TITLE PAGE

FULL/LONG TITLE OF THE TRIAL

Efficacy, patient acceptability and safety of topical treatment versus systemic treatment: a randomised, multicenter, comparative pragmatic trial in adult patients suffering from diverse localized neuropathic pain (LNP) syndromes.

SHORT STUDY TITLE / ACRONYM

Localized neuropathic pain: topical treatment versus systemic treatment.

PELICAN (**P**r**E**gabalin**LI**docaine**CA**psaicin**N**europathicpain)

PROTOCOL VERSION NUMBER AND DATE

Protocol version 5.0 released on January 20, 2020

RESEARCH REFERENCE NUMBERS

Clinical Trials.gov	NCT03348735
EudraCT Number:	2018-003617-17
KCE Trial Number:	KCE-17007

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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TRIAL SUMMARY

Trial Title	Efficacy, patient acceptability and safety of topical treatment versus systemic treatment: a randomised, multicenter, comparative pragmatic trial in adult patients suffering from diverse localized neuropathic pain (LNP) syndromes.	
Internal ref. no. (short title)	KCE-17007 (Localized neuropathic pain: topical treatment versus systemic treatment)	
Trial Design	Multicenter three arm 1:1:1 randomised, open-label comparative trial.	
Trial Participants	Adult patients suffering from localized neuropathic pain (LNP) across a wide variety of etiologies, with a duration between 1 and 24 months (subacute to chronic neuropathic pain conditions).	
Planned Sample Size	591	
Treatment duration	24 weeks	
Follow up duration	2 weeks	
Planned Trial Period	21 months between first patient first visit and last patient last visit, 27 months till Clinical Study Report.	
	Objectives	**Endpoints**
Primary	To determine if topical treatment significantly improves health-related quality of life compared to systemic treatment in adult patients suffering from localized neuropathic pain across a wide variety of etiologies (LNP), with a duration between 1 and 24 months.	Change in EQ-5D-5L from baseline to 6 weeks.
Secondary	To compare the effectiveness in terms of pain relief between the treatment arms. To compare the effectiveness in different aspects of quality of life between the treatment arms.	Reduction in pain intensity (PI-NRS), time to worsening of the pain (PI-NRS and NPSI) and use of rescue medication (MSQ III-R). AUC for EQ-5D-5L measurements, global perceived effect (GPE), effect on mood (HADS), quality of sleep (NRS and ISI).

	To compare the drug tolerance between systemic and topical treatment. To identify the difference between topical and systemic treatment in terms of functional status of the patient.	Percentage of patients without systemic drug related side effects, percentage of patients who discontinue the study drug. Impact of pain on functioning (Interference – BPI), participation in activities (Utrecht Work Engagement Scale-9), Work Productivity and Activity Impairment (WPAI).
Interventions	Topical treatment 1: lidocaine 5% medicated plaster (Versatis) Topical treatment 2: capsaicin 8% patch (Qutenza) Systemic treatment: pregabalin (generics)	
Description of the intervention or Formulation, Dose, Route of Administration of IMP	Topical treatment 1: daily administration of lidocaine 5% medicated plaster, during 12 consecutive hours, with a maximum of 3 plasters at the same time. Topical treatment 2: capsaicin 8% patch, periodic administration upon reoccurrence of pain symptoms (mostly after 90 days), in a hospital setting during maximum 1 hour. Maximum number of patches is equal to the number needed to cover the painfull area. The surface of this area cannot be larger than 520cm2.Systemic treatment: pregabalin (oral administration), dose determined by up-titration in first 4 weeks with a maximum daily dose of 600mg.	

FUNDING AND SUPPORT IN KIND

KCE is the only funder of this study. No commercial funding for this study.

ROLE OF STUDY SPONSOR AND FUNDER

Antwerp University Hospital (UZA) as mentioned in KEY TRIAL CONTACT shall act as sponsor of the Study, as defined in the Law of 2004, and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2004. Antwerp University Hospital shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Subjects or the Regulatory Authorities as sponsor of the Study. Antwerp University Hospital acknowledges and agrees for the avoidance of doubt that KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and Antwerp University Hospital shall make no representations whatsoever in this respect.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

There will be a number of committees involved with the oversight of the trial.

A trial management group (TMG) will be installed for this study. The **TMG** will meet 3-weekly and will be responsible for the daily management of the study. During their short meetings they will discuss overall progression of the study, practical hurdles that are reported by participating centers, questions coming from the centers, database issues and all other minor practical issues that demand quick resolution. The TMG will be composed of executives of the clinical trial center (CTC) in addition to the chief investigator and members with specific interests. If important or relevant items for the sites were discussed, the respective site or – if relevant - all sites will receive this information through e-mail. Minutes from every meeting as well as the communication with the site(s) will be available in the Trial Master File.

In addition, a trial steering committee (TSC) will be installed for this study. The **Trial Steering Committee (TSC)** shall oversee the overall performance of the study and will discuss crucial topics in relation to the performance of the study. The TSC shall meet approximately every six months, but at least 1 time a year. A report will be made from each meeting and each report will be sent to KCE within 3 weeks following the meeting date. KCE will always receive an invitation to attend the meetings of the TSC. Two international, *independent*, experts with high expertise in the domain of painful neuropathies will be included in the TSC. Prof. Dr. R. Baron and Prof. Dr. K. Vissers will serve as independent high-level experts in the trial steering committee. These external experts were chosen both on the basis of their clinical expertise but also on the basis of their scientific expertise. Furthermore, the TSC will be composed of the CI, the trial statistician, the trial PM, two representatives of the participating centers (one Flemish and one from Wallonia), one member of the public and one member of the patient organisations, one representative of the general management of the Antwerp University Hospital (sponsor) and one KCE representative.

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC will closely monitor trial progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. If such decision needs to be taken the presence of a KCE representative will be mandatory. See table 1 for composition and names (if already available) of the members of the TSC on the next page of this protocol.

Table 1: Composition of TSC

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Kris VISSERS	Radboud University, Netherlands	kris.vissers@radboudumc.nl	External expert (special expertise in treatment of chronic pain conditions)
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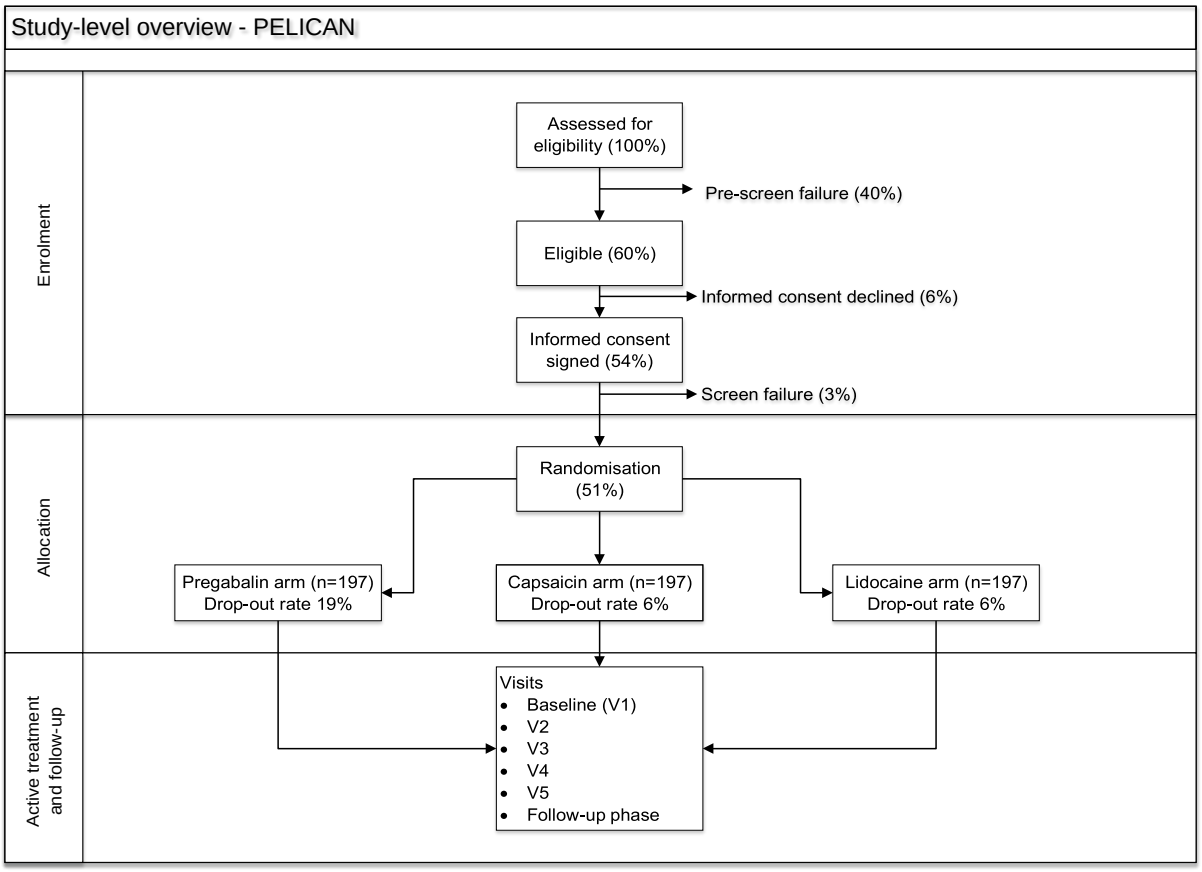
LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
APPI	Antwerp Personalized Pain Initiative
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTC	Clinical Trial Center
CTIMP	Clinical Trial of Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPE	Global Perceived Effect
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISI	Insomnia Severity Index
ISRCTN	International Standard Randomised Controlled Trials
KCE	Belgian Healthcare Knowledge Center
LNP	Localized Neuropathic Pain
MA	Marketing Authorisation
MPC	Multidisciplinary Pain Center
MQS III	Medication Quantification Score
MS	Member State
NIMP	Non-Investigational Medicinal Product
NNT	Number Needed to Treat
NP	Neuropathic Pain
NRS	Numeric Rating Scale
PDN	Painful Diabetic Neuropathy

