period (Extension Phase including Follow-up)

The minimum interval for IMP application starting at Visit 6 is 8 weeks. The Extension Phase (Week 13 to Week 42) of the Treatment Period includes further TC visits after 4 weeks (see Section 1.7). Further TCs without data collection but for potential scheduling of IMP application take place at least every 4 weeks until the next Site Visit. In case no further IMP applications take place after

V6, an obligatory Interim Site Visit is scheduled in week 22 +/-14 days for data collection (see Section 1.7).

11.1.3.1 TC Visit (telephone call)

- Check e-diary compliance and remind the subject to perform and record daily pain intensity assessments.
- Record concomitant medications and therapies. Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for PSNP separately.
- Record adverse events.
- Check the discontinuation criteria (Section 9.3.1).
- In case of trial discontinuation, arrange for a site visit and perform the Final Visit (see Section 11.1.3.3).

11.1.3.2 Site Visit/Interim Site Visit

- Record concomitant medications and therapies (for forbidden medication, see Section 1.4.2). Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for PSNP separately.
- Record adverse events.
- Check e-diary compliance and remind the subject to perform and record daily pain intensity assessments.
- Check the discontinuation criteria (Section 9.3.1).
- In case of trial discontinuation perform the Final Visit (see Section 11.1.3.3).
- Ask the subjects to complete the following questionnaires on the tablet computer at the site: NPSI, PGIC, MOS Sleep Scale, BPI Question 9A to 9G, SF-36, HADS.
- Evaluate the need for IMP re-application (consider the criteria in Section 9.3.2).
- If the IMP is to be re-applied:
  - Record vital signs 15 mins before local anesthetic application and at 55 mins after IMP application.
  - Perform dermal assessment 15 mins before local anesthetic application and immediately after IMP removal.
  - Ask subjects to rate their “pain now” 15 mins before local anesthetic application and 55 mins after the start of IMP application.
  - From female subjects of childbearing potential, collect urine and perform a urine ß-HCG pregnancy test.
  - Perform DMA (Section 12.2.2). Map and trace the DMA area and record the pain intensity in response to the cotton swab stroke.
  - Perform pinprick hyperalgesia assessment (Section 12.2.3.3).
  - Map the treatment area (Section 10.2.1).
  - Follow the procedures in Section 11.1.2.1.3.

Subsequent visits follow this schedule of TC visit and Site Visit until the Final Visit. If the last IMP application is at week 39 or later, the next visit has to take place not earlier than 14 days later and can be replaced by the Final Visit.

11.1.3.3 Final Visit or Early Termination Visit – independent of previous treatment intervals

- Record concomitant medications and therapies (for forbidden medication, see Section 1.4.2). Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for PSNP separately.
- Record adverse events.
- Perform physical examination, record changes to previous visit (for details, see Section 12.1.4).
- Perform and record neurological/sensory examination (for details, see Section 12.3.5).
- Perform DMA (Section 12.2.2). Map and trace the DMA area and record the pain intensity in response to the cotton swab stroke.
- Perform pinprick hyperalgesia assessment (Section 12.2.3.3).
- Mapping of treatment area (Section 10.2.1).
- From female subjects of childbearing potential, collect urine and perform a urine ß-HCG pregnancy test.
- Collect urine and perform the drugs of abuse test.
- Ask the subjects to complete the following questionnaires on the tablet computer at the site: NPSI, PGIC, MOS Sleep Scale, BPI Question 9A to 9G, SF-36, TSQM, HADS, and WPAI.
- Collect the e-diary.
- Collect the subject trial card.
- Collect actigraphy device from subject.

11.2 Examination hierarchy and time windows

All trial procedures not directly related to the IMP application (as described in Section 11.1.2.1.3) should be performed before the procedures related to the IMP application.

11.3 Conditions during the trial

11.3.1 Medical care

For any adverse events, a causal or symptomatic treatment according to standard medical practice should be provided, if deemed necessary, by the investigator. The medical care given to, and medical decisions made on behalf of, the subjects are the responsibility of a qualified physician.

See the guidance in the investigator’s brochure for precautions and the handling of emergencies.

11.3.2 Counseling of women of reproductive age and breast-feeding women

All women, including those with tubal ligation, will be considered to be of childbearing potential unless they have been postmenopausal for at least 2 years or have undergone a hysterectomy.

All women of childbearing potential must be counseled on the need to practice medically acceptable methods of birth control during the trial and on the importance of avoiding pregnancy.

Medically acceptable methods of birth control are methods with a failure rate (percentage of women experiencing an unintended pregnancy within 1 year of use of the method) of less than 1%, e.g., hormonal contraceptives or intra-uterine devices used according to the product's instruction for use, or double barrier method (male or female condom; diaphragm). The combination of 2 independent methods will result in multiplied failure rates per year, e.g., 0.63% for the concomitant use of a condom (with a 9% failure rate) and a diaphragm (with a 7% failure rate). Note: A female condom and a male condom must not be used together as friction between the 2 can result in either product failing.

Women will be counseled to contact the trial site staff immediately if pregnancy is suspected.

It is unknown whether capsaicin is excreted in human breast milk. Because capsaicin is rapidly cleared from the bloodstream after treatment and to minimize infant exposure, mothers will be asked to refrain from breast-feeding for 24 hours after topical system application.

11.4 Subject trial cards

Subjects who are screened in the trial will receive a subject trial card (the time of card distribution is given in Section 1.7). The trial card will list the following information:

- Name of the subject and a statement that he/she is currently participating in a clinical trial.
- Trial code.
- Dates of all individual visits.
- Name of the principal investigator for that trial site.
- Contact (telephone) number at the trial site.

The card will be collected at the subject's last visit.

11.5 Provisions of any additional care of subject after trial termination

After trial termination, subjects will be treated by their physicians according to the standard medical practice in the country concerned.

12 TRIAL ASSESSMENTS

12.1 Collection of demographic data and other baseline characteristics

For the timing of data collection, see the schedule of events (Section 1.7).

12.1.1 Demographic data

Demographic data to be collected and recorded for this trial include the date of signing the informed consent form, sex, race, ethnicity, age, weight, and height, where possible, according to local regulations.

Body mass index will be calculated automatically in the electronic CRF.

12.1.2 Relevant medical history and details of the surgery leading to PSNP

Relevant concomitant diseases or surgical interventions will be recorded in the CRF at the Screening Visit (Visit 1). Non-active pre-existing conditions will only be recorded if judged to be clinically relevant by the investigator.

Medical conditions controlled by medication will only be recorded if judged to be relevant by the investigator or if these could potentially give rise to an adverse event based on the pharmacology of capsaicin or based on the IMP application (e.g., allergy to plasters).

The date of the surgery leading to PSNP, the location and type of the surgery, and the indication for the surgery must be recorded on the separate page in the CRF. If possible, the subject's surgical records should be obtained and reviewed by the investigator to determine if there were any relevant complications or details that may impact the subject's eligibility in the trial. The date of onset of pain after surgery must also be recorded on this CRF page.

12.1.3 Prior and concomitant medication or therapies

All prior and concomitant medications, i.e., those requiring prescriptions (including oral contraceptives) and/or OTC medication used within 30 days before the Screening Visit and up to and including the Final Visit must be recorded in the CRF. Any change in dosage, regimen, or route must be recorded in the CRF as a new entry.

For concomitant medication, the trade name, dose, dose unit, frequency, route, reason for use, start date and stop date have to be recorded in the CRF. For any concomitant medication taken on IMP application visits, e.g., short-acting non-opioid analgesics for relief of application site pain or discomfort, the time of intake should also be recorded.

All therapies for PSNP used within 30 days before the Screening Visit and up to the end of the trial must be recorded in the CRF. Record any changes in PSNP-related background treatments or therapies and any newly-initiated medications or therapies for pain due to PSNP separately.

12.1.4 Physical examination

Physical examination should include assessments of the subject's general condition, skin, eyes, ears, nose and throat, mouth (including teeth and gums), head, neck, and thyroid, heart, lung, chest, abdomen, kidneys, liver, lymphatic, musculoskeletal, and neurological systems.

The physical examination will have a special focus on the post-surgical site and scar tissue. At the Screening Visit, the size of the scar will be documented, and whether the investigator considers the scar tissue to be normal or pathological. Any abnormality will be specified.

Prior to randomization, any clinically relevant findings from the physical examination will be documented as part of the medical history.

12.1.5 Neurological/sensory examination

The neurological/sensory examination, according to Gálvez et al. 2017, is described in Section 12.3.5.

12.1.6 Douleur Neuropathique 4 assessment

The DN4i questionnaire will be completed only at Visit 1 (Screening Visit). The outcome of this assessment is relevant for subject selection (Inclusion Criterion 4) and will be recorded in the tablet computer at the site.

The DN4 questionnaire (Section 18.2.1) was developed by the French Neuropathic Pain Group as a tool for the diagnosis of neuropathic pain. This questionnaire includes both pain descriptors and items related to bedside examinations. A score of at least 4 out of 10 is considered to indicate neuropathic pain (Bouhassira et al. 2005).

The topics addressed by the questions are:

- Question 1 addresses 3 items related to the description of pain.
- Question 2 addresses 4 items related to the association of paresthesia/dysesthesia within the painful area.
- Question 3 addresses 2 items related to sensory deficits (hypoesthesia to touch and prick).
- Question 4 addresses 1 item related to evoked pain (pain evoked by brushing).

Question 1 and Question 2 are based on the outcomes of an interview with a subject (DN4i). A score of at least 3 out of 7 items of Question 1 and Question 2 shows “likely” neuropathic pain (Bouhassira et al. 2005).

12.1.7 Urine beta-human chorionic gonadotropin pregnancy test

All female subjects of childbearing potential will provide urine samples at Visit 1, Visit 2, and the Final Visit, which will be tested locally using a urine ß-HCG pregnancy dipstick test. When the Site Visits in the Extension Phase are performed and include an IMP application, the pregnancy test will also be performed. The results of the dipstick test will be entered directly into the CRF. If this assessment is positive, the subject will be excluded from participation in the trial (Inclusion Criterion 3).

Pregnancy tests additional to those specified may be performed if required by local law or regulations.

12.1.8 Urine drugs of abuse test

Urine samples will be provided by all subjects at Visit 1, Visit 2, and the Final Visit for local testing for drugs of abuse using a urinary dipstick (performed at the site).

Test results for the following drugs of abuse will be recorded in the CRF: cocaine, MDMA (3,4-methylendioxy methamphetamine, ecstasy), amphetamines, cannabinoids, benzodiazepines, and opioids.

The outcome of this assessment is relevant for subject selection (Exclusion Criterion 10) and will be recorded in the CRF. Subjects who are receiving stable doses of prescribed medications containing amphetamines or benzodiazepines may participate (according to the judgement of the investigator) even if the test is positive.

12.2 Collection of efficacy data

The following efficacy data will be collected: pain intensity, treatment area size, intensity and area of DMA, as well as responses to NPSI, PGIC, MOS Sleep Scale, BPI Question 9A to 9G, SF-36, TSQM, HADS, WPAI questionnaire, and intake of concomitant analgesic medication for the treatment of PSNP.

For the timing of assessments, see the schedule of events (Section 1.7).

12.2.1 Pain intensity (11-point NPRS)

The 11-point NPRS is a recommended method of assessing pain intensity in subjects with various types of chronic pain (CPMP/EWP/252/03 Rev. 1, Dworkin et al. 2005).

Subjects will be asked to record their average PSNP-related pain intensity for the previous 24 hrs (recall period) in the e-diary at home once daily in the evening for the entire duration of the trial, using an 11-point NPRS (from 0 = “no pain” to 10 = “pain as bad as you can imagine”).

Subjects will be asked to answer the following question:

“Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours.”

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

12.2.2 Dynamic mechanical allodynia

Allodynia is defined as pain in response to a non-nociceptive stimulus. In cases of mechanical allodynia, even gentle mechanical stimuli such as a slight bending of hairs can evoke pain.

The identification of the DMA area and assessment of allodynia intensity will be conducted by the investigator or trained personnel with a cotton swab, provided by the sponsor, as described below.

Identification of the area of dynamic mechanical allodynia

- The subject should be placed in a comfortable recumbent or semi-recumbent position, which will be the same position in which the subject will be placed during the IMP application.
- From a marked point lying in the center of the usually most painful area, as indicated by the subject, 8 radii are drawn at approximately equal angles and approximately 1 cm in length. The area of DMA will be determined from outside the sensitive area towards the center of the sensitive area along the directions of the respective line, using a cotton swab which is gently stroking the subject’s skin.
- At the exact location where a light stroke with the cotton swab becomes unpleasant or painful (if applicable), the boundary of allodynia will be marked.

- Trace the boundaries of the area of allodynia with a colored skin marking pen and trace it onto plastic transparency or special tracing paper of a digital, standardized device for recording and calculation of the area.
- The tracing will be labeled with "DMA", visit number, subject number, tracer's initials, and date. The labeled tracing of the DMA area will be used to determine the DMA area size according to instructions that will be provided by the sponsor prior to the start of the trial.

Assessment of intensity of dynamic mechanical allodynia

- The subject should be placed in a comfortable recumbent or semi-recumbent position.
- Identify the most painfully sensitive area of DMA.
- Using a cotton swab, make 3 strokes in rapid succession in the center of the DMA area within 5 seconds at a rate of 5 cm/second. Cotton swab strokes should be performed proximal to distal with the examiner keeping fairly constant force.
- Ask the subject to rate the intensity of the pain created by the procedure on an 11-point NPRS (from 0 to 10), (DMA-NPRS). Subjects will be asked to answer the following question:

"Please rate your pain related to the procedure by selecting the one number that best describes how much pain you have right now."