PHN	PostHerpetic Neuralgia
PI	Principal Investigator
PI-NRS	Pain Intensity Numeric Rating Scale
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QST	Quantitative Sensory Testing
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
WPAI	Work Productivity and Activity Impairment

TRIAL FLOW CHART



STUDY PROTOCOL

1 BACKGROUND

Neuropathic pain (NP), caused by a lesion or disease affecting the somatosensory nervous system, has a considerable impact on patients' quality of life, and is associated with a high economic burden on the individual and society.[1-7] It is now considered as a distinct clinical entity despite a large variety of etiologies. NP remains a challenging clinical problem. People with NP often have several comorbidities and a high risk of drug–drug interactions, presenting a serious limitation to therapy. To achieve good pain relief, a combination of two or more drugs (multimodal approach) is often needed, increasing the risk of drug–drug interactions and side effects. When peripheral NP affects a specific, clearly demarcated area of the body, it can be described as **localized neuropathic pain syndrome** (LNP).[8-13] Examples include postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN), as well as post-surgical and post-traumatic pain (CPSP). General population studies, using validated screening instruments, have found that 7 – 8% of adults in Europe currently have chronic pain with strong neuropathic characteristics.[14,15] Based on the population figures of 2016, this corresponds to a potential of 718,586 Belgian patients.

Until very recently LNP syndromes were hardly recognized as being a distinct clinical entity within the broad range of NP syndromes. However, LNP syndromes are much more frequent than often perceived. Up to 83% of patients suffering from PHN complain of an LNP syndrome. Considering all clinical entities of NP, recent epidemiological studies clearly indicate that in **approximately 60% of patients** it affects a specific, clearly demarcated area of the body and can be described as 'localized neuropathic pain' (LNP). This means that up to **431,151 individuals may be suffering from LNP in Belgium**. In order to help physicians distinguish LNP from other types of neuropathic pain, the following definition of LNP was proposed in 2010, based upon the broader IASP[1] definition of NP: 'A type of peripheral neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain associated with abnormal sensitivity of the skin and/or spontaneous symptoms characteristic of neuropathic pain, for example, burning pain'.[10] By identifying patients with LNP this definition facilitates an evidence-based approach to the management of NP. Instead of treating these LNP conditions with systemic treatment options, these conditions can be treated more effectively by topical treatment. It should be stressed that topical treatment refers to pharmaceutical agents that act locally on the peripheral nervous system, in contradiction to medications such as buprenorphine and fentanyl that can be applied to the skin, but which exert their effect on the CNS following transdermal systemic absorption. Such topical route offers significant advantages over systemic administration. Notably, only a small fraction of the dose reaches the systemic circulation, thereby reducing the risk of systemic adverse effects, drug–drug interactions and overdose.

In current routine clinical practice, patients with neuropathic pain conditions (including LNP) are still treated with oral pharmacological drugs as first-line therapy, as recommended by national and international guidelines.[16-20] However, hardly one-third of these patients seem to achieve satisfying and clinically relevant analgesia.[21] When increasing drug dosage also fails to reduce pain, treatment is adapted to a drug from a

[1] International Association for the Study of Pain.

different group or to combination pharmacotherapy. During this mostly exhausting phase of trial and error, the outcome may be biased by decreasing patient compliance. The experience of ineffective drugs with unpleasant adverse effects (such as weight gain, xerostomia, dizziness, nausea, or cognitive impairment) reduces the motivation of the patient. The fact that oral medications also needs individual titration and regular daily intake is an additional limitation reducing flexibility in life. Drug-drug interactions may further limit treatment options, especially in patients with comorbidities. In case of renal or hepatic impairment drug dosage needs to be adapted. The effect of oral analgesic drugs starts late; Pregabalin requires an intake period of 6-8 weeks at the maximum dose before drug efficacy can be judged. Meanwhile, precious time is lost which can lead to development of central sensitization and irreversible chronification of pain. In LNP conditions, topical treatment options may be an excellent alternative for both treating physician and the patient.[22] Two topical agents are currently licensed by the EMA, the lidocaine 5% medicated plaster specifically for patients with PHN and the capsaicin 8% patch for adults with peripheral NP.

In order to provide an overview of the efficacy and safety of the lidocaine 5% medicated plaster in treating LNP, Mick et al. reviewed 60 clinical studies, as well as case reports and pharmacological studies.[10] Most are related to PHN, PDN or post-surgical/post-traumatic/scar pain, but other LNP conditions are also included, such as idiopathic sensory polyneuropathy, complex regional pain syndrome and carpal tunnel syndrome sequelae. In the majority of studies, the lidocaine plaster was added to the existing analgesic regimen. The plaster was found to be efficacious in both short-term and long-term controlled, randomised or open-label studies. Patients' quality of life (QoL) markedly improved in a variety of NP conditions and pain relief was sustained over long-term treatment. The plaster was very well tolerated, the most common adverse drug reactions (ADRs) being mild to moderate application site reactions. A later reappraisal of the clinical evidence for using the lidocaine 5% medicated plaster retrieved all relevant efficacy and safety studies from a literature search up to September 2015.[23] Analysis suggested that the lidocaine plaster is an effective and well-tolerated treatment option in patients with LNP. It was found to be easy to use, to improve patients' QoL, to have an excellent tolerability profile and to be associated with both a lack of systemic ADRs and a low potential for drug-drug interactions. Furthermore, its safety profile and ease of use can significantly increase patients' adherence to chronic treatment, with consequent benefits on efficacy and rehabilitation. Taking a wider perspective, a number of studies have recorded significantly better QoL scores following commencement of treatment with the lidocaine plaster.[24] Allodynia is often a prominent feature of LNP, and is usually considered to be one of the most distressing and debilitating symptoms of NP.[25,26] Therefore, one contributory factor to the improved QoL scores is likely the reduction in the area of allodynia – typically $>$ 50% - produced by treatment with the lidocaine plaster.[27,28] Reducing the painful area, which can increase tolerance of bathing and contact with clothing, is therefore a justifiable treatment goal for this medication.