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

- Record the intensity of pain in the source notes and in the CRF.

12.2.3 Treatment area size

12.2.3.1 Treatment area is a combined area

The treatment area is the combined area of the usually most painful area indicated by the subject (Section 12.2.3.2), and/or the sensitive area with presence of DMA (Section 12.2.2), and/or the area of pinprick hyperalgesia (Section 12.2.3.3). These 3 areas are not necessarily identical but may be overlapping or contained within each other.

- If no DMA and/or pinprick hyperalgesia is observed, then the usually most painful area will be mapped (Section 10.2.1) and treated.
- If DMA and/or pinprick hyperalgesia is present, then the usually most painful area as indicated by the subject plus any additional area(s) of DMA and/or pinprick hyperalgesia beyond the usually most painful area will be treated, up to a maximum of 1120 cm^2. The labeled tracing of the treatment area (Section 10.2.1) will be used to determine the treatment area size according to instructions that will be provided by the sponsor prior to the start of the trial.

12.2.3.2 Most painful area(s) as indicated by the subject

Subjects will be asked to indicate the usually most painful area(s) on his or her body if possible, and/or describe the location of such area(s).

The subject should be placed in a comfortable recumbent or semi-recumbent position, which will be the same position in which the subject will be placed during the IMP application.

Using a colored skin marking pen, the boundaries of the usually most painful area(s) will be marked on the subject's skin.

12.2.3.3 Pinprick hyperalgesia

The identification of the pinprick hyperalgesia area will be done by the investigator or trained personnel with a von-Frey hair provided by the sponsor. Pinprick stimuli will be applied along the radii from outside the sensitive area towards the center of the sensitive area following the same principle as for the DMA assessment. At the exact location where a pinprick stimulus becomes unpleasant or painful (if applicable), the boundary of hyperalgesia will be marked using a colored skin marking pen.

12.2.4 Medical Outcomes Study Sleep Scale

The MOS Sleep Scale (Hays and Stewart 1992) measures 6 dimensions of sleep, including sleep disturbance, sleep quantity, sleep adequacy, somnolence, awaken short of breath, and snoring. A sleep problem index, grouping items of the former dimensions, can also be scored. The scale has shown good psychometric properties in patients with neuropathic pain (Hays et al. 2005, Rejas et al. 2007, Viala-Danten et al. 2008).

The higher the score, the worse the sleep, except when referring to the dimensions sleep quantity and adequacy of sleep, which are interpreted in the opposite manner.

Subjects will complete the MOS Sleep Scale (Section 18.2.2) using the tablet computer maintained at the site.

12.2.5 Patient Global Impression of Change

The PGIC is a subject-rated instrument that measures the change in the subject's overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). It is a recommended and validated outcome measure for pain-related clinical trials (Dworkin et al. 2005).

Using the tablet computer maintained at the site, subjects will complete the PGIC (Section 18.2.3) to rate their overall improvement and satisfaction with treatment.

12.2.6 Neuropathic Pain Symptom Inventory

The NPSI is a self-administered questionnaire designed specifically for the evaluation of different neuropathic pain qualities and intensity of neuropathic pain components. The questionnaire includes a list of 10 descriptors and 2 temporal items resulting in a total score from 0 to 1. Based on factor analysis, it is recommended to calculate 5 subscores reflecting burning (superficial spontaneous) pain, pressing (deep spontaneous) pain, paroxysmal pain, evoked pain, and dysesthesia/paresthesia.

The NPSI has been validated in pain of at least moderate intensity which could be clearly attributed to peripheral or central nervous system injury. Pain of mixed origin was excluded from the validation study (Bouhassira et al. 2004). The NPSI is sensitive to changes over time during treatment. It has a recall period of 24 hrs.

Subjects will complete the NPSI (Section 18.2.4) using the tablet computer maintained at the site.

12.2.7 Brief Pain Inventory Question 9A to 9G

The BPI is a subject-completed questionnaire that measures severity of pain and its interference with daily function (Cleeland 1991); the tool is recommended by IMMPACT (Dworkin et al. 2005). The questionnaire has demonstrated both reliability and validity across cultures and languages (Cleeland and Ryan 1994).

This trial uses the BPI Questions 9A to 9G on interference of pain with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life in the last 24 hrs. The 11-point NPRS of the BPI Questions 9A to 9G is anchored at 0 = “does not interfere” and 10 = “completely interferes”.

Subjects will complete the BPI Questions 9A to 9G (BPI short form given in Section 18.2.5) using the tablet computer maintained at the site.

12.2.8 Short Form-36® Health Survey

The Short Form-36 Health Survey is a subject-based health status survey used to compare the burden of different diseases, to differentiate the health benefits produced by different treatments, and to screen individual subjects. The instrument is sensitive to change. The 36 questions in the survey generate a health profile that consists of 8 scales and 2 summary measures that describe health-related functional status (Ware and Sherbourne 1992). Increasing values over time indicate improvement.

Subjects will complete the SF-36 short version (Section 18.2.6) with a recall period of the previous week, using the tablet computer maintained at the site.

12.2.9 Treatment Satisfaction Questionnaire for Medication

The TSQM Version 1.4 (Atkinson et al. 2004) has 14 single questions, assessed on 7-point Likert-type scales, that are transformed into 4 TSQM scores (effectiveness score, side effects score, convenience score, global satisfaction score) ranging from 0 to 100.

Subjects will complete the TSQM (Section 18.2.7), with a recall period of 2 weeks to 3 weeks or since the subject last used it, using the tablet computer maintained at the site.

12.2.10 Hospital Anxiety and Depression Scale

The HADS is a brief self-reported screening tool, developed by Zigmond and Snaith (1983), to investigate the prevalence of emotional distress in non-psychiatric populations. The validity of the HADS has been reviewed by Bjelland et al. 2002. The scale consists of 14 items rated on a 4-point Likert-type scale. There are 2 sub-scales, one assessing depression and the other anxiety. The 7-item depression and anxiety subscales yield scores of 0 to 1 that are interpreted with the following cut-off points: 0 to 7, normal; 8 to 10, mild mood disturbance; 11 to 14, moderate mood disturbance; and 15 to 21, severe mood disturbance.

Subjects will complete the HADS (Section 18.2.8) using the tablet computer maintained at the site.

12.2.11 Work Productivity and Activity Impairment questionnaire

The WPAI questionnaire is an instrument that measures impairments in both paid work and unpaid work (Reilly et al. 1993). It measures absenteeism and presenteeism as well as impairments in unpaid activity because of health problems during the past 7 days.

Subjects will complete the WPAI questionnaire (Section 18.2.10) using the tablet computer maintained at the site.

12.2.12 Actigraphy Device

Change in activity and sleep will be measured in a subset of US sites by use of an actigraphy device that will be handed out by the investigator. Specifications will be described in a separate document.

12.3 Collection of safety data

The following safety data will be collected: adverse events, vital signs, physical examination, dermal assessment, neurological/sensory examination, “pain now” (current pain intensity on the NPRS) related to the IMP application site, and data on occupational exposure.

Clinically relevant abnormal values (investigator’s judgment) must be recorded as adverse events.

12.3.1 Adverse events

Adverse events will be documented from the time of screening (i.e., the time the informed consent form is signed) up to the time of the last protocol scheduled contact, i.e., date of last visit/contact (can be a phone call, e.g., in case of withdrawal).

Definition of adverse events

An adverse event is any untoward medical occurrence in a subject enrolled in a clinical trial. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing diseases or conditions occurring before screening are not considered to be adverse events but medical history unless there is an untoward change in intensity, frequency, or quality after screening.

Lack of efficacy, as such, is not considered to be an adverse event while its consequences (e.g., deterioration of the treated disease) are considered to be an adverse event.

A newly diagnosed pregnancy of a screened female subject will not be considered an adverse event itself unless it is suspected that the IMP interacted with a contraceptive method. In this case, the pregnancy will be considered an adverse event. A congenital anomaly as an outcome of a pregnancy will be considered a serious adverse event (SAE).

All newly diagnosed pregnancies of screened female subjects must be reported to the responsible drug safety department of the sponsor (or authorized sponsor representative) within 24 hrs after first knowledge. These pregnancies will be documented using a pregnancy reporting form with all available information provided and followed up to determine the outcome post parturition.

Definition of serious adverse events

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered a clinically important medical event. The medical concepts included in Section 18.1 should be considered when applying this seriousness criterion.

An elective hospital admission, e.g., for pre-planned surgery, will not be considered an SAE if documented at screening. Short-lasting (<24 hrs) hospital admissions, e.g., for clinical check-ups, not meeting any of the other above mentioned criteria will also not be considered SAEs.

Special procedures for serious adverse events

If SAEs occur that are not tolerable, the investigator will decide whether to stop the trial participation and/or treatment of the subject. For further details, see Section 9.3.

Expectedness of adverse events

Expectedness will be assessed by the sponsor.

An unexpected adverse event is one where the nature or intensity is not consistent with the information in the investigator's brochure.

Furthermore, reports that add significant information about the specificity or severity of a known, already documented adverse reaction, constitute unexpected adverse events. For example, an adverse event more specific or more severe than expected would be considered "unexpected".

Definition of adverse drug reactions

An adverse drug reaction is any untoward and unintended response to an IMP or a medicinal product related to any dose administered.

A list of adverse drug reactions for the IMP is given in the investigator's brochure.

Documentation of adverse events

Subjects will be questioned about possible adverse events with non-leading questions before administration of the IMP and at regular intervals thereafter, as defined in Section 1.7.

All adverse events reported spontaneously by subjects at any time point will also be documented.

All adverse events will be documented in the CRF with the following information, where appropriate:

- Description (adverse event reported term).
- Start date/time.
- End date/time or continuation.
- Whether adverse event was serious.
- Intensity.

- Outcome.
- Action taken with IMP.
- Countermeasures.
- Causal relationship to IMP.

Definition of intensity

The clinical intensity of an adverse event will be classified as:

Mild:	Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.
Moderate:	Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.
Severe:	Symptoms which affect usual daily activity.

For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will be documented.

Adverse events occurring in the Screening Period but before first application of IMP, and worsening on or after IMP application, will be documented as new adverse events.

Definition of outcome at the time of last observation

The outcome at the time of last observation will be classified as:

- Recovered/Resolved.
- Recovering/Resolving.
- Not recovered/Not resolved.
- Recovered/Resolved with sequelae.
- Fatal.
- Unknown (unknown should only be used if, at the time of the last visit for a subject in a trial, the outcome of the adverse event is unknown to the investigator, e.g., because the subject is lost to follow-up).

Definition of countermeasures

"Countermeasures" will be defined as:

None:	No countermeasure given.
Newly started medication:	A newly started medication or change in dose or route of application of a medication due to the adverse event (to be listed on the prior/concomitant medication page) that is used as a countermeasure.
Trial discontinuation:	It was necessary to discontinue the subject from the trial due to the adverse event.
Other:	All other countermeasures, e.g., physical therapy, surgery.

Except for none, multiple countermeasures for 1 adverse event can be recorded.

Classification of action taken with IMP when an adverse event occurs:

- Drug interrupted.
- Not applicable.
- Unknown.

Classification of causation

The causal relationship of an adverse event to IMP will be classified using the following terminology. The given criteria for each term are for consideration and are neither exhaustive nor required to be fulfilled in total for the selection of the respective term:

Terms for classification of causation	Criteria for the selection of causality classification terms
Conditional/ Unclassified:	Additional data for a proper assessment are under examination.
Unassessable/ Unclassifiable:	The available data cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.
Not related:	Data with sufficient evidence to accept that there is no causal relationship to IMP administration (i.e., there is no temporal relationship to IMP administration or proved other cause).
Unlikely:	Data without sufficient evidence to accept that there is no causal relationship to IMP administration, but also with no evidence or argument to suggest a causal relationship (e.g., the temporal relationship to IMP administration makes a causal relationship improbable, and other drugs, chemicals, or underlying disease[s] provide plausible explanations).
Possible:	Data with limited evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, but the adverse event could also be explained by concurrent disease[s] or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear).
Probable/likely:	Data with sufficient evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, the adverse event is unlikely to be attributed to concurrent disease[s] or other drugs or chemicals, and a clinically reasonable response on withdrawal [dechallenge]).
Certain:	Data with clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, and it cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [dechallenge] should be well defined and clinically plausible, using a satisfactory rechallenge procedure if appropriate).

Follow-up of subjects with an adverse event

Any adverse event or clinically relevant abnormal laboratory or vital sign result will be followed until it reaches a satisfactory resolution, or becomes stable, or clinical judgment indicates that further evaluation is not warranted.

Notification of serious adverse events

All SAEs (including death, irrespective of cause) during the trial, regardless of their relationship to IMP, must be reported as soon as possible but no later than 24 hrs after learning of the event. Before

any trial-related procedure is performed, the trial site must be provided with contact details at the responsible drug safety department of the sponsor (or authorized sponsor representative) for this reporting.

The investigator must submit a report, called a safety reporting form, which includes a description of the event, the therapy instituted, and trial procedures. The following information should be communicated with the first notification of an SAE:

- Trial identifier.
- Subject's identifier.
- Subject's date/year of birth (if available, see local data protection requirements) or age (at adverse event onset).
- Subject's sex.
- First administration of IMP (date and time, if available).
- Last administration of IMP (date and time, if available).
- Adverse event verbatim term (specific diagnosis, if possible).
- Adverse event onset (date and time, if available).
- A brief description of the event, the course, and the countermeasures taken.
- Intensity.
- Seriousness criterion.
- Outcome.
- Concomitant medication at onset of the event and whether one of the concomitant medications is also suspected to have caused the event.
- Relevant history/pre-existing medical conditions.
- Investigator's assessment of the relationship to IMP(s).
- Whether and when blinding was broken.

All additional information concerning the adverse event until trial termination or definite outcome must be communicated per follow-up report without delay.

The immediate and follow-up reports must only identify the subjects using the unique subject identifier.

The investigator must comply with applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authorities and the relevant IEC(s) or IRB(s).

Notification of serious adverse reactions

All suspected adverse drug reactions related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious, are subject to expedited reporting.

Once a year throughout the clinical trial, the sponsor will provide the member states in whose territory the clinical trial is being conducted and the IEC(s) with a listing of all suspected unexpected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

In addition, the sponsor will ensure that all reportable events are reported in compliance with applicable international and national regulatory requirements.

12.3.2 Vital signs

Vital signs comprise systolic/diastolic blood pressure, heart rate, and respiratory rate.

Vital signs will be measured as per local standard of care after resting for 10 mins. While resting, the subject should not receive anything to drink or eat.

Clinically relevant abnormal values must be recorded as adverse events.

Vital signs will be assessed 15 mins before local anesthetic application and at 55 mins after IMP application (Section 1.7).

12.3.3 Physical examinations

Physical examinations should include assessments of the general condition, skin, eyes, ears, nose and throat, mouth (including teeth and gums), head, neck, and thyroid, heart, lung, chest, abdomen, kidneys, liver, lymphatic, musculoskeletal, and neurological systems. The physical examination will have a special focus on the post-surgical site and scar tissue.

After randomization, any clinically relevant findings from the physical examination will be documented as adverse events.

12.3.4 Dermal assessments

Dermal assessments will be performed on an 8-point dermal assessment scale:

- 0 = no evidence of irritation.
- 1 = minimal erythema, barely perceptible.
- 2 = definite erythema, readily visible; minimal edema or minimal papular response.
- 3 = erythema and papules.
- 4 = definite edema.
- 5 = erythema, edema, and papules.
- 6 = vesicular eruption.
- 7 = strong reaction spreading beyond test site.

Dermal assessments will be performed 15 mins before local anesthetic application and immediately after IMP removal (Section 1.7).

12.3.5 Neurological/sensory examinations

Neurological/sensory examinations (Section 18.2.9) will be performed according to the “bedside tests” of response to warm, pinprick, and cold sensation described by Gálvez et al. 2017. The objective of the neurological/sensory examinations is to assess sensory function at baseline and to re-assess the same following treatment with IMP. The examinations will be performed by the investigator who will have received training, and findings will be captured in the CRF using pre-defined scales. Ideally, assessments should be performed by the same person for a subject.

For the timing of assessments, see the schedule of events (Section 1.7).

12.3.6 "Pain now" (current pain intensity on the NPRS) related to the IMP application site

Subjects will be asked to rate their "pain now" (current pain intensity on the NPRS) related to the IMP application site on an 11-point NPRS using the tablet computer at the site. "Pain now" will be rated at the following time points: 15 mins before local anesthetic application and at 55 mins after IMP application.

The subject will be asked to answer the following question:

*"Please rate your pain related to the IMP application site by selecting the one number that best describes how much pain you have **right now**."*

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

12.3.7 Data on occupational exposure

Data on occupational exposure (i.e., exposure occurring in trial personnel) will be collected through an additional safety report form for trial personnel and documented in the drug safety database only. These data will not be collected in relation to a specific trial endpoint. The additional safety reporting form enables the trial personnel to report accidental exposure, which would not be possible with a safety report form intended for adverse event reporting in subjects.

12.4 Appropriateness of measurements

The unidimensional 11-point NPRS is a recommended method for assessing pain intensity in subjects with neuropathic pain (CPMP/EWP/252/03 Rev. 1) and a recommended efficacy outcome measure for subjects with various types of chronic pain (Dworkin et al. 2005).

The DN4 is a screening tool used to identify neuropathic pain based on an interview (DN4i) and a bedside examination. This tool has been validated in many chronic pain indications and has shown high sensitivity and specificity for recognizing both peripheral and central neuropathic pain. The DN4 tool is recommended for use in clinical trials by the NeuPSIG and the European Federation of Neurological Societies (EFNS) (Üçeyler and Sommer 2011).

The DMA measurement is part of the Quantitative Sensory Testing (QST) protocol developed by the German Research Network on Neuropathic Pain as a comprehensive battery of sensory tests to quantify functions of the human somatosensory nervous system (Rolke et al. 2010).

The dermal assessments performed before IMP applications will ensure skin integrity and will evaluate potential skin irritation. Assessments will occur 15 mins before application of local anesthetic and immediately after IMP removal, as was done in previous clinical trials investigating Qutenza in another indication (e.g., Simpson et al. 2017).

The neurological/sensory examination (Section 18.2.9) will be performed according to the "bedside sensory tests" described in an open-label long-term safety trial investigating repeated applications of Qutenza in subjects with different types of PNP (Gálvez et al. 2017).

Validated questionnaires such as the NPSI, PGIC, MOS Sleep Scale, BPI, SF-36, TSQM, HADS, and WPAI, and safety assessments such as adverse events, vital signs, and physical examination are standard practice in clinical trials.

12.5 Compliance

Compliance is the adherence to all requirements of the trial protocol.

Trial site compliance will be assured by the implementation of a quality system and the performance of a combination of trial site visits, training, and monitoring visits. Non-compliance should lead to prompt action by the sponsor to secure compliance.

All IMPs will be applied by qualified personnel at the site.

Compliance of the subjects to record their pain intensity assessments in the e-diary will be checked by the investigator at the respective visits and remotely before the telephone calls. A non-compliant subject may be withdrawn from treatment at the discretion of the investigator.

Completion of questionnaires will be done using the tablet computers maintained at the site in the presence of qualified trial staff.

Relevant deviations from the protocol will be documented and described in the integrated clinical trial report.

13 DOCUMENTATION OF TRIAL DATA

Trial data documentation must be adequate for the reconstruction of the trial.

13.1 Case report forms

CRFs for each subject will be provided to the investigator by the sponsor in electronic format to document trial data.

The investigator and personnel delegated the task will use CRFs to record information required by the protocol.

All CRF entries, corrections, and alterations will be made by the investigator or other authorized personnel under their supervision. Entries will be checked against appropriate source documents by authorized sponsor representatives, as deemed appropriate in the monitoring guidelines.

Data collection will be done using a validated electronic CRF system. The collected data will reside on servers of the CRF provider. Entry, corrections and alterations of data within the system can only be performed by the investigator or other authorized personnel under their supervision and will be captured by the system’s audit trail.

Dedicated users (e.g., the investigator, designated persons at the trial site, authorized sponsor representatives, and from other parties involved, e.g., data management) will be trained and receive access rights according to their role in the trial. All users will retain access to the system and be able to review their data on an ongoing basis.

After completion of the subject's CRF, the CRF must be signed electronically by the investigator. With the investigators signature, it is confirmed that the data in the CRF are checked, are complete, accurate, and in alignment with the source data. Changes to the CRF after initial signing by the investigator will require re-signing of the CRF.

With database lock, the edit rights to the CRFs will be removed but the investigator will retain access to view the CRFs until receipt of a certified copy of all data captured for his or her subjects (site archive). These data will be delivered in a human readable form for retention in their files.

13.2 Subject-reported outcomes

Subject-reported outcomes will be collected using a validated electronic subject-reported outcome system (electronic diaries and tablet computers) including audit trail.

The investigator will be trained on the use of the electronic subject-reported outcome system and the related oversight system. The oversight system will allow the investigator to review all data entered by the subjects at his or her site on an ongoing basis.

Subjects will receive a personal e-diary at the trial site to be used at home during the trial period and will be instructed on how to use it.

Subjects will receive access to a personal tablet computer when at the trial site and will be instructed on how to use it. The personal tablet computer will remain at the trial site.

No queries will be issued to the investigator for these data, except for clarification of subject identifiers and any operational issues. No queries will be raised to the subject.

With database lock, the writing access to the electronic subject-reported outcome system will be removed. The investigator will receive all data captured for his or her subjects, in a human readable form, on read-only media for his or her files. The information will be provided to the investigator prior to system decommissioning.

13.3 Data management

Data management will be performed by sponsor personnel or by authorized sponsor representatives. Documentation of the responsibilities and delegation thereof will be maintained in the TMF.

All aspects of the data management process, including data validation and query management, medical coding, handling of external data, and data lock procedures, will be described in the Data Management Plan. Details on data validation will also be described in the Data Validation Plan.

13.4 Source data

Source data are defined by GCP as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)".

Source data comprise clinical documentation, data, and records (e.g., clinic/hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, and data and records arising from departments such as the pharmacy, laboratory, and medico-technical departments) that describe or record the methods, conduct, or results of the trial, the factors affecting the trial, and the actions taken.

All source data arising from the trial will be kept by the investigator, who must provide direct access for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents, e.g., race, ethnicity, sex. When this occurs, the CRF is considered to be the source document.

The nature and location of all source data/clinical documentation will be identified and documented by the investigator to ensure that all sources of original data required to complete the CRF are known to the sponsor and/or trial site personnel and are accessible for verification during trial-related monitoring, audits, relevant IEC/IRB review, and inspection(s).

For subject-reported outcomes captured directly via an e-diary, source data are defined as the data residing in the vendor's database.

13.5 Investigator's site file and the TMF

The principal investigator is responsible for the filing of all essential documents in an investigator's site file. The sponsor is responsible for the timely filing of all essential documents in the TMF. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

14 QUANTITATIVE ANALYSES

14.1 Sample size rationale

The sample size rationale for the trial is provided in Section 1.5.1.

Sample size calculations were performed with nQuery Advisor 7.0.

14.2 General description of statistical analyses

The primary analysis will be performed once all subjects have completed the Extension Phase of the trial at Week 42 (Final Visit), the corresponding data have been cleaned, and database lock and unblinding have been completed.

The statistical analysis of this trial will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates.

The data collected and derived from the trial will be presented in subject data listings.

Data collected in this trial will be summarized according to their nature as follows:

- Continuous variables: arithmetic mean, standard deviation, minimum and maximum values, median and quartiles depending on the number of observations.
- Categorical variables: absolute and relative frequencies.
- For time-to-event variables: number of subjects, number of subjects with event, number of censored subjects, first quartile (Q1), median and its 95% confidence interval, third quartile (Q3). In addition, Kaplan Meier plots will be produced together with event rates at time points of interest.

All statistical analyses will be performed by treatment group.

Full details of the planned statistical analyses will be described in the trial statistical analysis plan.

14.3 Analysis populations (analysis sets)

For the definition of analysis populations, please refer to Section 1.5.2.

14.4 Analysis of subject disposition

Subject disposition will be summarized descriptively for all screened subjects. Discontinuations will be summarized descriptively for all randomized subjects.

14.5 Analysis of demographic data and other baseline characteristics

Demographics and other baseline characteristics (e.g., medical history and prior and concomitant medications) will be summarized descriptively by treatment group and overall for the FAS and the SAF.

14.6 Analysis of efficacy data

All primary and secondary efficacy parameters will be summarized by descriptive statistics. The analysis of the primary efficacy endpoint, additional sensitivity analyses, and the analysis of all other efficacy parameters will be performed on the FAS.

14.6.1 Multiple testing strategy

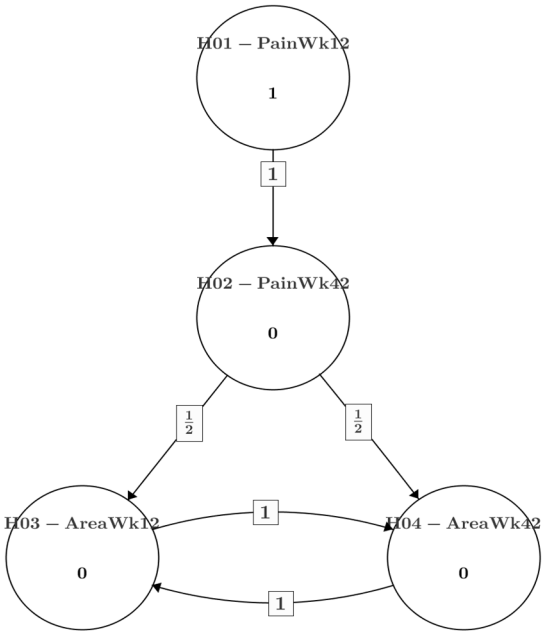
Each of the primary and secondary endpoints of the trial will be investigated by a formal statistical test (see Section 14.6.2 for the statistical hypothesis and test for the primary efficacy analysis, and Section 14.6.3 for analyses of secondary endpoints). Testing multiple hypotheses, however, may

increase the family-wise type I error rate, the probability to erroneously reject at least one true null hypothesis, beyond the pre-specified one-sided significance level of $\alpha = 2.5\%$. To control the family-wise type I error rate in the strong sense, a sequentially rejective multiple testing procedure (Bretz et al. 2009) will be used. The statistical tests T_1, T_2, T_3, and T_4, corresponding to the elementary null hypotheses $H_{0,1}$, $H_{0,2}$, $H_{0,3}$, and $H_{0,4}$, are the following:

- T_1: test for superiority of Qutenza over low-dose capsaicin control for the primary efficacy endpoint (Section 14.6.2).
- T_2: test for superiority of Qutenza over low-dose capsaicin control for change from baseline in the 24-hr average pain intensity at Week 42.
- T_3: test for superiority of Qutenza over low-dose capsaicin control for change from baseline to Week 12 of treatment area size (Section 14.6.3 for all secondary endpoints).
- T_4: test for superiority of Qutenza over low-dose capsaicin control for change from baseline to Week 42 of treatment area size.