One can conclude that the lidocaine plaster would appear to be indicated as the first step in the treatment of LNP. However, this is not always reflected in national and international guidelines, as well as reimbursement modalities in Belgium, and there are various reasons for this.[29] Guidelines for analgesic agents are generally based on the results of randomised, double-blind, placebo-controlled clinical trials using the NNT for a defined level of pain relief as the measure of efficacy. In a review of 105 randomised, double-blind, placebo-controlled trials in patients with NP, the 5% lidocaine-medicated plaster had an NNT of 4.4, comparable to antidepressants (1.2–6.9) and anticonvulsants (1.4–

7.4).[29,30] However, many trials of the lidocaine 5% medicated plaster used the time to withdrawal to indicate efficacy, for which it was not possible to calculate NNTs. These trials are therefore excluded when drawing up the guidelines. Furthermore, the value of NNTs in the development of guidelines is limited on several counts.[23] Firstly, reliable NNT data from multiple studies require trials with comparable inclusion and exclusion criteria. The statistical design of the lidocaine plaster trials varied from study to study. Secondly, NNTs are primarily derived from patients' evaluations of pain, which researchers now recognize may be inappropriate, so that other criteria (patient global impression of pain improvement, psychosocial functioning, activities of daily living, gait, quality of life) are used to provide a more complete assessment of analgesic efficacy.

The capsaicin 8% patch was first approved for nondiabetic patients with peripheral NP but has subsequently received EU approval for a label extension to include all patients with peripheral NP. Capsaicin is the active component in fruits of the genus Capsicum and an agonist of the transient receptor potential vanilloid-I receptor (TRPVI).[31] It causes an initial enhanced sensitivity of TRPV1-expressing cutaneous nociceptors, followed by persistent desensitization leading to a durable analgesic effect. Morphologically, capsaicin causes a significant reduction in epidermal nerve fiber density, recovering after 24 weeks in healthy volunteers.[32] Each 14 x 20 cm patch is designed to deliver a single therapeutic dose of capsaicin over maximum 60 minutes, after which the patch is removed. Only healthcare professionals should apply the capsaicin 8% patch. A maximum of four

patches can be applied in a single treatment, to be repeated every 90 days if required. The study findings that led to the approval of the capsaicin 8% patch are supported by a Cochrane review of six randomised, double-blind, placebo-controlled studies involving 2,073 patients: four studies of PHN and two of painful HIV neuropathy.[33] More patients achieved high levels of controlled pain relief with the capsaicin 8% patch vs. control (0.04% capsaicin for blinding), and patients with high levels of pain relief reported additional improvements in sleep, fatigue, depression, and improved QoL. Serious adverse effects were no different between the two groups.[33] STRIDE *(Safety and Effectiveness of Repeated Administration of QUTENZA Patches for Treatment of Pain Caused by Nerve Damage)* was the first prospective study to assess the long-term safety, tolerability, and analgesic effectiveness of capsaicin 8% patch repeat treatment (up to six retreatments) over 52 weeks, in 306 patients with a broad range of peripheral NP etiologies. Repeated treatment with the capsaicin 8% patch was well tolerated and did not raise any new safety concerns. Although a large proportion of patients discontinued the study (42.5%), only 1% of cases were due to ADRs. Patient Global Impression of Change improved during capsaicin 8% patch treatment: > 31% of patients reported to be ''very much improved'' or ''much improved''.[34]

At present, only **one** study has compared the lidocaine 5% medicated plaster directly with a first-line oral agent and **one** study has compared the capsaicin 8% patch directly with a first-line oral agent. Non-inferiority was not shown for the lidocaine 5% plaster when investigated head-to-head with pregabalin,[35] but the ELEVATE trial successfully showed that capsaicin 8% patch was non-inferior to pregabalin when compared head- to-head across a wide variety of peripheral NP etiologies.[36]

2 RATIONALE

Considering the above described limited evidence, there is an urgent need for more high-quality studies to enable direct comparisons of treatment outcomes with current first-line oral therapies. The need for tailored protocols with a congruous number of patients, proper randomisation, large follow-up duration and indicators other than NNT, seems to be of high importance for the further conceptualization of the topical treatment of NP. As described in a very recent overview publication[37], future **studies should be of sufficient duration and include specific patient subtypes of refractory peripheral NP**, approaching real life settings as much as possible. Our current research proposal nicely fits within the scope of the KCE Trials program since the pragmatic research design applies to the current treatment regimens in the real world. There are no restraining inclusion criteria leading to hyperselected patient populations, and real-world drug dosing regimens are applied. The proposed protocol also includes a follow-up. Predicting the patient profile that would gain the most benefit from early treatment would be advantageous, thereby avoiding ‘‘trial and error’’ management scenarios that often arise.[38] Evidence from the studies for capsaicin 8% patch supports early treatment use with short duration of pain having a positive predictive value. Very recently a study using quantitative sensory testing (QST) identified patients with a partial loss of cutaneous nerve fibers or receptors as more likely to respond to the application of capsaicin patches.[39] In contrast, when severe nerve damage or normal cutaneous sensations are present, the pain is likely due to central sensitization and thus not responsive to capsaicin. Evidence of predictors of efficacy with the lidocaine 5% medicated plaster is not as strong, but it has been proposed that they are effective for localized pain, hyperalgesia, and/or allodynia, presence of positive sensory input[40], and in patients who are treatment naive or refractory to oral treatment.[41,42] In the proposed design an evidence-based stratified analysis will be performed based on phenotypic sensory symptoms (Boston Bedside Quantitative Sensory Testing Battery and the NPSI questionnaire – see exploratory objectives) that might predispose to a successful outcome.[43-46] Based on the QST results, the patients will be classified as patients with either “irritable nociceptors” or “non-irritable nociceptors”.[47-52]

Currently, the standard approach to all types of neuropathic pain – including the localized neuropathic pain syndromes – is the use of systemic treatment options. However, such systemic treatment often (in a vast majority of patients) leads to systemic side effects such as nausea, vomiting, dizziness, sedation and peripheral edema. These side effects are extremely uncomfortable for the patients and have a high negative impact on their overall quality of life (which is already negatively impacted by the disease state). It is therefore important for patients to avoid the occurrence of systemic side effects.[53] Providing a topical treatment to their localized neuropathic pain syndromes allows patients to avoid systemic side effects, since no systemic absorption occurs during topical administration of analgesic substances. These considerations are especially important since neuropathic pain syndromes are almost always chronic in duration, so long-term (chronic) therapeutic options have to be provided.

2.1 Assessment and management of risk

This study should be considered as a **low-intervention clinical trial**, based on the risk assessment at the clinical trial level. Part of the proposed use of the therapies in this study is off label use but well established in international literature. However this study does not meet the criteria to obtain a pilot label exemption rule by the FAGG.
The investigational medicinal products are authorised and used in accordance with the terms of the marketing authorisation, with the exemption of the lidocaine plaster that has only a marketed authorisation for postherpetic neuralgia (PHN). Their application in neuropathic pain syndromes is furthermore evidence-based and supported by published scientific evidence on the safety and efficacy of these investigational medicinal products.

The study will be performed in recognized Multidisciplinary Pain Centers (MPC), that are all familiar with the neuropathic pain conditions which are investigated, the therapeutic approach to these conditions and the specific handling of the investigated medicinal products.

In the years to come (2018-2020) there will be no major competing trial(s) to be expected in the field of localized neuropathic pain syndromes, since no innovative treatment options are currently in an immediate pre-clinical stage of development.

3 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

3.1 Primary objective

To determine if topical treatment with lidocaine 5% patch (daily administration) or capsaicin 8% patch (periodic administration – upon reoccurrence of pain symptoms) significantly improves health-related quality of life after 6 weeks of treatment compared to systemic (oral) treatment with pregabalin as standard of care in adult patients suffering from localized neuropathic pain across a wide variety of etiologies (LNP), with a duration between 1 and 24 months (subacute to chronic neuropathic pain).

We are interested in 3 comparisons, between on the one hand the systemic versus the topical treatment options (pregabalin versus capsaicin 8% patch, pregabalin versus lidocaine 5% patch), and on the other hand within the topical treatment options (capsaicin 8% patch versus lidocaine 5% patch - as they imply a considerable difference in cost).