The initial allocation of significance level $\alpha = (0.025,0,0,0)$ attributes the entire significance level to the primary null hypothesis. The first 4 hypotheses are tested each at their initial local significance level α_i. If a hypothesis $H_{0,i}$ can be rejected, its significance level gets reallocated to the remaining, non-rejected hypotheses, which are then re-tested at their updated respective local significance level. This procedure is repeated until no further hypothesis can be rejected. If all hypotheses of the multiple testing procedure are rejected, then further hypotheses based on additional efficacy or safety endpoints may also be tested.

This testing procedure controls the family-wise type I error rate in the strong sense (Bretz et al. 2009, Section 2.2). Figure 3 illustrates the planned testing procedure. Each node represents an elementary null hypothesis with initially allocated portion of the significance level. The edges between the nodes determine the reallocation of significance level in case of rejection of an elemental null hypothesis and are labeled by the according reallocation weights w_{ij}.



PainWk12 = Change from baseline in 24-hr average pain intensity at Week 12; AreaWk12 = Change from baseline in treatment area size at Week 12; PainWk42 = Change from baseline in 24-hr average pain intensity at Week 42; AreaWk42 = Change from baseline in treatment area size at Week 42.

Figure 3: Graphical illustration of the planned testing procedure

As mentioned earlier, if all hypotheses of the multiple testing procedure are rejected, then further hypotheses based on additional efficacy or safety endpoints may also be tested. An extension of the multiple testing procedure will be pre-specified in detail in the statistical analysis plan.

14.6.2 Analysis of the primary endpoint

14.6.2.1 Primary efficacy analysis

The primary objective of the trial is to demonstrate superiority of Qutenza over low-dose capsaicin control in change from baseline in the 24-hr average pain intensity, in subjects with PSNP. It will be investigated by the primary analysis of the primary efficacy endpoint of the trial (Section 1.2).

Primary endpoint

In the US, the primary efficacy endpoint will be the change from baseline to the weekly average score of Week 12 in the 24-hr average pain intensity.

In non-US countries/regions, the primary efficacy endpoint will be the change from baseline to the average score of the entire period between Week 2 and Week 12 in the 24-hr average pain intensity.

The 24-hr average pain intensity will be assessed once daily in the evening using an 11-point NPRS. Baseline pain will be calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of the last 7 days must be available. Each trial week is defined as a sequential 7-day interval subsequent to the Randomization Visit (Visit 2). The weekly average pain of a trial week is defined as the average of non-missing 24-hr average pain assessments for the respective trial week.

The estimand of interest for the primary efficacy analysis is the difference in treatment group means in the primary efficacy endpoint in all subjects in the FAS attributable to the randomized treatment regimen.

Discontinuation of the trial and start of intake of forbidden medication will be handled as intercurrent events (Section 14.6.4).

Statistical hypothesis for the primary analysis

An effective drug is expected to lead to lower pain intensity and, hence, to a negative change from baseline. The one-sided null hypothesis,

$$H_{0,1}: \mu_{qu} - \mu_{ldc} \geq 0$$

will be tested versus the alternative,

$$H_{A,1}: \mu_{qu} - \mu_{ldc} < 0$$

at the one-sided significance level 2.5% ($\alpha = 0.025$), where μ_{qu} is the mean change from baseline of the Qutenza treatment group and μ_{ldc} is the mean change from baseline of the low-dose capsaicin control treatment group.

Primary analysis model

The primary efficacy analysis will be performed using an MMRM. The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline pain intensity and an unstructured covariance matrix to model the covariance structure of the repeated measures. The degrees of freedom of the denominator will be estimated using the Kenward-Roger approximation (Kenward and Roger 1997).

Individual sites will be pooled by geographic region. Geographic regions will be defined in the statistical analysis plan and correspond to the country/region used in the stratified randomization.

This analysis will be performed based on all available post-baseline weekly average values of the 24-hr average pain intensity, excluding pain measurements at the day of, and during the first 5 consecutive days after, any IMP application, because of the potential for treatment-associated pain during the application procedure and the permitted use of short-acting (non-opioid) analgesics (Section 1.4.2.3).

If the default Newton-Raphson algorithm used by statistical analysis software (SAS) PROC MIXED fails to converge, the Fisher scoring algorithm up to iteration 2 will be used (via the SCORING=2 option of the PROC MIXED statement) to obtain the initial values of covariance parameters (Mallinckrodt et al. 2008). If this alternative also fails to converge, then, in addition the no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T = 12 is the total number of weeks in the 12-week trial period) will be used, which effectively performs the Cholesky decomposition of the covariance matrix and is numerically more stable.

If the model still fails to converge, then, in addition to the changes described above, the variable pooled trial site will be dropped from the model. When the above strategies fail, then, in addition to

the changes described above, a model with the less complex heterogeneous Toeplitz covariance structure (TOEPH) will be fitted. When the above strategies fail, then, in addition to the changes described above, a model with the less complex compound symmetry covariance structure (CS) will be fitted. If a structured covariance matrix is needed, a robust variance estimator will be used (e.g., sandwich estimator).

The first algorithm that leads to convergence in this sequence of fallback measures will be the algorithm used for the primary analysis of the trial.

Using the mixed-effects model described above, $\delta = \mu_{qu} - \mu_{ldc}$ is the contrast (i.e., mixed model Wald tests) of Qutenza versus low-dose capsaicin control at Week 12 of the trial for the primary endpoint for the US region and over the period between Week 2 to Week 12 of the trial for the primary endpoint for non-US countries/regions. Results of the primary analysis will contain an estimate of the treatment difference between Qutenza and low-dose capsaicin control at the respective time point, as well as standard error, 95% confidence interval, and p-value.

14.6.2.2 Key sensitivity analyses

Sensitivity analyses will be conducted to assess the robustness of the primary analysis results with respect to the missingness assumption MAR.

The primary efficacy endpoint will be investigated by applying an analysis of covariance (ANCOVA) model with the same covariates as the primary analysis model to multiple imputation datasets:

- Imputed with the MAR assumption.
- Imputed with the MAR assumption and incorporating a penalty delta in the Qutenza group only, with delta = 15%. The penalty of 15% was chosen to correspond to an absolute change from baseline of 1 point on the NPRS, assuming an average baseline measurement of approximately 6.5 points on the NPRS.
- A tipping point analysis to identify the highest delta penalty that would still result in a statistically significant difference between treatment groups (Permutt 2016).

Missing data handling is described in Section 14.6.4. All sensitivity analyses will be described in detail in the statistical analysis plan.

14.6.3 Analysis of the secondary endpoints

14.6.3.1 Analysis of treatment area size

Treatment area size (cm^2) is defined as the size of the combined area of the usually most painful area of PSNP as indicated by the subject, and the sensitive area identified in the DMA and pinprick assessments (see Section 12.2.3). Change of treatment area size from baseline to Week 12 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline treatment area size, as covariates.

The 1-sided null hypothesis,

$H_{0,3}$: $\mu_{qu} - \mu_{ldc} \geq 0$

will be tested versus the alternative,

$H_{A,3}$: $\mu_{qu} - \mu_{ldc} < 0$

at the 1-sided significance level 2.5% ($\alpha = 0.025$), where μ_{qu} is the mean of the change in treatment area size assessment from baseline to Week 12 in the Qutenza treatment group and μ_{ldc} is the corresponding mean of the change in treatment area size assessment from baseline to Week 12 in the low-dose capsaicin control treatment group.

Baseline values and the change from baseline to Week 12 will also be summarized descriptively by treatment group.

The same analysis of the treatment area size will also be conducted at Week 42; the corresponding null and alternative hypotheses $H_{0,4}$ and $H_{A,4}$ are equivalent.

Missing data will be imputed under the MAR assumption using multiple imputation.

Sensitivity analyses will be specified in the Statistical Analysis Plan (SAP).

14.6.3.2 Analysis of 24-hr average pain intensity from baseline to Week 42

The change in 24-hr average pain intensity from baseline to Week 42 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline pain intensity, as covariates.

The 1-sided null hypothesis,

$H_{0,2}$: $\mu_{qu} - \mu_{ldc} \geq 0$

will be tested versus the alternative,

$H_{A,2}$: $\mu_{qu} - \mu_{ldc} < 0$

at the 1-sided significance level 2.5% ($\alpha = 0.025$), where μ_{qu} is the mean of the change in average pain from baseline to Week 42 in the Qutenza treatment group, and μ_{ldc} is the corresponding mean of the change in average pain from baseline to Week 42 in the low-dose capsaicin control treatment group.

Missing data will be imputed under the MAR assumption using multiple imputation. For handling of intercurrent events, see Section 14.6.4. Sensitivity analyses will be specified in the SAP.

Additional supportive analyses will be conducted at other timepoints (by week or month). ANCOVA or MMRM models may be applied dependent on technical feasibility and details will be specified in the SAP.

14.6.3.3 Analysis of 24-hr average pain intensity from baseline between Week 2 and Week 42

The change in 24-hr average pain intensity from baseline to the entire period between Week 2 and Week 42 will be analyzed using an ANCOVA model with treatment group, country/region, gender,

time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline pain intensity, as covariates.

Missing data will be imputed under the MAR assumption using multiple imputation. For handling of intercurrent events, see Section 14.6.4.

14.6.3.4 Analysis of other efficacy endpoints

14.6.3.4.1 Medical Outcomes Study Sleep Scale

Change in the 9-item sleep problem index (Sadosky et al. 2009) of the MOS Sleep Scale from baseline to Week 12 and to Week 42 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline 9-item sleep problem index assessment, as covariates.

Missing data will be imputed under the MAR assumption using multiple imputation.

14.6.3.4.2 Patient Global Impression of Change

The summary of the PGIC is a subjective assessment of how one feels after treatment. The responses are on a 7-point scale:

- "Very much improved"
- "Much improved"
- "Slightly improved"
- "No change"
- "Slightly worse"
- "Much worse"
- "Very much worse"

The PGIC at Week 12 and Week 42 will be analyzed as response to treatment, with PGIC response defined as "very much improved" or "much improved". Subjects with any other answer or with missing answers will be classified as non-responders.

For the PGIC responder analysis, a logistic regression model with treatment group, country/region, gender, time since onset of pain after surgery (<1 year or ≥1 year) and intake of concomitant medication for treatment of PSNP, as covariates will be fitted. Based on that model, response rates per treatment group and odds ratios for the active treatment group compared to low-dose capsaicin control will be estimated and presented together with the corresponding 95% confidence intervals.

14.6.3.4.3 Responder analysis

The percentage change from baseline in 24-hr average pain intensity at Week 12 will be calculated as:

$$\%\ \text{change} = \frac{\text{Baseline Pain} - \text{weekly average of 24-hr average pain intensity at Week 12}}{\text{Baseline Pain}} \times 100$$

Subjects who show an increase in their 24 hr average pain, or who discontinue the trial due to AEs or due to lack of efficacy, will be considered as non-responders for all weeks following the discontinuation. Missing data from subjects who discontinue due to other reasons will be imputed under MAR (using multiple imputation), and response to treatment will be determined based on the imputed data.

For the responder analysis at Week 12 and Week 42, with response to treatment defined as a reduction from baseline pain intensity of at least 30%, a logistic regression model with treatment group, country/region, gender, time since onset of pain after surgery (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline pain intensity, as covariates will be fitted. Based on that model, response rates per treatment group and odds ratios for the active treatment groups compared to low-dose capsaicin control will be estimated and presented, together with the corresponding 95% confidence intervals.

In addition, the analysis of pain response to treatment will include a cumulative responder analysis at Week 12, where responder rates will be calculated for different thresholds for the percentage change from baseline in average pain intensity. The results will be presented graphically where the Y-axis is the proportion of responders and the X-axis is the percentage of pain relief achieved.

14.6.3.4.4 Additional endpoints

Analyses of additional efficacy endpoints (time to onset of response, relevant response to treatment, average interval length between IMP applications, intake of concomitant analgesic medication, DMA intensity and area size. NPSI, BPI interference, SF-36, TSQM, HADS, WPAI and actigraphy) will be pre-specified in detail in the SAP.

14.6.4 Handling of intercurrent events and missing data

Diligent attempts will be made to limit the amount of missing data and to follow-up all randomized subjects to collect the primary and secondary efficacy endpoints for the statistical analysis.

There are 2 distinct event categories of premature IMP discontinuation: At each IMP application, the topical system may potentially be removed before completion of the planned treatment duration of 60 mins (Section 11.1.2.1.3). Discontinuation from repeated IMP application can occur if repeated IMP application is considered to pose an undue risk to the subject (Section 9.3.2). For both of these event categories, the observed values for the variable of interest will be used regardless of whether the event occurred (treatment policy strategy).

Premature trial discontinuation will be handled as an intercurrent event. Unobserved assessments after discontinuation will be handled by the primary analysis (MMRM) as MAR. Topically applied high-concentration capsaicin induces reversible dermo-epidermal denervation and depletion of capsaicin-sensitive nociceptors (Section 6.2). In the Core Phase, the IMP application occurs only once at the Randomization Visit (Visit 2/Day 1). The pharmacodynamic effect of the IMP is not expected to be affected by a potential trial discontinuation, and the MAR assumption appears to be a plausible missingness mechanism for the primary and other Week 12 efficacy endpoints. The treatment regimen allows for re-application of the IMP in the Extension Phase, 12 weeks after the first IMP application, with a minimum time interval of 8 weeks between applications. Nevertheless, given the long-lasting pharmacodynamic effect of the IMP, the MAR assumption also appears justified for the analysis of the endpoints at Week 42.

For the Core Phase, the intake of forbidden concomitant medication (see Section 1.4.2) for pain related to PSNP will also be handled as an intercurrent event through a composite strategy. All pain assessments collected after the start of intake of forbidden concomitant medication for pain due to PSNP during Weeks 2 through 12 will be ignored and the ignored assessments will be imputed by the subject's baseline pain score.

In the Extension Phase, changes in PSNP-related background treatments or therapies, and newly-initiated medications or therapies for PSNP, are allowed per protocol and need to be reported separately (see Section 1.4.2.4). However, for the estimand of interest, these will also be considered as intercurrent events. For the Extension Phase, pain assessments collected between the start of intake of forbidden concomitant medication or start of change in background medications for pain due to PSNP, and the subsequent next IMP application, will be ignored and imputed by the last available weekly average of pain scores before the start of the intercurrent event.

The imputation strategies for these intercurrent events allow for an estimation of treatment difference, which cannot be influenced by the effect of forbidden concomitant medication intake or by medications taken after trial discontinuation, thereby allowing investigation of the primary estimand of treatment effect attributable to the randomized treatment regimen (Section 14.6.2.1).

Robustness against the MAR assumption in the primary analysis will be investigated with a sensitivity analysis (tipping point, Section 14.6.2.2).

Missing values in all other efficacy endpoints will not be imputed unless explicitly mentioned otherwise in the statistical analysis plan.

14.6.5 Subgroup analyses

Subgroup analyses may be done if appropriate and will be specified in the statistical analysis plan.

14.7 Analysis of safety data

The analysis of safety data will be performed using the SAF. No statistical tests for comparison of safety data between treatment groups will be performed. Safety data will be summarized descriptively.

14.7.1 Analysis of adverse events

A definition of adverse event is given in Section 12.3.1.

A TEAE is defined as any adverse event which, based on start and start time information, occurs after the first IMP application (included) until the last visit (Final Visit).

All TEAEs will be summarized for the entire trial, and by Core Phase and Extension Phase.

An overview of the number and percentage of subjects (incidence of TEAEs) with at least 1 TEAE, treatment-emergent SAEs, non-serious TEAEs, unexpected TEAEs, related TEAEs, related treatment-emergent SAEs, related TEAEs by intensity, TEAEs by intensity, TEAEs leading to discontinuation from IMP, TEAEs leading to discontinuation from the trial, and deaths, will be created.

The number and percentage of subjects with adverse events and the number and percentage of events will be summarized by System Organ Class and Preferred Term for TEAEs, treatment-emergent SAEs, non-serious TEAEs, and related TEAEs.

Additional summaries by intensity, causal relationship, outcome, countermeasure, and time to onset, will be provided.

Subjects with SAEs and subjects with adverse events leading to trial/treatment discontinuation will also be listed.

14.7.2 Analysis of vital signs

Vital sign parameters (including changes from baseline as applicable) will be summarized descriptively per visit.

14.7.3 Analysis of dermal assessment

Absolute and relative frequencies of the dermal assessment score categories on the day of treatment will be summarized by treatment group and overall.

In an additional table, absolute and relative frequencies of the dermal assessment score categories on the day of treatment will be summarized by treatment group and by the number of IMP applications.

14.7.4 Analysis of neurological/sensory examination

Neurological/sensory assessments will be summarized by neurological/sensory examination test and by assessment time point. Categorical changes from screening will be presented for Week 12 and Week 42, as specified in detail in the statistical analysis plan.

14.7.5 Analysis of “pain now” related to the IMP application site

“Pain now” (current pain intensity) related to the IMP application site, rated on an 11-point NPRS, will be analyzed after IMP application by summarizing the NPRS scores as well as change from baseline by time point of measurement, with the measurement at 15 mins before local anesthetic application as baseline.

14.8 Interim analysis

A blinded interim analysis will be conducted when at least 265 subjects (i.e., approximately 65% of 408 subjects) have completed Visit 6 or discontinued from the trial, to re-estimate and increase the sample size up to a maximum of 500 subjects if the standard deviation is >30.5%. This approach can preserve the power of at least 90% for an observed standard deviation of ≤33.75%.

The standard deviation of the relative change from baseline assessments will be estimated using the one sample variance estimator (Friede and Kieser 2013). This estimate is blinded and, therefore, maintains the trial integrity. The type I error rate is controlled in this superiority trial. An increase of the sample size is not mandatory, and the result of the blinded interim analysis and the decision on the size of the sample size increase, will be documented in the clinical trial report.

15 QUALITY SYSTEM, AUDIT, AND INSPECTION

15.1 Quality system

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

15.2 Data quality assurance

The accuracy and reliability of the trial data will be assured by careful trial site, investigator and CRO selection, and by monitoring of trial site performance by a combination of trial site staff training, trial site visits, monitoring visits, remote verification by the sponsor of appropriate use of electronic tools by the trial site, data cleaning, and audits.

Trial site monitoring, as defined by GCP, will be performed by sponsor personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial.

Corrections, amendments, or clarifying statements resulting from monitoring visits should be made by the investigator, where necessary.

Appropriate checking against source documents must be done by the sponsor.

Audits, as defined by GCP, should be performed for this trial. The auditors will be independent of the trial and its performance.

15.3 Inspections

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

16 GENERAL CONDITIONS AND AGREEMENTS

16.1 Insurance

If required by applicable regulatory requirements, the sponsor will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance. The investigator must inform all subjects about this insurance and (if requested) be prepared to explain the relevant terms and conditions of this insurance to the subject.

If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor will inform the investigators who will then inform their subjects about relevant changes.

16.2 Legal regulations

This trial will be carried out in compliance with any applicable regulatory requirements.

Before initiating the trial, if required by the applicable regulatory requirements, the sponsor or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.

16.3 Contracts

Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial site(s), and the sponsor or its local offices, or CRO or its affiliates authorized by the sponsor, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation may serve as the basis of such contracts. In case of discrepancies with other contracts, the provisions of the protocol prevail.

In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator's participation in the trial will be specified in a contract between the investigator and sponsor, if applicable.

16.4 Subject data and data protection

Subject trial data will be stored in a manner maintaining confidentiality in accordance with applicable regulatory requirements. Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor and its personnel shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons. The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study, according to local laws and regulations. The investigator will obtain permission for direct access to original subject data from the subject as part of the written informed consent procedure (see Section 4.2). This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions, within the constraints of the applicable regulatory requirement(s), to maintain the confidentiality of the subject's identity and sponsor's proprietary information.

The sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act [HIPAA]). For US sites, the HIPAA Privacy Rule provides federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable

health information of subjects participating in sponsored clinical trials. "Authorization" is required from each research subject, i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined into the Informed Consent document (approved by the IRB) or it may be a separate document (approved by the IRB or designated Privacy Board [PB]) or provided by the investigator or sponsor (without IRB or PB approval). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

16.5 Public disclosure

The results of this trial will be publicly disclosed in accordance with applicable regulatory guidance. Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information, is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

- This trial will be registered in a primary internet registry endorsed by the WHO before enrollment of the first subject.
- Upon request via the principal investigator, trial subjects will be given access to their health data collected during the clinical trial.
- Results for all predefined outcome measures, irrespective of outcome, will be submitted for publication in academic journals wherever possible, ideally to journals providing free public full text access. The results (or parts thereof) of this trial may also be published at congresses (e.g., as a poster or oral presentation).
- The sponsor reserves the right to review any proposed full publication or poster or presentation of the results of this trial by the investigator at their respective site before they are submitted for publication or public disclosure.
- Neither the sponsor nor the investigator has the right to prohibit publication unless it can be shown to affect possible patent rights.
- Upon request, the clinical trial report will be shared with qualified scientific or medical researchers.
- Upon request individual trial subject data will be shared with qualified scientific or medical researchers if the request is approved by the sponsor and an independent Scientific Review Board.

16.6 Trial results reporting

After completion of the entire trial (Core Phase including the primary endpoint analysis and including the Extension Phase) and final statistical analysis, one final clinical trial report integrating

the outcome of all predefined outcome measures, irrespective of outcome, will be prepared by the sponsor or the sponsor's designee. The coordinating investigator will approve the final report on behalf of the participating investigators.

The outcomes of the actigraphy device measurements will be reported separately and will not be part of the final clinical trial report.

The sponsor will provide the competent authorities and relevant IECs or IRBs with a summary of the trial results in accordance with applicable regulatory requirements.

16.7 Approval

16.7.1 Sponsor

This protocol has been approved in accordance with sponsor SOPs.

16.7.2 Coordinating investigator

This protocol has been approved by the coordinating investigator.

17 REFERENCES

Other references

Investigator's brochure Qutenza (capsaicin) 8% patch, current edition.

World Health Organization. International Classification of Diseases 11th Revision. Online version available at https://icd.who.int/en/.

Guidance documents

European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical medicinal products intended for the treatment of neuropathic pain. CPMP/EWP/252/03 Rev. 1. 24 Jan 2007.

International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use. ICH harmonised guideline E9(R1). Estimands and sensitivity analysis in clinical trials. Current Step 2 version dated 16 June 2017.

Literature

Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004; 2(1): 12.

Babbar S, Marier JF, Mouksassi MS, et al. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration capsaicin patch to patients with peripheral neuropathic pain. Ther Drug Monit 2009; 31(4): 502-10.

Backonja M, Malan TP, Vanhove GF, Tobias JK; C102/106 Study Group. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. Pain Med 2010; 11(4): 600-8.

Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. Lancet Neurol 2008; 7(12): 1106-12.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale – An updated literature review. J Psychosom Res 2002; 52(2): 69-77.

Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the neuropathic pain symptom inventory. Pain 2004; 108: 248-57.

Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005; 114: 29-36.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009; 28(4): 586-604.

Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23(2): 129-38.

Cleeland CS. Pain assessment in cancer. In: Effect of Cancer on Quality of Life. Chapter 21, CRC Press-Boca Raton 1991, p. 293-305.

Dualé C, Guastella V, Morand D, et al. Characteristics of the neuropathy induced by thoracotomy: a 4-month follow-up study with psychophysical examination. Clin J Pain 2011; 27(6): 471-80.

Durkin B, Page C, Glass P. Pregabalin for the treatment of postsurgical pain. Expert Opin Pharmacother 2010; 11(16): 2751-8.

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113(1-2): 9-19.

Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016; 157(8): 1599-606.

Freeman R, Edwards R, Baron R, et al. AAPT Diagnostic criteria for peripheral neuropathic pain: focal and segmental disorders. J Pain 2019; 20(4): 369-93.

Friede T, Kieser M. Blinded sample size re-estimation in superiority and noninferiority trials: bias versus variance in variance estimation. Pharm Stat 2013; 12(3): 141-6.

Gálvez R, Navez ML, Moyle G, et al. Capsaicin 8% Patch Repeat Treatment in Nondiabetic Peripheral Neuropathic Pain: A 52-Week, Open-Label, Single-Arm, Safety Study. Clin J Pain 2017; 33(10): 921-31.

Haanpää M, Cruccu G, Nurmikko TJ, et al. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. Eur J Pain 2016; 20(2): 316-28.

Hansson P, Jensen TS, Kvarstein G, Strömberg M. Pain-relieving effectiveness, quality of life and tolerability of repeated capsaicin 8% patch treatment of peripheral neuropathic pain in Scandinavian clinical practice. Eur J Pain 2018; 22(5): 941-50.

Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013; 154(1): 95-102.

Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med 2005; 6(1): 41-4.

Hays RD, Stewart AL. Sleep measures. In: Stewart AL and Ware JE, editors. Measuring functioning and well-being: The medical outcomes study approach. Durham, NC: Duke University Press; 1992. pp. 235-59.

Irving GA, Backonja MM, Dunteman E, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. Pain Med 2011; 12(1): 99-109.

Katz J, Weinrib AZ, Clarke H. Chronic postsurgical pain: From risk factor identification to multidisciplinary management at the Toronto General Hospital Transitional Pain Service. Canadian J Pain 2019; 3(2): 49-58.

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367(9522): 1618-25.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53(3): 983-97.

Lantéri-Minet M, Perrot S. QAPSA: post-marketing surveillance of capsaicin 8% patch for long term use in patients with peripheral neuropathic pain in France. Curr Med Res Opin 2019; 35(3): 417-26.

Lavand'homme P. 'Why me?' The problem of chronic pain after surgery. Br J Pain 2017a; 11(4): 162-5.

Lavand'homme P. Transition from acute to chronic pain after surgery. Pain 2017b; 158: 50-54.

Lo Vecchio S, Andersen HH, Arendt-Nielsen L. The time course of brief and prolonged topical 8% capsaicin-induced desensitization in healthy volunteers evaluated by quantitative sensory testing and vasomotor imaging. Exp Brain Res 2018; 236(8): 2231-44.

Maihöfner CG, Heskamp ML. Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study. Eur J Pain 2014; 18(5): 671-9.

Mallinckrodt CH, Lane PW, Schnell D, et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inf J 2008; 42: 303-19.

Mankowski C, Poole CD, Ernault E, et al. Effectiveness of the capsaicin 8% patch in the management of peripheral neuropathic pain in European clinical practice: the ASCEND study. BMC Neurol 2017; 17(1): 80.

Martini CH, Yassen A, Krebs-Brown A, Passier P, Stoker M, et al. A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia. Eur J Pain 2013; 17(10): 1491-501.

Mick G, Baron R, Finnerup NB, et al. What is localized neuropathic pain? A first proposal to characterize and define a widely used term. Pain Manag 2012; 2(1): 71-7.