3.2 Secondary objectives

- To compare the quality of life profiles over the 24 weeks' treatment period between the treatment arms.
- To compare the effectiveness in terms of pain relief between the treatment arms.
- To compare the effectiveness in different aspects of quality of life (sleep, mood) between the treatment arms.
- To compare the drug tolerance between systemic and topical treatment.
- To identify the difference between topical and systemic treatment in terms of functional status of the patient.

3.3 Endpoints

For details on the primary and secondary endpoints we refer to section 3.4 and 3.5.
The EQ-5D-5L was chosen as primary outcome because this is a generic QoL scale recommended by most HTA agencies as this scale can easily be converted to utilities, which is for example not the case with the SF-36. In addition, there exists a validated version in Dutch, French and German. The other option would be to use the SF-36 (v2) questionnaire which has been validated in Dutch and French versions (even specifically for Belgium). However, not much is known about the application of the SF-36 in neuropathic pain conditions as well as during topical treatment conditions (mostly used in mechanical – somatic - pain conditions which are quite distinct from neuropathic pain conditions). In these mechanical pain conditions, a good correlation between SF-36 and the EQ-5D has been shown. For all of the above-mentioned reasons it was decided not to use the SF-36 in this study protocol, but instead use the EQ-5D-5L as the primary endpoint.

All the other measured outcomes are essential to obtain the necessary information regarding the efficacy and tolerability of the therapeutic strategies and their impact on Quality of Life (QoL) and functional status of the treated patients. All proposed

questionnaires are validated and regularly used in the pain setting (belonging in many instances to routine clinical practice).

3.4 Primary endpoint

The primary endpoint is the change in EQ-5D-5L between baseline and week 6.

EQ-5D-5L is a standardized instrument for use as a measure of health outcome, describing states of health in five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression.

This endpoint is chosen to reflect efficacy (beneficial effect of the compared treatments).

3.5 Secondary endpoints

- Long term quality of life profile;
- Reduction in pain intensity (PI-NRS);
- Time to worsening of the pain and use of rescue medication for pain (MQS III-R);
- Global perceived effect (GPE);
- Effect on mood (Hospital Anxiety and Depression Scale);
- Quality of sleep (NRS and ISI);
- Percentage of patients without systemic drug related side effects (dizziness, fatigue, vertigo, somnolence, headache, blurred vision);
- Time to discontinuation of the study drug and proportion of patients stopping the drug;
- Participation in activities (Utrecht Work Engagement Scale-9);
- Impact of pain on functioning (interference – BPI);
- Work Productivity and Activity Impairment (WPAI: Neuropathic Pain, v2.2, Belgium);
- Neuropathic Pain Symptom Inventory (NPSI).

3.6 Exploratory endpoints

To design a profile of the patient-selective sensory phenotypes (using Neuropathic Pain Symptom Inventory (NPSI)) suitable for both topical treatment options. It is our special interest here to investigate the presence of mechanical allodynia in these patients and study the impact of the active treatment options on this sensory abnormality.

4 TRIAL DESIGN

A multicenter three arm, 1:1:1 randomised, open-label comparative trial evaluating topical treatment options versus oral systemic treatment in adult patients suffering from localized neuropathic pain (LNP) syndromes. A wide variety of peripheral neuropathic pain syndromes will be included such as (but not limited to) post-herpetic neuralgia (PHN), post-surgical NP/post-traumatic NP/scar pain, post-amputation NP, post-radiation therapy NP, complex regional pain syndrome (CRPS) type 1.

591 adult patients suffering from LNP will be **randomised 1:1:1** to receive pregabalin, lidocaine 5% medicated plaster or capsaicin 8% patch. Stratification according to positive sensory phenomena such as hyperalgesia and allodynia, spontaneous positive sensory phenomena (such as dysesthesia) and duration of pain will be applied to keep the treatment arms balanced per stratum variable. The Neuropathic Pain Symptom Inventory (NPSI) will be used for this matter. Its factorial structure makes it suitable to capture different aspects of neuropathic pain (NP). The NPSI has been used in several double-blind trials as a secondary outcome measure, with some dimensions being differentially sensitive to treatment effects.

Stratified randomisation by site and NPSI will be applied, and coordinated centrally which randomizes eligible patients to one of three treatment arms. All investigational medicinal products will be dispensed by the hospital pharmacies of the individual participating multidisciplinary pain centers as is now already routinely done. Relabelling is necessary by the hospital pharmacy since the lidocaine plasters are used off-label. All study drugs will need to be relabelled by the hospital pharmacies.

Patients who want to withdraw from the study medication will be offered an alternative according to standard clinical practice. This will imply that patients on the pregabalin arm will be offered an alternative systemic drug treatment (gabapentin) and patients on the topical arm will be offered a different topical drug (failing treatment with lidocaine medicated plasters will be treated with capsaicin patches and otherwise). Hence there will be no crossover from systemic to topical or vice versa, to preserve the comparison between the systemic versus topical treatment as much as possible during the trial.

5 STUDY SETTING

The study is conceived as a nation-wide multicenter study, involving at least 13 multidisciplinary pain centers (MPC) in Belgium. All the included pain centers are officially recognized by the Belgian health authorities (FOD) and have been shown to share the same experience in the diagnosis and treatment of neuropathic pain conditions. Especially, they share specialized competence in the diagnosis of localized neuropathic pain conditions following the recognized international guidelines.

Patients suffering from neuropathic pain conditions are found both in primary care as well as secondary care. This is due to the fact that neuropathic pain can result from all sorts of medical conditions, such as diabetes, surgery, trauma, entrapment syndromes, chemotherapy, HIV, radiation and so on. Such patients will therefore consult primary care physicians but will often also look for specialist care in later instance. Many of these patients will consult the pain centers for evaluation and treatment of these painful neuropathies. In addition, it should be stressed that all participating pain centers have intensive collaboration with primary care physicians so the referral of patients who are eligible for participation in this trial will cause no problems.

There are no different types of sites participating in this trial. All participating centers will screen and include patients and will take part in the follow-up of the treatment results. The participating physician-investigators in the different pain centers are specialists with each at least 5 years of experience in pain treatment. There will be no major differences between the centers participating in this trial since the requirements imposed on the centers are identical for all of them.

6 ELIGIBILITY CRITERIA

All patients suffering from **localized neuropathic pain syndromes (LNP)** are eligible for participation in the proposed trial. The definition of LNP was originally based on the International Association for the Study of Pain (IASP) definition of neuropathic pain, which is the most detailed that can currently be proposed: 'Localized neuropathic pain is a type of neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain'. Pain which has distinct neuropathic features should be circumscribed to the same area or areas of maximal pain and sensory disturbances (see underneath for international definition). These skin areas are in accordance with underlying pathology and should be able to be covered by the maximum number of patches/plasters. Considering the area of the applied patches the maximum size of the painful skin area is limited to 520cm^2 (= 40 x 13cm).

This localized neuropathic pain (LNP) is often described by patients with symptoms such as shooting, burning, stabbing, or being like an electric shock. In addition, LNP can also show symptoms of irritable nociceptors, such as allodynia (mechanical) and hyperalgesia (cold). Allodynia is when a normally not painful stimulus – e.g. light touch or clothing running over the skin - becomes painful. If a minor/mild pain stimulus is causing severe pain it is called hyperalgesia.

Localized neuropathic pain is a type of neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain, associated with positive sensory signs and/or spontaneous symptoms characteristic of neuropathic pain

All patients suffering from such neuropathic pain conditions can be screened for participation in this trial. The inclusion of patients will in no way be limited to certain etiologies such as post-herpetic neuralgia (PHN), diabetic polyneuropathy (DPN) or post-radiation neuropathies. In most commercial clinical neuropathic studies inclusion of patients will be limited to one single etiology (in most cases either PHN or DPN), and in addition many inclusion and exclusion criteria will be imposed. This is NOT the case in this pragmatic trial where all adult patients suffering from localized neuropathic pain (= clearly defined by the international definition) can be included in this study. There are no exclusions based on concomitant medication, such as analgesics or anti-depressants. These drug classes are also included in the calculation of the medication quantification score (MQS-III-R score).