Permutt T. Sensitivity analysis for missing data in regulatory submissions. Stat Med 2016; 35(17): 2876-9.

Pickering G, Martin E, Tiberghien F, et al. Localized neuropathic pain: an expert consensus on local treatments. Drug Des Devel Ther 2017; 11: 2709-18.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; 4(5): 353-65.

Rejas J, Ribera MV, Ruiz M, Masrramón X. Psychometric properties of the MOS (Medical Outcomes Study) Sleep Scale in patients with neuropathic pain. Eur J Pain 2007; 11(3): 329-40.

Rolke R, Andrews K, Magerl W, Treede R-D. A standardized battery of Quantitative Sensory Testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS), v2.1, 2010. Accessed at http://www.neuro.med.tu-muenchen.de/dfns/pdfs/QST-Investigators_brochure_Version_2_1_final_english_2010_07_09.pdf.

Sadosky A, Dukes E, Evans C. Reliability of a 1-week recall period for the Medical Outcomes Study Sleep Scale (MOS-SS) in patients with fibromyalgia. Health Qual Life Outcomes 2009; 7: 12.

Scholz J, Finnerup NB, Attal N, et al. Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG). The IASP classification of chronic pain for ICD-11: Chronic neuropathic pain. Pain 2019; 160(1): 53-9.

Schug SA, Lavand'homme P, Barke A, et al. IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain 2019; 160(1): 45-52.

Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled study. J Pain 2017; 18(1): 42-53.

Treede RD, Kern KU, Husstedt IW, et al. Mechanism- and experience-based strategies to optimize treatment response to the capsaicin 8% cutaneous patch in patients with localized neuropathic pain. Curr Med Res Opin 2013; 29(5): 527-38.

Üçeyler N, Sommer C. Neuropathic pain assessment - an overview of existing guidelines and discussion points for the future. Eur Neurol Rev 2011; 6(2): 128-31.

Viala-Danten M, Martin S, Guillemin I, Hays RD. Evaluation of the reliability and validity of the Medical Outcomes Study sleep scale in patients with painful diabetic peripheral neuropathy during an international clinical trial. Health Qual Life Outcomes 2008; 6: 113.

Vinik AI, Perrot S, Vinik EJ, et al. Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: A randomised, 52-week, open-label, safety study. BMC Neurol 2016; 16(1): 251.

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6): 473-83.

Wohlrab J, Neubert RH, Heskamp ML, Michael J. Cutaneous drug delivery of capsaicin after in vitro administration of the 8% capsaicin dermal patch system. Skin Pharmacol Physiol 2015; 28(2): 65-74.

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67(6): 361-70.

18 APPENDIX

18.1 List of potentially important medical concepts – classified by System Organ Class

Blood and lymphatic system disorders		
Agranulocytosis	Aplastic anaemia	Blast cell proliferation (myeloproliferative and lymphoprolipherative disorders)
Bone marrow depression	Disseminated intravascular coagulation (DIC)	Haemolytic anaemia
Histiocytosis	Loss of anticoagulation control	Pancytopenia
Splenic haemorrhage, infarction or thrombosis	Thrombocytopenia (<30000)	Thrombotic thrombocytopenic purpura
Cardiac disorders		
Angina unstable	Atrial flutter	Atrioventricular block complete
Cardiac arrest	Cardiac failure acute	Cardiac fibrillation
Cardiac tamponade	Cardiogenic shock	Cardiomyopathy acute
Coronary artery spasm	Cor pulmonale decompensated	Myocardial infarction
Torsade de pointes	Ventricular fibrillation	Ventricular tachycardia
Ear and labyrinth disorders		
Deafness	Vestibular ataxia	
Endocrine disorders		
Adrenocortical insufficiency acute		
Eye disorders		
Cataract/lens opacity	Glaucoma	Keratitis/corneal opacification
Macular degeneration	Optic neuropathy, atrophy	Papilloedema
Ptosis	Retinal artery/vein occlusion	Retinitis
Scotoma	Sudden visual loss	Uveitis
Vitreous detachment		
Gastrointestinal disorders		
Colitis haemorrhagic	Gastric ulcer haemorrhage	Gastric ulcer perforation
Haematemesis	Haemoperitoneum	Ileus
Intestinal ischaemia	Intestinal perforation	Melaena
Mesenteric occlusion	Mesenteric vein thrombosis	Pancreatitis
Peritonitis		
General disorders and administration site conditions		
Malignant hyperthermia		
Hepatobiliary disorders		
Hepatic failure	Hepatitis fulminant	Hepatic necrosis
Hepatorenal syndrome	Portal hypertension	Reye’s syndrome

Immune system disorders		
Amyloidosis	Anaphylactic reaction	Anaphylactic shock
Graft versus host disease		
Infections and infestations		
Endotoxic shock	Sepsis	Toxic shock syndrome
Transmission of an infectious agent via a medicinal product		
Injury, poisoning and procedural complications		
Transplant failure	Wound dehiscence	
Metabolism and nutrition disorders		
Diabetic coma	Failure to thrive	Hypercalcaemia (CTC IV)
Hyperkalaemia (CTC IV)	Hypocalcaemia (CTC IV)	Hypokalaemia (CTC IV)
Lactic acidosis	Porphyria	Shock hypoglycaemic
Tetany		
Musculoskeletal and connective tissue disorders		
Aseptic necrosis bone	Fracture pathological	Muscle necrosis
Osteomalacia	Rhabdomyolysis	Systemic lupus erythematosus
Systemic sclerosis		
Nervous system disorders		
Amnesia	Anticholinergic syndrome	Aphasia
Cerebral oedema	Chorea	Coma
Convulsions	Demyelination	Encephalitis
Encephalopathy	Epilepsy	Guillain-Barré syndrome
Hydrocephalus	Intracranial haemorrhage	Meningitis
Multiple sclerosis	Myasthenia gravis	Myelitis
Neuroleptic malignant syndrome	Opisthotonus	Paralysis
Paresis	Parkinson’s syndrome	Serotonin syndrome
Stroke	Tunnel vision	
Pregnancy, puerperium and perinatal conditions		
Abortion	Eclampsia	Intra-uterine death
Psychiatric disorders		
Anorexia nervosa	Delirium	Drug abuse
Drug dependence	Homicidal ideation	Intentional misuse
Self-injurious ideation/attempt	Suicidal ideation/attempt	Suicide completed
Renal and urinary disorders		
Anuria	Goodpasture’s syndrome	Haemolytic uraemic syndrome
Nephritis/nephritic syndrome	Nephrotic syndrome	Oliguria
Renal failure acute	Renal tubular necrosis	Urinary obstruction/retention

Reproductive system and breast disorders		
Metrorrhagia/uterine haemorrhage	Priapism	
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	Adult respiratory distress syndrome	Alveolitis allergic
Asphyxia	Bronchospasm	Laryngeal oedema
Pulmonary fibrosis	Pulmonary haemorrhage	Pulmonary infarction
Pulmonary vasculitis	Respiratory arrest	Status asthmaticus
Pulmonary oedema		
Skin and subcutaneous tissue disorders		
Angioneurotic oedema	Erythema nodosum	Pemphigus
Stevens-Johnson syndrome	Toxic epidermal necrolysis	Vascular purpura
Vascular disorders		
Acute circulatory failure	Embolism	Malignant hypertension
Necrosis ischaemic	Thrombosis	

Status: Dec 2017

CTC = Common Toxicity Criteria also referred to as the Common Terminology Criteria for Adverse Events (CTCAE).

18.2 Other assessment tools

The included assessment tools are examples. Copies of the versions used in the trial will be filed in the TMF.

18.2.1 Douleur Neuropathique 4 interview



Questionnaire DN4-Interview

Please complete this questionnaire by checking one answer for each item in the 2 questions below:

PATIENT INTERVIEW

Question 1: Does the pain have one or more of the following characteristics?

	YES	NO
1 - Burning	☐	☐
2 - Painful Cold	☐	☐
3 - Electric Shocks	☐	☐

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	YES	NO
4 - Tingling	☐	☐
5 - Pins and Needles	☐	☐
6 - Numbness	☐	☐
7 - Itching	☐	☐

Patient Score: /7

DN4© 2005. Bouhassira D. All rights reserved.
DN4 - United States/English - Version of 28 Jun 2019 - Mapi.
ID0295-TR-83448 / DN4-Interview_AU1.2_eng-US.doc

18.2.2 Medical Outcomes Study Sleep Scale

Translation Copyright © YEARS QualityMetric Incorporated. All rights reserved. (Country (Language) MOS 12-Item Sleep Scale Acute–Revised)
Your Sleep For each of the following questions, please select the one response that best describes your answer.
How long did it usually take for you to fall asleep during the past week? 0-15 minutes 16-30 minutes 31-45 minutes 46-60 minutes More than 60 minutes
On the average, how many hours did you sleep each night during the past week?

How often during the <u>past week</u> did you… Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)? All of the time Most of the time Some of the time A little of the time None of the time
How often during the <u>past week</u> did you… Get enough sleep to feel rested upon waking in the morning? All of the time Most of the time Some of the time A little of the time None of the time
How often during the <u>past week</u> did you… Awaken short of breath or with a headache? All of the time Most of the time Some of the time A little of the time None of the time
How often during the <u>past week</u> did you… Feel drowsy or sleepy during the day? All of the time Most of the time Some of the time A little of the time None of the time

How often during the past week did you… Have trouble falling asleep? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Awaken during your sleep time and have trouble falling asleep again? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Have trouble staying awake during the day? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Snore during your sleep? All of the time Most of the time Some of the time A little of the time None of the time

How often during the past week did you… Take naps (5 minutes or longer) during the day? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Get the amount of sleep you needed? All of the time Most of the time Some of the time A little of the time None of the time

18.2.3 Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(US/English)

PGIC - USA/English – Original version
PGI-C_TS1.0_ID2036-2387_eng-USori.doc

18.2.4 Neuropathic Pain Symptom Inventory

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI)

Correspondence: Dr Didier Bouhassira
INSERM U-792, Centre d'Evaluation et de Traitement de la Douleur
Hôpital Ambroise Paré, 92100 Boulogne-Billancourt, France
didier.bouhassira@apr.ap-hop-paris.fr

Date: .....

First Name: ..... **Last Name:** .....

Sex: .....

Age: .....

You are suffering from pain due to injury or disease of the nervous system. There may be several types of this pain. You may have spontaneous pain, that is pain in the absence of any stimulation, which may be long-lasting or occur as brief attacks. You may also have pain provoked or increased by brushing, pressure, contact with something cold on the painful area. You may feel one or several types of pain. This questionnaire has been developed to help your doctor to better evaluate and treat the various types of pain you feel.

*We wish to know if you feel spontaneous pain, that is pain without any stimulation. For each of the following questions, please circle the number that best describes the **average severity of your spontaneous pain during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q1/. Does your pain feel like burning?

No burning	0	1	2	3	4	5	6	7	8	9	10	Worst burning imaginable

Q2/. Does your pain feel like squeezing?

No squeezing	0	1	2	3	4	5	6	7	8	9	10	Worst squeezing imaginable

Q3/. Does your pain feel like pressure?

No pressure	0	1	2	3	4	5	6	7	8	9	10	Worst pressure imaginable

Q4/. **During the past 24 hours**, your spontaneous pain has been present:

Tick the response that best describes your case.

Permanently	/_/
Between 8 and 12 hours	/_/
Between 4 and 7 hours	/_/
Between 1 and 3 hours	/_/
Less than 1 hour	/_/

*We wish to know if you have brief attacks of pain. For each of the following questions, please circle the number that best describes the **average severity of your painful attacks during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q5/. Does your pain feel like electric shocks?

No electric shocks	0	1	2	3	4	5	6	7	8	9	10	Worst electric shocks imaginable

Q6/. Does your pain feel like stabbing?

No stabbing	0	1	2	3	4	5	6	7	8	9	10	Worst stabbing imaginable

Q7/. **During the past 24 hours**, how many of these pain attacks have you had?

Tick the response that best describes your case.

More than 20	/_/
Between 11 and 20	/_/
Between 6 and 10	/_/
Between 1 and 5	/_/
No pain attack	/_/

NPSI © 2004. Bouhassira D. et al. All rights reserved.
NPSI - United Kingdom/English - MAPI Institute.
ID6919 / NPSI_AU1.0_eng-GBorl.doc

We wish to know if you feel pain provoked or increased by brushing, pressure, contact with something cold on the painful area. For each of the following questions, please circle the number that best describes the average severity of your provoked pain during the past 24 hours. Circle the number 0 if you have not felt such pain. (Circle one number only.)

Q8/. Is your pain provoked or increased by brushing on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q9/. Is your pain provoked or increased by pressure on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q10/. Is your pain provoked or increased by **contact** with something cold on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

We wish to know if you feel abnormal sensations in the painful area. For each of the following questions, please circle the number that best describes the average severity of your abnormal sensations during the past 24 hours. Circle the number 0 if you have not felt such sensations. (Circle one number only.)

Q11/. Do you feel pins and needles?

No pins & needles	0	1	2	3	4	5	6	7	8	9	10	Worst pins & needles imaginable

Q12/. Do you feel tingling?

No tingling	0	1	2	3	4	5	6	7	8	9	10	Worst tingling imaginable

RESULTS

TOTAL SCORE	SUBSCORES
1 – Q1 = ...	(SUPERFICIAL SPONTANEOUS) BURNING PAIN: Q1= ...../10
2 – (Q2+Q3) = ...	(DEEP SPONTANEOUS) PRESSING PAIN: (Q2+Q3)/2 = .../10
3 – (Q5+Q6) = ...	PAROXYSMAL PAIN: (Q5+Q6)/2 = .../10
4 – (Q8+Q9+Q10) = ...	EVOKED PAIN: (Q8+Q9+Q10)/3= ...../10
5 – (Q11+Q12) = ...	PARESTHESIA/DYSESTHESIA: (Q11+Q12)/2 = .../10
(1+2+3+4+5) = .../100	

NPSI © 2004. Bouhassira D. et al. All rights reserved.
NPSI - United Kingdom/English - MAPI Institute.
ID5919 / NPSI_AU1.0_eng-GBorl.doc

18.2.5 Brief Pain Inventory Questions 9A to 9G

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

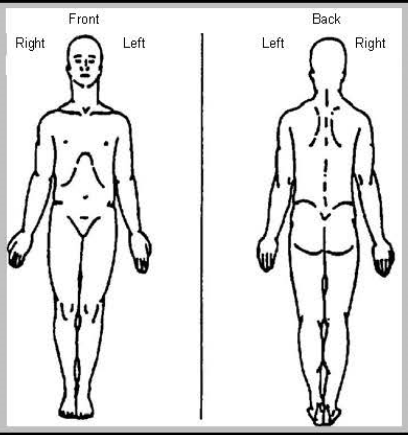
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

18.2.6 Short Form-36 Health Survey

Your Health and Well-Being

SAMPLE

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36v2™ Health Survey © 1992-2002 by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(IQOLA SF-36v2 Acute, English (United Kingdom) 8/02)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	<u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Had <u>difficulty</u> performing the the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

SAMPLE

8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. **These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

Thank you for completing these questions!

18.2.7 Treatment Satisfaction Questionnaire for Medication

TSQM *(Version 1.4)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please select the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Copyright © Quintiles. All Rights Reserved.

4. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

Copyright © Quintiles. All Rights Reserved.

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

Copyright © Quintiles. All Rights Reserved.

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Copyright © Quintiles. All Rights Reserved.

18.2.8 Hospital Anxiety and Depression Scale

The lines for name and date, as well as scores will not be shown in the version that the subject completes.

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

HADS copyright © R.P. Snaith and A.S. Zigmond, 1983, 1992, 1994.
Record form items originally published in *Acta Psychiatrica Scandinavica*, 67, 361–70,
copyright © Munksgaard International Publishers Ltd, Copenhagen, 1983.
This edition first published in 1994 by nferNelson Publishing Company Ltd.
GL Assessment, 9th Floor East, 389 Chiswick High Road, London W4 4AL.
GL Assessment is part of the GL Education Group.
This form may not be reproduced by any means without first obtaining permission from the publisher.
Email: permissions@gl-assessment.co.uk

f:\institut\cuttadap\project\4480\study4480\questionnaire\original\forproject\hadsukoriq03_mapi.doc_18/01/08_aja

18.2.9 Neurological/sensory examination

The objective of the neurological/sensory examination is to assess sensory function at baseline and to re-assess the same following treatment with IMP. The examinations will be performed by the investigator who will have received training. The findings will be captured in the CRF using pre-defined scales. Ideally, assessments should be performed by the same person for a subject.

The following tests will be performed within the boundaries of the treatment area.

Warm sensation

- Assess the warm sensation using a warmed electronic thermometer (to be provided to all trial sites by the sponsor).
- Heat the thermometer probe in hot water, remove and dry it and allow it to cool, if needed, until the displayed temperature is **43ºC to 44ºC**. *To avoid injury, the thermometer should never exceed 44ºC when placed in contact with the subject.*
- Ask the subject to keep his/her eyes closed during the assessment.
- As a demonstration, apply the distal flat end of the warmed thermometer to the unaffected area for **2 seconds to 3 seconds** and ask the subject to rate what he/she feels.
- Subsequently, re-warm the thermometer in hot water, remove and dry it and allow it to cool, if needed, until the displayed temperature is 43ºC to 44ºC.
- Apply the distal flat end in sequence to the test area for **2 seconds to 3 seconds**. Re-warm the thermometer following each application, or as often as needed to maintain a displayed temperature of 43ºC to 44ºC prior to a subsequent application.
- Ask the subject to rate what he/she feels during each application of the thermometer.
- Capture the subject's rating for the most intense sensation evoked, according to the Warm Rating Scale below.

Warm Rating Scale

0 = Warm probe is not felt (absent).

1 = Warm probe is barely felt (diminished).

2 = Warm probe is felt normally (normal).

3 = Warm probe is felt more than usual, but not paresthetic/dysesthetic nor painful (increased).

4 = Warm probe is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal).

5 = Warm probe is felt more than usual, and is painful (increased and painful).

Pinprick

- Pinprick will be assessed using a device (to be provided to all trial sites by the sponsor).
- Ask the subject to keep their eyes closed during the assessment.

- As a demonstration, apply the device to the subject's unaffected area every **2 seconds to 3 seconds**.
- Subsequently, apply the device to several locations within the treatment area in the same manner.
- Perform the assessments at several locations within the treatment area, and only rate the most intense sensation evoked.
- Ask the subject to rate what he/she feels during each application.
- Capture the subject's rating application using the Pinprick Rating Scale below.
- Since pinprick may be considered painful even by normal subjects, the sensation should be compared with the unaffected reference area and should be documented as normal if the evoked sensation is the same.

Pinprick Rating Scale

0 = Pinprick is not felt (absent).

1 = Pinprick is barely felt (diminished).

2 = Pinprick is felt normally (normal).

3 = Pinprick is felt more than usual, but not paresthetic/dysesthetic nor painful (increased).

4 = Pinprick is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal).

5 = Pinprick is felt more than usual, and is painful (increased and painful).

Cold sensation

- Assess cold sensation using a tuning fork dipped in ice water and dried.
- Ask the subject to keep his/her eyes closed during the assessment.
- As a demonstration, apply the distal flat end of the tuning fork to the anterior thigh or upper forearm for **2 seconds to 3 seconds** and ask the subject to rate what he/she feels ("not cold, slightly cold, cold, or painfully cold").
- Apply the distal flat end in sequence to several locations within the treatment area for **2 seconds to 3 seconds**. *Make sure to dip the tuning fork in ice water to cool it back down following each application*.
- Ask the subject to rate what he/she feels during each application of the tuning fork ("not cold, slightly cold, cold, or painfully cold").
- Capture the subject's rating for the most intense sensation evoked for each test area, according to the Cold Rating Scale, below.

Cold Rating Scale

0 = Tuning fork is felt as not cold (absent).

1 = Tuning fork is felt as slightly cold (diminished).

2 = Tuning fork is felt as cold (normal).

3 = Tuning fork is felt as painfully cold (increased).

4 = Tuning fork is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal).

5 = Tuning fork is felt more than usual, and is painful (increased and painful).

18.2.10 Work Productivity and Activity Impairment questionnaire - for neuropathic pain

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: NEUROPATHIC PAIN V2.0 (WPAI:NEUROPATHIC PAIN)

The following questions ask about the effect of your Neuropathic Pain on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ No ___ Yes
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Neuropathic Pain? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Neuropathic Pain. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: NEUROPATHIC PAIN V2.0 (WPAI:NEUROPATHIC PAIN)

5. During the past seven days, how much did your Neuropathic Pain affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Neuropathic Pain affected your work only a little, choose a low number. Choose a high number if Neuropathic Pain affected your work a great deal.

Consider only how much Neuropathic Pain affected productivity while you were working.

Neuropathic Pain had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Neuropathic Pain completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Neuropathic Pain affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Neuropathic Pain affected your activities only a little, choose a low number. Choose a high number if Neuropathic Pain affected your activities a great deal.

Consider only how much Neuropathic Pain affected your ability to do your regular daily activities, other than work at a job.

Neuropathic Pain had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Neuropathic Pain completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-65.

19 PROTOCOL AMENDMENTS

19.1 Protocol Amendment 01

Amendment rationale

This amendment has been implemented to introduce changes to improve recruitment into the trial:

- The Screening Period has been extended by 1 week to allow more flexibility for the sites in planning the Randomization Visit. This change also allows subjects more freedom to plan their travel to the sites and to adapt to their working schedule.
- Inclusion Criterion 4 has been updated to allow a history of post-surgical pain with a duration of up to 60 months rather than 36 months.

Based on published data (Martini et al. 2013), it is assumed that with longer duration of symptoms the chance for treatment response might decrease gradually over time. However, there is no data available supporting a specific cut-off timeline. The extension of history of post-surgical pain up to 60 months is similar to the time frame chosen in a recent trial in this indication (NCT01701362). With this adaptation, treatment can be made available to a wider patient population with a clinically relevant medical need for treatment.

A description of the impact of the COVID-19 pandemic has also been added to the benefit-risk assessment, as requested by the Polish ethics committee. Additional specifications relating to COVID-19 were added to Exclusion Criterion 14.

The following changes have also been made:

- For clarity, a more precise description of the calculation of the baseline pain value was included.
- For clarity and to take into account the history of pain duration, “time since diagnosis of PSNP” was changed to “time since onset of pain after surgery” and “date of the diagnosis of PSNP” was changed to “date of onset of pain after surgery”.
- To improve clarity, an example of an acceptable dermal assessment score was added to Inclusion Criterion 8.
- To improve clarity, a specification was added to Exclusion Criterion 6, to avoid exclusion of subjects otherwise eligible.
- To synchronize with vital signs assessments, the timing of the “pain now” assessment has been changed from “55 minutes after IMP removal” to “55 minutes after IMP application” in Section 12.3.6.
- To differentiate application-associated pain from pain induced by neurological examination (as part of the dynamic mechanical allodynia assessment), the term “DMA-NPRS” has been introduced. The respective NPRS scale has also been added.
- Pain rating diagrams have been updated to ensure equal spacing between the numbers on the scales.
- The method of collection of the DN4i has been clarified. This assessment will be recorded in the tablet computer at the site rather than the electronic CRF. This will allow adjudicators to access the data they require more easily.

- To avoid additional work for the sites, the description of the physical examination assessments was clarified.
- Descriptions of the ANCOVA model in Section 14.6.3.2 and Section 14.6.3.3 were corrected to replace reference to "baseline treatment area size" with "baseline pain intensity" as a covariate.
- Reference to analysis of expectedness of adverse events has been removed as this will no longer be collected in the clinical database due to revised internal processes. This change does not affect the process of assessment of expectedness of SAEs reported to the Global Drug Safety Database.
- Reference to the data on occupational exposure being presented in the final study report has been removed. This data will only be collected in the safety database, not in the clinical database. As the data is not related to the study objectives, no analysis will be presented in the final clinical trial report.
- The DN4i is now presented correctly in Section 18.2.1.
- All 14 questions of the TSQM are now displayed correctly in Section 18.2.7.
- As the medical monitor is not required to sign the protocol, reference to this role has been removed from the title page.
- The EudraCT number has been referenced on the title page to facilitate interactions with the EU authorities.
- The Universal Trial Number has been added to the title page.
- The affiliation of the Sponsor's signatory has been corrected to GRT US Holding, Inc.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

<table>
<tr><td colspan="4">Changes to this protocol include:</td></tr>
<tr><td colspan="2">Formerly read:</td><td colspan="2">Now reads:</td></tr>
<tr><td colspan="4">Title page</td></tr>
<tr><td><s>Medical monitor:</s><s>*</s>
Sponsor's signatory:</td><td><s>n.n.</s>
Lizandra Marcondes, MD, Head of Medical Affairs and Clinical Development, G<s>rünenthal</s> US Holding, Inc.</td><td>[Row deleted]
Sponsor's signatory:</td><td>Lizandra Marcondes, MD, PhD
Head of Medical Affairs and Clinical Development, GRT US Holding, Inc.</td></tr>
<tr><td colspan="2">[…]
IND number: 063354</td><td colspan="2">[…]
IND number: 063354
EudraCT number: 2021-001409-64
Universal Trial Number: U1111-1272-1340</td></tr>
</table>

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.1.1: Flow diagram summary of the trial	
Figure 1: Flow diagram of the Screening Period (Day ~~-12~~ to Day -1) and the Core Phase of the Treatment Period (Day 1 to Week 12)	Figure 1: Flow diagram of the Screening Period (Day *-19* to Day -1) and the Core Phase of the Treatment Period (Day 1 to Week 12)
[The V1 box within the figure was also updated to reflect the new time period of Day-19 to Day-7.]	
Section 1.1.2: Brief description of the sequence and duration of all trial periods	
After a Screening Period of up to ~~12~~ days, including the Baseline Phase from Day -7 to Day -1, subjects will be allocated to Qutenza or to low-dose capsaicin control topical system…	After a Screening Period of up to *19* days, including the Baseline Phase from Day -7 to Day -1, subjects will be allocated to Qutenza or to low-dose capsaicin control topical system…
Section 1.3.1: Inclusion criteria	
4. Documented diagnosis of PSNP by the following criteria: a. A history of post-surgical pain with a duration of at least 6 months to maximally ~~36~~ months that is plausibly related to the surgical intervention as documented on a body map. […] 6. The subject has moderate to severe pain with a baseline value for 24-hr average pain intensity of at least 4 points on the NPRS. The baseline value is calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1). At least 5 (out of 7) pain ratings should be available during the Baseline Phase. If less than 5 pain ratings are available, the subject may be rescheduled for Visit 2 (1 time only) after having received appropriate re-training in the use of the e-diary to ensure compliance. […] 8. The skin in the area where the IMP will be applied, and that may also contain the scar tissue, is intact, dry, and non-irritated (i.e., there are no signs and symptoms of skin disease, skin irritation, inflammation or injury, such as active herpes zoster lesions, atopic dermatitis, ulceration, wounds).	4. Documented diagnosis of PSNP by the following criteria: a. A history of post-surgical pain with a duration of at least 6 months to maximally *60* months that is plausibly related to the surgical intervention as documented on a body map. […] 6. The subject has moderate to severe pain with a baseline value for 24-hr average pain intensity of at least 4 points on the NPRS. The baseline value is calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1). At least 5 (out of *the last* 7 *days*) pain ratings should be available during the Baseline Phase. If less than 5 pain ratings are available *in the last 7 days*, the subject may be rescheduled for Visit 2 (1 time only) after having received appropriate re-training in the use of the e-diary to ensure compliance. […] 8. The skin in the area where the IMP will be applied, and that may also contain the scar tissue, is intact, dry, and non-irritated (i.e., there are no signs and symptoms of skin disease, skin irritation, inflammation or injury, such as active herpes zoster lesions, atopic dermatitis, ulceration, wounds). *This is reflected by a dermal assessment score of 0 = "no evidence of irritation" or 1 = "minimal erythema, barely perceptible".*
Section 1.3.2: Exclusion criteria	
6. Other painful conditions in the body area that is affected by PSNP and may affect efficacy or safety assessments including infectious, non-infectious, inflammatory or neuropathic conditions which could also be complications related to the previous surgical procedure. […]	6. Other painful conditions in the body area that is affected by PSNP and may affect efficacy or safety assessments *and cannot be discriminated from the target pain by the subject,* including infectious, non-infectious, inflammatory or neuropathic conditions which could also be complications related to the previous surgical procedure.