Patients can use their own rescue mediation since all analgesic medications will be recorded through the MQS-III score (online registration).[54-57] As such, the investigators will be able to evaluate and objectivize the intake of analgesic medication (lower intake of analgesics will result in lower MQS-III scores during the course of the trial). In addition, investigators will be able to closely monitor the need for analgesic rescue medication (to treat acute episodes of pain or exacerbations of chronic painful neuropathy in our case).

6.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfil all of the following criteria:

- Subjects should be capable of giving their informed consent with sufficient knowledge of the Dutch, French or German language;
- Males and females, 18 years and older;
- Be assessed as suffering from moderate to severe neuropathic pain across the screening process with pain intensity (numeric rating scale – NRS) ≥ 4/10;
- At the time of screening pain symptoms have to be present for at least one (1) month, with a maximum of 24 months;
- Sensory disturbances present in the skin area of maximal pain;
- At the time of screening pain is clearly related to the presence of a localized neuropathic pain syndrome;
- Male or female patients of child producing potential* must agree to use contraception or take measures to avoid pregnancy during the study and until after the final treatment;
- Women can only be included after negative pregnancy test;

For female patients: Women of childbearing potential* must be willing and able to use an acceptable effective contraception until treatment discontinuation.

For male patients: Men who are fertile** with partners of childbearing potential must be willing to use an acceptable effective contraception until treatment discontinuation.

*A women is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

**A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Birth control methods which may be considered effective when used consistently and correctly:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral

- Injectable
- Implantable

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Intrauterine device
- Intrauterine hormone-releasing system
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

List of contraception methods meeting the criteria is also provided in the patient information.

6.2 Exclusion criteria

- Age < 18;
- Pregnant and breastfeeding women;
- Infection in the painful skin region;
- Poorly healed or non-healed wound or scar in the painful skin region as well as presence of cutaneous abnormalities (non-intact skin barrier) within the painful skin region related to dermatological conditions;
- Known and/or strong suspicion of allergy to the study medication, known skin disorder (resulting in disruption of the normal skin barrier);
- Previous treatment with any of the three medications included in the study protocol for the same painful area within the last 12 months at the time of screening;
- Risk of heart failure and/or renal failure.

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Patient identification

Several routes of recruitment will be actively used in this trial.

- Patients will be recruited through the multidisciplinary pain centers. Recruited patients will both constitute of new patients, visiting the pain center for the first time, as well as patients who are already known in the center but never before had been treated with any of the analgesic medications investigated in this trial for similar painful conditions;
- Each multidisciplinary pain center has an official collaboration with the multidisciplinary algological teams of hospitals which do not have a pain center. This collaboration allows the pain centers to recruit patients coming from all acute hospitals in Belgium;
- In addition, patients will be recruited from an extensive network of general practitioners who work together with pain centers. GP's will be informed about this study through medical professional publications and scientific medical associations (e.g. Domus Medica). As such, GP's will be able to refer patients suffering from localized neuropathic pain syndromes directly to the participating pain centers.

Only members of the patient's existing clinical care team will have access to patient records to check if they meet the inclusion criteria.

No patient or disease registers will be used in this trial to identify potential participants. The clinical care teams of the different participating multidisciplinary pain centers will contact primary care physicians in their network to discuss the ongoing trial and ask their involvement to rapidly identify patients suffering from subacute to chronic localized neuropathic pain conditions and refer them to the pain centers for screening and possible inclusion in the trial. GP's will be able to consult the recently developed screening tool for localized neuropathic pain online, to allow a quick and easy pre-screening for presence of a localized neuropathic pain condition (this screening tool is also shown in the appendix 5 – Dutch and French versions of the screening tool will be made available for GP's.) [11]

7.1.2 Screening

There will be a pre-screening based on the presence of a localized neuropathic pain syndrome with maximal pain and sensory disturbances in a circumscribed skin area (clinical evaluation). A pre-screening log will be kept on paper with patient initials and year of birth as well as the reason and date of pre-screening failure or the date of ICF signature. If pre-screening is completed, the patient will be asked for informed consent during screening visit.

Patients who have a successfully completed pre-screening and have signed the informed consent will be considered for screening. From then onwards data entry in the eCRF (OpenClinica) starts and the patient will get a unique enrolment ID consisting of a site number followed by a consecutive number.

Reasons for screening failure will be documented in patient file (medical record) and OpenClinica (eCRF).

Screen failures i.e. patients who do not meet eligibility criteria at time of screening (such as for example duration of pain of two weeks) may be eligible for rescreening subject to acceptable parameters after consulting the CI. In the case of rescreening a new enrolment ID will be used for these patients.

A subject screening and enrolment log will be kept on paper and will contain enrolment ID, date and version of ICF, stratifying variables, treatment arm and allocation ID from QMinim. Randomisation is done after screening is completed. In case of screen failure, the date and reason for this screen failure will also be completed on the subject screening and enrolment log.

A template for a subject identification list will be maintained at each site, containing the following information: enrolment id, first and last name of the patient, hospital identification number, address as well as phone/email.

The screening assessment takes place maximum 21 days prior to start of the active treatment. In general, the trial schedule will be day -21 to day -2 screening, day -21 to -1 randomisation and day 0: start of the active treatment.

Screening will include:

- A check of inclusion/exclusion criteria;
- Demographics
    - Year of birth, age, sex, race, level of education, family situation;
- Medical and surgical history
    - Relevant history and current medical condition will be noted;
- Frequency of alcohol consumption
- Sensory testing (based on Boston Bedside Quantitative Sensory Testing Battery)
    - Basic clinical sensory testing (as per standard practice in multidisciplinary pain centers) will be performed to detect sensory changes to light touch, vibration, pinprick, cold or pressure by a clinical examination.
    - The following modalities will be tested in this basic sensory testing protocol:
        - Static mechanical allodynia
            - Application of the plastic base of a von Frey hair in the area of maximum pain for 10 seconds;
        - Dynamic mechanical allodynia
            - Evoked by gently stroking the area of maximum pain with a foam brush (stroke 4 times at speed of 3-5cm/s);

- Punctate hyperalgesia
    - Evoked by pinprick over a reference area first, then over the area of maximum pain with safety pin (supplied to centers);
    - The stimulus is applied twice for about half a second with a 5 seconds interval between stimuli for each site;
- Temporal summation to tactile stimuli
    - Evoked by repeated tapping of the area of maximum pain with a 300g (6.65) von Frey hair, 2 taps per second for 60 seconds or less if pain is intolerable;

Since all scheduled visits (including screening visit) in this protocol are considered as standard of care (routine) of localized neuropathic pain syndromes, no travel expenses will be paid to the participants.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at his/her site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will always be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site. Potential participants will always be given ample time and possibilities to ask questions regarding participation in the trial.

The right of a participant to refuse or stop (withdraw of consent) participation without giving reasons will always be respected in every participating center. If the patient refuses the trial or withdraws his/her consent, the normal and appropriate treatment will be given to the patient.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents. The sponsor will provide to investigators an informed consent form (Dutch and French version) that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens

- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, their interests will be particularly protected by allowing them extra time to make a decision (never put them under pressure to decide while being in the cabinet/hospital). These candidates will be contacted at home a few days later, in order to receive additional information, answer all of their remaining questions and discuss potential participation with a member of the study team. Only then, the participants will be asked if they are willing to participate or not.

A potential participant is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. This research proposal will never allow the inclusion of subjects who lack the capacity to consent for themselves.

Where a participant is able to consent for this clinical trial but later becomes incapacitated, the original consent given endures the loss of capacity, providing that the trial has not significantly altered.

In all participating sites informed consent must be obtained in accordance with the applicable regulations and legislation.

7.3 The randomisation scheme

Randomisation will be performed at day -21 to day -1. Stratified randomisation will be used. Stratification according to site and the 3 stratifying variables: hyperalgesia/allodynia (absent or not), spontaneous positive sensory phenomena (such as dysesthesia) (absent or not) and duration of pain (less or more than 3 months) will be applied to keep the treatment arms balanced per stratum variable.

We will use a **minimisation procedure to randomize**. Minimisation assures similar distribution of selected participant factors between study groups. The first participant is truly randomly allocated; for each subsequent participant the imbalance score is computed based on all previous allocations as well as the hypothetical allocation of the current patient to each treatment. The preferred treatment is then selected by choosing the treatment allocation associated with the smallest imbalance score.