<table>
<tr><td colspan="4">Changes to this protocol include:</td></tr>
<tr><td colspan="2">Formerly read:</td><td colspan="2">Now reads:</td></tr>
<tr><td colspan="2">14. Patients with current clinically significant disease(s) or condition(s) (including clinically significant cardiovascular disease and/or significant pain in other areas) that may affect efficacy or safety assessments, or any other reason which, in the investigator’s opinion, may preclude the subject’s participation in the full duration of the trial.</td><td colspan="2">[…]
14. Patients with current clinically significant disease(s) or condition(s) (including clinically significant cardiovascular disease and/or significant pain in other areas) that may affect efficacy or safety assessments, or any other reason which, in the investigator’s opinion, may preclude the subject’s participation in the full duration of the trial. Patients with current signs and symptoms consistent with Coronavirus disease 2019 (COVID-19) (e.g., dry cough, dyspnea, sore throat, fatigue, fever) or patients who had those symptoms within the last 14 days prior to screening and had a positive SARS-CoV2 PCR test result.</td></tr>
<tr><td colspan="4">Section 1.5.3.1: Analysis of the primary endpoint</td></tr>
<tr><td colspan="2">The baseline pain will be calculated from the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of 7 must be available.
[…]
The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since <s>diagnosis of PSNP</s> (<1 year…</td><td colspan="2">The baseline pain will be calculated from the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of the last 7 days must be available.
[…]
The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since onset of pain after surgery (<1 year…</td></tr>
<tr><td colspan="4">Section 1.7: Schedule of events</td></tr>
<tr><td></td><td>Screening Visit</td><td></td><td>Screening Visit</td></tr>
<tr><td>Day</td><td><s>-12</s> to -7</td><td>Day</td><td>-19 to -7</td></tr>
<tr><td colspan="2">[…]
c) Including relevant surgical history (date of surgery, location and type of surgery leading to PSNP, and indication for the surgery) and date of <s>diagnosis of PSNP</s>.</td><td colspan="2">[…]
c) Including relevant surgical history (date of surgery, location and type of surgery leading to PSNP, and indication for the surgery) and date of onset of pain after surgery.</td></tr>
<tr><td colspan="4">Section 3.1: Abbreviations</td></tr>
<tr><td>BPI</td><td>Brief Pain Inventory</td><td>BPI</td><td>Brief Pain Inventory</td></tr>
<tr><td>CRO(s)</td><td>Contract Research Organization(s)</td><td>COVID-19</td><td>Coronavirus disease 2019</td></tr>
<tr><td></td><td></td><td>CRO(s)</td><td>Contract Research Organization(s)</td></tr>
</table>

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 8.2: Benefit/risk analysis	
Beyond the risks described above, there are no other trial-related risks, e.g., due to the use of invasive or non-standard procedures. **Benefits/risks conclusion**	Beyond the risks described above, there are no other trial-related risks, e.g., due to the use of invasive or non-standard procedures. ***Risks relating to the COVID-19 pandemic*** *Based on the clinical experience with Qutenza, which is applied topically, it is not considered to affect the patient's health status in such a way that the susceptibility to COVID-19 disease would be increased beyond the basic susceptibility of the individual patient based on the prevailing medical condition and comorbidities.* *Before patients are enrolled into the trial, a proper eligibility assessment is performed including assessment of their general health status. Patients will be excluded if they meet any criteria that could affect their underlying condition and susceptibility to COVID-19 (see Exclusion Criteria 10 to 14).* *The patient's personal visits to the sites are reduced to a minimum to ensure scientific validity of the trial by adhering to the essential endpoint assessments. Frequent telephone contacts or more extensive telephone visits are implemented to lower the burden of the patients and to avoid unnecessary travel. During the Extension Phase of the trial, the patient returns to the site only for re-application of the IMP, or, in case no further IMP applications take place, one time at the midpoint of the Extension Phase to keep the patient in the trial and thus to support scientific validity of the outcome of the trial.* **Benefits/risks conclusion** […] *The risk for SARS-Cov-2 exposure and COVID-19 disease is unlikely impacted or increased by participation in this clinical trial.*
Section 10.3: Method of assigning subjects to treatment groups (randomization)	
A stratified block randomization will be performed by country/region with the stratification factors, intake of concomitant medication for treatment of PSNP (no/yes), and time since ~~diagnosis of PSNP~~ (categories short duration [≤1 year] and long duration [>1 year]).	A stratified block randomization will be performed by country/region with the stratification factors, intake of concomitant medication for treatment of PSNP (no/yes), and time since *onset of pain after surgery* (categories short duration [≤1 year] and long duration [>1 year]).
Section 11.1.1.1: Screening Visit (Visit 1, Day -19 to Day -7)	
11.1.1.1 Screening Visit (Visit 1, Day -~~12~~ to Day -7) […] and date of ~~PSNP diagnosis~~. The documentation…	11.1.1.1 Screening Visit (Visit 1, Day -*19* to Day -7) […] and date of *onset of pain after surgery*. The documentation…

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.1.2: Relevant medical history and details of the surgery leading to PSNP	
The date of ~~the diagnosis of PSNP~~ must also be recorded on this CRF page.	The date of *onset of pain after surgery* must also be recorded on this CRF page.
Section 12.1.4: Physical examination	
The physical examination will have a special focus on the post-surgical site and scar tissue. The size of the scar will be documented, and whether the investigator considers the scar tissue to be normal or pathological. Any abnormality will be specified.	The physical examination will have a special focus on the post-surgical site and scar tissue. *At the Screening Visit, t*he size of the scar will be documented, and whether the investigator considers the scar tissue to be normal or pathological. Any abnormality will be specified.
Section 12.1.6: Douleur Neuropathique 4 assessment	
The DN4i questionnaire will be completed only at Visit 1 (Screening Visit). The outcome of this assessment is relevant for subject selection (Inclusion Criterion 4) and will be recorded in the ~~CRF~~.	The DN4i questionnaire will be completed only at Visit 1 (Screening Visit). The outcome of this assessment is relevant for subject selection (Inclusion Criterion 4) and will be recorded in the *tablet computer at the site.*
Section 12.2.1: Pain intensity (11-point NPRS)	
[The pain rating diagram was updated to ensure an equal spacing between all numbers.]	
Section 12.2.2: Dynamic mechanical allodynia	
• Ask the subject to rate the intensity of the pain created by the procedure on an 11-point NPRS (from 0 to 10).	• Ask the subject to rate the intensity of the pain created by the procedure on an 11-point NPRS (from 0 to 10)*, (DMA-NPRS). Subjects will be asked to answer the following question:* *"Please rate your pain related to the procedure by selecting the one number that best describes how much pain you have right now."* *[0 to 10 pain scale added]*
Section 12.3.6: "Pain now" (current pain intensity on the NPRS) related to the IMP application site	
"Pain now" will be rated at the following time points: 15 mins before local anesthetic application and at 55 mins after IMP ~~removal~~.	"Pain now" will be rated at the following time points: 15 mins before local anesthetic application and at 55 mins after IMP *application*.
[The pain rating diagram was updated to ensure an equal spacing between all numbers.]	
Section 12.3.7: Data on occupational exposure	
The additional safety reporting form enables the trial personnel to report accidental exposure, which would not be possible with a safety report form intended for adverse event reporting in subjects. ~~The collected data on occupational exposure (i.e., exposure occurring in trial personnel) will be analyzed and presented in the final study report.~~	The additional safety reporting form enables the trial personnel to report accidental exposure, which would not be possible with a safety report form intended for adverse event reporting in subjects.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.6.2.1: Primary efficacy analysis	
The 24-hr average pain intensity will be assessed once daily in the evening using an 11-point NPRS. Baseline pain will be calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of 7 must be available. […] **Primary analysis model** The primary efficacy analysis will be performed using an MMRM. The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since ~~diagnosis of PSNP~~ (<1 year…	The 24-hr average pain intensity will be assessed once daily in the evening using an 11-point NPRS. Baseline pain will be calculated as the average of the 24-hr average pain intensity ratings of the Baseline Phase (Day -7 to Day -1); at least 5 pain ratings out of *the last* 7 *days* must be available. […] **Primary analysis model** The primary efficacy analysis will be performed using an MMRM. The model will include fixed effects of treatment, country/region, gender, time (corresponding to trial week), and treatment-by-time interaction, time since *onset of pain after surgery* (<1 year…
Section 14.6.3.1: Analysis of treatment area size	
Change of treatment area size from baseline to Week 12 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since ~~diagnosis of PSNP~~ (<1 year…	Change of treatment area size from baseline to Week 12 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since *onset of pain after surgery* (<1 year…
Section 14.6.3.2: Analysis of 24-hr average pain intensity from baseline to Week 42 Section 14.6.3.3: Analysis of 24-hr average pain intensity from baseline between Week 2 and Week 42	
[…] will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since ~~diagnosis of PSNP~~ (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline ~~treatment area size~~, as covariates.	[…] will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since *onset of pain after surgery* (<1 year or ≥1 year), intake of concomitant medication for treatment of PSNP, and baseline *pain intensity*, as covariates.
Section 14.6.3.4.1: Medical Outcomes Study Sleep Scale	
Change in the 9-item sleep problem index (Sadosky et al. 2009) of the MOS Sleep Scale from baseline to Week 12 and to Week 42 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since ~~diagnosis of PSNP~~ (<1 year…	Change in the 9-item sleep problem index (Sadosky et al. 2009) of the MOS Sleep Scale from baseline to Week 12 and to Week 42 will be analyzed using an ANCOVA model with treatment group, country/region, gender, time since *onset of pain after surgery* (<1 year…
Section 14.6.3.4.2: Patient Global Impression of Change	
For the PGIC responder analysis, a logistic regression model with treatment group, country/region, gender, time since ~~diagnosis of PSNP~~ (<1 year…	For the PGIC responder analysis, a logistic regression model with treatment group, country/region, gender, time since *onset of pain after surgery* (<1 year…
Section 14.6.3.4.3: Responder analysis	
For the responder analysis at Week 12 and Week 42, with response to treatment defined as a reduction from baseline pain intensity of at least 30%, a logistic regression model with treatment group, country/region, gender, time since ~~diagnosis of PSNP~~ (<1 year…	For the responder analysis at Week 12 and Week 42, with response to treatment defined as a reduction from baseline pain intensity of at least 30%, a logistic regression model with treatment group, country/region, gender, time since *onset of pain after surgery* (<1 year…

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.7.1: Analysis of adverse events	
Additional summaries by intensity, causal relationship, outcome, countermeasure, time to onset, ~~duration, and expectedness~~, will be provided.	Additional summaries by intensity, causal relationship, outcome, countermeasure, *and* time to onset, will be provided.
Section 17: References	
Mankowski C, Poole CD, Ernault E, et al. Effectiveness of the capsaicin 8% patch in the management of peripheral neuropathic pain in European clinical practice: the ASCEND study. BMC Neurol 2017; 17(1): 80. Mick G, Baron R, Finnerup NB, et al. What is localized neuropathic pain? A first proposal to characterize and define a widely used term. Pain Manag 2012; 2(1): 71-7.	Mankowski C, Poole CD, Ernault E, et al. Effectiveness of the capsaicin 8% patch in the management of peripheral neuropathic pain in European clinical practice: the ASCEND study. BMC Neurol 2017; 17(1): 80. *Martini CH, Yassen A, Krebs-Brown A, Passier P, Stoker M, et al. A novel approach to identify responder subgroups and predictors of response to low- and high-dose capsaicin patches in postherpetic neuralgia. Eur J Pain 2013; 17(10): 1491-501.* Mick G, Baron R, Finnerup NB, et al. What is localized neuropathic pain? A first proposal to characterize and define a widely used term. Pain Manag 2012; 2(1): 71-7.
Section 18.2.1: Douleur Neuropathique 4 interview	
[The Douleur Neuropathique 4 was replaced with the Douleur Neuropathique 4 interview.]	
Section 18.2.7: Treatment Satisfaction Questionnaire for Medication	
[Questions 10 to 14 of the Treatment Satisfaction Questionnaire for Medication were added to the section.]	