The distance measure used to calculate the imbalance score is marginal balance. Marginal balance computes the cumulative difference between every possible pairs of level counts (i.e. the number of patients in that particular factor level).

The allocation of the new patient is then made at random with a heavy weighting in favour

of the intervention that would minimise imbalance (a probability of 0.75 will be used). The remaining probability is equally divided between the non-preferred treatments.

Method of implementing the allocation sequence

A web based randomisation system QMinim will be used.

If the screening is successfully completed, the researcher at the site fills out a Request to randomisation in OpenClinica. This randomisation form contains the unique enrolment ID from OpenClinica, month and year of birth, gender and values for the 3 stratifying variables. This form needs to be signed by the principal investigator or a delegated member of the study team. Thereafter the researcher informs the sponsor about the request by mail (randompelican@uza.be) including only the unique enrolment ID from OpenClinica. A person independent to the rest of the trial will fill in the values for the site and stratifying variables in QMinim in order to randomize the patient. The allocated treatment arm and allocation ID (from QMinim) are send back to the site by mail. All requests for randomisation are answered within 24 hours on weekdays (9 am-5 pm). The researcher fills out the treatment arm and allocation ID (from QMinim) in OpenClinica. The patient can start the treatment the next day. ***The patient can be informed about the treatment arm after the baseline questionnaires have been completed.***

At the study site (pain centre), the principal investigator or a delegated member of the study team keeps the subject screening and enrolment log as well as the subject identification list as mentioned in 7.1.2.

There is no need to have access to randomisation codes in case of an emergency as the study is open label hence treatment will be known by the patient as well as the treating physician and recorded in the medical record (patient file) and the eCRF (OpenClinica).

7.4 Blinding

No blinding is necessary for this open label trial.

Blinded assessment for the 3 treatment arms seems impossible in this case considering the clear difference in treatment modalities for the three therapeutic regimens. There is only one systemic treatment, versus two topical treatment solutions. In addition, the two topical treatment strategies differ significantly from each other (daily application versus three-monthly application, no skin reaction compared to neurogenic inflammation during a couple of hours after application of capsaicin). As such trial participants, pharmacists and care providers are unblinded to intervention groups.

7.5 Unblinding

Not applicable for this protocol.

7.6 Baseline data (pre-randomisation, to be collected before randomisation)

The baseline data will be collected between one week before day 0 and at least 48 hours before day 0 through the online system. Baseline data will be collected in all cases before the patient is randomised and starts the treatment. The researcher will be able to check the completion of the baseline data in the online system.

Baseline status (V1) on the following variables (*measurements belonging to standard care are indicated in **bold***):

- Health-related quality of life (EQ-5D-5L)
- **Medication use (MQS III – Medication Quantification Score)**
- Pain using PI-NRS (pain intensity) and NPSI (Neuropathic Pain Symptom Inventory)
- **The Pain Intensity Numeric Rating Scale (PI-NRS) is an 11-point scale for patient self-reporting of pain**
- The Neuropathic Pain Symptom Inventory (NPSI) is a 12-item patient reported outcome measure that contains 10 descriptors representing 5 dimensions of pain (burning pain, deep/pressing pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia) and 2 temporal items designed to assess pain duration and the number of pain paroxysms
- **Quality of life of the patient using several questionnaires: Insomnia Severity Index (ISI), quality of sleep (NRS), HADS (Hospital Anxiety and Depression Scale)**
- The Insomnia Severity Index (ISI) is a validated seven-item patient questionnaire used to quantify insomnia severity
- The Hospital Anxiety and Depression Scale (HADS) is a self-rated questionnaire to detect states of depression, anxiety and emotional distress
- Functional status of the patient using several questionnaires: Interference BPI (impact of pain on functioning), Utrecht Work Engagement Scale-9 and WPAI (Work Productivity and Activity Impairment)

Demographics will be collected at the time of the screening where the following variables are considered important (**all belonging to standard clinical care**): age, gender, level of education and family situation.

7.7 Trial assessments

The study comprises a screening period of maximum 21 days, randomisation (d-21 to d-1), a baseline visit at day 0 (start of treatment), a treatment period of 24 weeks and a post-treatment period of 2 weeks (24-26 weeks). Considering the pragmatic nature of the proposed trial clinic visits are kept to an absolute minimum.

The **clinical visits** take place at day 0 (V1), week 4 (V2), 12 (V3), 18 (V4), 24 (V5) and 26 (V6) which is comparable to a schedule which would be maintained in routine clinical care. A deviation of +/- 5 days is allowed for the clinical visits. The assessments made at these visits are (*routine care assessments are indicated in **bold***):

- **Documentation of the study intervention: number of patches (lidocaine and capsaicin), location, dosage used (pregabalin and gabapentin), compliance and discontinuation check**
- **Documentation of size of painful area**
- **Assessment of adverse events**
- **Assessment of systemic drug related side effects (e.g. dizziness, fatigue, vertigo, somnolence, headache, blurred vision) (not on baseline visit)**

- **Concomitant medication use**
- **Only during V2 and V4 clinical sensory testing will be repeated (using the Boston Bedside Quantitative Sensory Testing Battery)**

The majority of the assessments (patient reported outcomes and experiences) will be performed by making use of an online platform, enabling patients to complete the different assessments themselves without having to schedule a clinic visit. The use of the online platform will significantly reduce the work load for the patients involved in this study. Per regular weekly online assessment, the required time investment will not exceed 15 minutes. The online assessments on a monthly basis (n = 7 in total) will never require more than 30 minutes (which can be split over different moments).

Online assessments: *weekly basis*
A deviation of max. 48 hours is allowed for the completion
The following procedures and assessments will be carried out:

- Assessment of reduction in pain intensity using PI-NRS
- Assessment of analgesic medication use (using MQS III)
- Quality of sleep: Sleep NRS
- Assessment of systemic drug related side effects (not collected at baseline)
- Discontinuation of study drug (not collected at baseline)
- Participation in activities: Utrecht Work Engagement Scale-9

Online assessments: *monthly basis* **(baseline, week 6, 10, 14, 18, 22)**

Apart from baseline which needs to be completed before randomisation, a deviation of max. 7 days (3 days for week 6) will be allowed for the completion of the different assessments at every time point.

The following procedures and assessments will be carried out:

- Assessment of health-related quality of life (EQ-5D-5L)
- Global perceived effect (GPE) (not collected at baseline)
- Insomnia Severity Index (ISI)
- Assessment of effect on mood: HADS (Hospital Anxiety and Depression Scale)
- Assessment of impact of pain on functioning (Interference BPI)
- Functional status of the patient: WPAI (Work Productivity and Activity Impairment)
- Assessment of pain using NPSI (Neuropathic Pain Symptom Inventory)

For the assessment of compliance as the patient will be taking/applying two of the IMP's at home, we refer to section 8.8 Assessment of compliance. The assessments are also available on paper for patients who have no access to a tablet or computer to complete

the online assessments.

7.8 Table of trial procedures

KCE Trial - PELICAN							
		Treatment Phase					
Visit (V) ([o])	**Screening [a]**	**Baseline (V1) [b]**	**V2**	**V3**	**V4**	**V5 ([m])**	**FU Phase (V6)**
Timing of visits (in weeks)	-1	0	4	12	18	24	26
Informed consent	x						
Inclusion/Exclusion criteria	x						
Demographics [c]	x						
Frequency of alcohol consumption	x						
Medical and surgical history	x						
Pregnancy test	x						
Sensory Testing	x		x		x		
Documentation of study intervention ([p])		x	x	x	x	x	
Documentation of size of painful area		x	x	x	x	x	x
Adverse event assessments		x	x	x	x	x	x
Assessments of systemic drug related			x	x	x	x	x
Concomitant medication		x	x	x	x	x	x
Weekly online questionnaire (Appi@Home) ([n]) - PI-NRS - MQS-III - Sleep NRS ([f]) - Systemic drug related side effects [d] - Discontinuation of study drug [d] - Utrecht Work Engagement Scale		—	—	—	—	—	x
Monthly [e] extended online questionnaire (Appi@Home) - EQ-5D-5L ([g]) - GPE [d] [h] - HADS ([i]) - Interference BPI ([j]) - WPAI ([k]) - NPSI ([l]) - ISI ([q])		x —	—	—	—	—	x

(a) Screening is performed d-21 to d-2 prior to the start of the active treatment
(b) Randomisation is performed d-21 to d-1 prior to the start of the active treatment
(c) Year of birth, age, sex, race, level of education, family situation
(d) These variables are not collected at baseline but are included in all other assessments
(e) Assessed at baseline, week 6, 10, 14, 18, 22 and 26. Apart from baseline, a deviation of max. +2 days for week 6 and max. +6 days for the other weeks will be allowed for the completion of the different assessments at every time point. Baseline assessment needs to occur one week before V1 and at least 48 hours before V1
(f) Sleep NRS: Sleep Numerical Rating Scale: quality of sleep
(g) EQ-5D-5L: Health-related quality of life
(h) GPE: Global Perceived Effect
(i) HADS: Hospital Anxiety and Depression Scale
(j) Interference BPI: Impact of pain on functioning
(k) WPAI: Work Productivity and Activity Impairment
(l) NPSI: Neuropathic Pain Symptom Inventory
(m) Discontinuation of pregabaline needs to be done gradually over a minimum period of 1 week
(n) A deviation of max. 48 hours is allowed for the completion of the different assessments at every time point
(o) A deviation of +/-5 days is allowed for the clinical visits
(p) Number of patches, location, dosage used, compliance and discontinuation check
(q) ISI: Insomnia Severity Index
Assessments in **bold** are standard of care

7.9 Long term follow-up assessments

Patients will be monitored 2 weeks after the end of the protocol-related treatment period. During these two weeks patients will continue to fill in the weekly online assessments (*routine assessments are indicated in **bold***):

- **Assessment of reduction in pain intensity using PI-NRS;**
- **Assessment of analgesic medication use (using MQS III);**
- **Sleep NRS**
- **Assessment of systemic drug related side effects;**
- Participation in activities: Utrecht Work Engagement Scale-9.

At week 26 (monthly in table detailing trial procedures) they also complete the following information on the online system *(routine assessments are indicated in **bold**):*

- **Documentation of the study intervention: number of patches (lidocaine and capsaicin), location, dosage used (pregabalin and gabapentin), compliance and discontinuation check**
- **Documentation of size of painful area**
- Assessment of health-related quality of life (EQ-5D-5L);
- **Global perceived effect (GPE);**
- **Assessment of effect on mood: HADS (Hospital Anxiety and Depression Scale);**

- Assessment of impact of pain on functioning (Interference BPI);
- Functional status of the patient: WPAI (Work Productivity and Activity Impairment);
- **Assessment of pain using NPSI (Neuropathic Pain Symptom Inventory).**
- **Insomnia Severity Index (ISI)**

At week 26 there will be a follow-up clinical visit (V6) during which the clinician will document the study intervention (location and number of patches for lidocaine and capsaicin, dosage for pregabalin and gabapentin, compliance and discontinuation) and document the size of the painful area. During this visit the clinician will discuss adverse events, any residual systemic drug related side effects and the use of concomitant analgesic medication. This visit closely resembles routine clinical practice since patients will have the possibility to continue their active treatment (in case of positive analgesic efficacy and no significant side effects) outside the perspective of the pragmatic trial protocol. For the IMP's which are not reimbursed, a medical need programme will be initiated. In routine clinical care discussion between physician and patient is also kept in order to decide on whether or not to continue the analgesic treatment.

As the follow-up period is quite short and all assessments are made online we do not anticipate a large number of missing values.

7.10 Qualitative assessments – nested studies

Not applicable.

7.11 Withdrawal criteria

A patient has to be withdrawn from active treatment in case any of the following applies:

- The patient requests discontinuation of active treatment;
- The patient is no longer able to participate in the study (e.g. AE, surgery, pregnancy, concomitant diagnoses, concomitant therapies, or administrative reasons). The investigator may also stop a patient's treatment, if the patient is no longer able to attend study visits;
- Significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made after discussion between the sponsor and the investigator at this site;
- The patient cannot tolerate the active treatment:
  - Patients who interrupt or discontinue pregabalin or lidocaine for no more than two weeks or capsaicin for no more than four weeks can continue with their treatment. If the respective treatment interval is longer than described previously, a discussion between the local investigator and the sponsor/Chief Investigator will be necessary and documented in the patient file.
  - A switch between capsaicin and lidocaine or from pregabalin to gabapentin is allowed in case of side effect based on CTCAE v4.03 only if nausea, vomiting, dizziness or decreased level of consciousness grade3 or higher is met. In addition, a switch between capsaicin and lidocaine or from pregabalin

to gabapentin is allowed in case of insufficient pain relief (reduction between 0 – 30%) at maximum dose. If an investigator wants to switch for another side effect than mentioned, the sponsor/Chief Investigator will be contacted by mail and/or phone (if urgent) and the discussion will be made together. A note will be added to the patient file in the medical record (inclusive discussion details like date, participants, side effect and final decision).

- Supportive treatment (standard of care) is allowed at all circumstances at the discretion of the investigator (but no dedicated concomitant medication will be used within the protocol to treat side effects since they are expected to be minimal and of short duration).

Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nausea	Loss of appetite without alteration in eating habits.	Oral intake decreased without significant weight loss, dehydration or malnutrition.	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated.	-	-
Vomiting	1 – 2 episodes (separated by 5 minutes) in 24 hours.	3 – 5 episodes (separated by 5 minutes) in 24 hours.	>=6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Dizziness	Mild unsteadiness or sensation of movement.	Moderate unsteadiness or sensation of movement; limiting instrumental ADL.	Severe unsteadiness or sensation of movement; limiting self care ADL.	-	-
Depressed level of consciousness	Decreased level of alertness.	Sedation; slow response to stimuli; limiting instrumental ADL.	Difficult to arouse.	Life-threatening consequences.	Death.

If cross-over of active treatment (pregabalin to gabapentin, lidocaine to capsaicin or capsaicin to lidocaine) occurs as well as if active treatment is stopped, the corresponding visits will be performed as described in the flow chart. The patient remains in the study and will be followed up as if he/she was still on active treatment.

All withdrawals will be documented and the reason for withdrawal recorded in the patient file (medical record) and in the eCRF and discussed, as necessary, in the clinical trial report.

Patients who fail screening will not be included in the analysis but will be entered into the

trial database (eCRF – OpenClinica). The reason for failure will be documented in the patient file and in the eCRF and reported descriptively and by patient listing in the report of this trial.

Patients who fail screening will be replaced. Patients who initially may not meet eligibility criteria (e.g. for administrative reasons or assessments are out of time window) may be re-screened at investigator's discretion after consulting with the Sponsor (CI). Patients who withdraw from the study after randomisation will not be replaced.

The sponsor reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Emergence of any efficacy/safety information that could significantly affect continuation of the trial;
- Violation of good clinical practice (GCP), the clinical trial protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

7.12 End of trial

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period
- Lost to follow-up, after 3 attempts to reach the patient. The attempts should be documented in patient record.
- Refusal to be followed-up (e.g. if patients discontinues the study due to adverse events but refuses to be followed up)
- Withdrawal of informed consent

The end of the entire trial will occur when one of the following situations occurs:

- When all patients have completed their follow-up period or are lost to follow-up.
- If the trial is ended by the sponsor for any reason when patients are still being treated with a clinical benefit, the patients will be offered treatment in a follow-up trial which will allow patients to continue to receive treatment as long as the treating investigator deems it appropriate.
- If the trial is terminated by the sponsor for safety reasons.

The main Ethics Committee will be notified of the end of trial by the sponsor within 90 days.

8 TRIAL INTERVENTION / MEDICATION

8.1 Name and description of intervention(s)

In this protocol three (3) investigational drugs will be used and compared to each other. All three drugs are licensed and generic names are used in the protocol.

(1) Pregabalin (licensed drug): generics providing similar packaging and dosing formats of this IMP will be used in all participating centers - Capsules of 75mg

(2) Lidocaine 5% medicated plaster (licensed drug) - VERSATIS®

(3) Capsaicin 8% patch (licensed drug, only for in hospital use) - QUTENZA®

- Rescue medication: Gabapentin (licensed drug): generics providing similar packaging and dosing formats of this IMP will be used in all participating centers - Capsules of 300mg

8.2 Legal status of the intervention

The three investigational medicinal products and the rescue medication are licensed in BE as well as in all other European countries.

Pregabalin	CNK: 2329-498	EU/1/04/279/011-013 (Lyrica)
Topical lidocaine plaster	CNK: 2481-042	BE312462
Capsaicin patch	CNK: 2723-047	EU/1/09/524/001-002
Gabapentin	CNK: 0780-221	BE268046

8.3 Summary of Product Characteristics (SmPC)

For this study the SmPC will be used for all three investigational medicinal products and for the rescue medication. Twice a year the e-compendium.be website will be checked to see if an updated version of the SmPC has become available for the investigational products and rescue medication so that information for the participants can be updated according to the latest version of the SmPC. If the local site will use another generic product of pregabalin and/or gabapentin the SmPC will be provided by the sponsor.

Pregabalin (Lyrica)	SmPC dating from 12/2018
Lidocaine 5% medicated plaster (Versatis)	SmPC dating form 5/2018
Capsaicin 8% patch (Qutenza)	SmPC dating from 3/2019
Gabapentin (EG)	SmPC dating from 12/2017

8.4 Drug storage and supply

The drugs will be ordered by the sponsor and made available through the site pharmacy at drug prices agreed by the sponsor with the company marketing both topical treatment options in the context of this trial.

Pregabalin and gabapentin will be provided by the local hospital pharmacy and the

hospital pharmacy will be compensated for its expenses

The Sponsor will carefully document the study drugs used for the trial at each site (using eCRF or other means). The study drugs will be covered by the study budget. Patients will not be charged for the study drugs. The study drugs that will be handed over to the patients will be relabelled by the site pharmacy.

The labels will be as detailed below (see 8.5 for further information on labelling).

The Sponsor will arrange for the patient that they retain post-trial access to their respective investigational medicinal products if they have good analgesic efficacy without (or with minor) side effects and patients wish to continue this treatment for a longer duration. The post-trial access for off-label applications of the different drugs will be discussed case-by-case with the sponsor/Chief Investigator and documented in the medical record (inclusive date, participant and final decision).

8.5 Preparation and labelling of investigational medicinal product

The dispensing of the investigational medicinal product requires no preparation. The site pharmacy will dispense sufficient medication until the next scheduled dispensing visit. Before delivery to the patient the investigational medicinal product will be labelled as follows by the site pharmacy:

VERSATIS

PELICAN TRIAL - NCT03348735 – KCE-17007

TRIAL subject ID: _____ **Initialen:** _____

ENKEL VOOR STUDIEGEBRUIK

Gebruiksaanwijzing: zie voorschrift – UITWENDIG gebruik

Buiten het zicht en bereik van kinderen houden

UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE

Mode d'emploi: selon prescription – usage EXTERNE

Tenir hors de la vue et de la portée des enfants

NUR STUDIENGEBRAUCH KLINISCHER

Gebrauchsanweizung: siehe Rezept – zur ÄUßERLICHEN Anwendung

Arzneimittel für Kinder unzugänglich aufbewahren

PI: _____ **Tel**.: _____

SPONSOR: UZ Antwerpen Wilrijkstraat 10, 2650 Edegem

QUTENZA

PELICAN TRIAL - NCT03348735 – KCE-17007

TRIAL subject ID: _____ Initialen: _____

ENKEL VOOR STUDIEGEBRUIK

Gebruiksaanwijzing: zie voorschrift – UITWENDIG gebruik

Buiten het zicht en bereik van kinderen houden

UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE

Mode d'emploi: selon prescription – usage EXTERNE

Tenir hors de la vue et de la portée des enfants

NUR STUDIENGEBRAUCH KLINISCHER

Gebrauchsanweizung: siehe Rezept – zur ÄUßERLICHEN Anwendung

Arzneimittel für Kinder unzugänglich aufbewahren

PI: _____ Tel.: _____

SPONSOR: UZ Antwerpen Wilrijkstraat 10, 2650 Edegem

PREGABALINE

PELICAN TRIAL - NCT03348735 – KCE-17007

TRIAL subject ID: _____ Initialen: _____

ENKEL VOOR STUDIEGEBRUIK

Gebruiksaanwijzing: zie voorschrift – Voor ORAAL gebruik –

Buiten het zicht en bereik van kinderen houden

UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE

Mode d'emploi: selon prescription – Voie ORALE –

Tenir hors de la vue et de la portée des enfants

NUR STUDIENGEBRAUCH KLINISCHER

Gebrauchsanweizung: siehe Rezept – ORALE Anwendung –

Arzneimittel für Kinder unzugänglich aufbewahren

PI: _____ **Tel.:** _____

SPONSOR: UZ Antwerpen Wilrijkstraat 10, 2650 Edegem

GABAPENTINE

PELICAN TRIAL - NCT03348735 – KCE-17007

TRIAL subject ID: _____ **Initialen:** _____

ENKEL VOOR STUDIEGEBRUIK

Gebruiksaanwijzing: zie voorschrift – Voor ORAAL gebruik –

Buiten het zicht en bereik van kinderen houden

UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE

Mode d'emploi: selon prescription – Voie ORALE –

Tenir hors de la vue et de la portée des enfants

NUR STUDIENGEBRAUCH KLINISCHER

Gebrauchsanweizung: siehe Rezept – ORALE Anwendung –

Arzneimittel für Kinder unzugänglich aufbewahren

PI: _____ **Tel.:** _____

SPONSOR: UZ Antwerpen Wilrijkstraat 10, 2650 Edegem

8.6 Dosage schedules

The following dosage schedules will be applied during the study. It should be stressed that all doses concern adult dosing, since no infants or children will be included in this study.

(1) **Pregabalin** (oral route of administration) - generics providing pregabalin 75mg capsules in packages containing 200 capsules

a. Should be swallowed two times a day (morning and evening). Administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

b. Pregabalin treatment should be started with a dose of 150mg per day given as two divided doses (2 x 75mg per day). Based on individual patient response and tolerability, the dose may be increased to 225mg per day after an interval of 3 days, and if needed, then to a daily dose of 300mg after an additional 3-days interval. Or can be decide otherwise if in accordance with current clinical practice or patient-specific conditions requiring changes to the dosing schedule.

c. Pregabalin treatment can be further increased to a maximum dose of 600mg per day through dosage increases of 75mg every 72 hours.

d. In case of vomiting after intake of pregabalin, no additional intake is necessary and regular dosing schedule will be maintained.

e. In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

f. In patients with mild or moderate renal impairment a dosage adjustment is not required. If creatinine clearance is < 30 ml/min, a dose adjustment is required per protocol.
Renal impairment: pharmacokinetics

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately (50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary.

g. No dose adjustment is required for patients with hepatic repairment.

h. Patients should take a missed dose as soon as possible, except when it is time for the next dose. It is important not to take a double dose.

(2) **Lidocaine 5% medicated plaster** (topical administration) – Versatis

a. One daily application during 12 consecutive hours within a 24 hours period.

b. Each plaster must be worn no longer than 12 hours. The subsequent plaster-free interval must be at least 12 hours. The plaster can be applied during the day or during the night. If patients forget to remove the plaster after 12 hours, the plaster should be removed as soon as noticed.

c. Maximum of 3 plasters during the same application.

d. In patients with mild or moderate renal impairment a dosage adjustment is not required. If creatinine clearance is < 30 ml/min, a dose adjustment is required per protocol (max daily dose 1.5 patch).

e. In patients with mild or moderate hepatic impairment a dosage adjustment is not required. In patient with severe hepatic impairment, the plaster should be used with caution.

f. The plaster should not be applied to mucous membranes. Eye contact with the plaster should be avoided.

g. The plaster may only be placed on dry, intact, skin.

(3) **Capsaicin 8% patch** (topical administration) - Qutenza

a. Treatments with the capsaicin 8% patch may be repeated every 90 days, as warranted by the persistence or return of pain.

b. Patch should be applied to the most painful skin area. Maximum number of patches is equal to the number needed to cover the painfull area. The surface of this area cannot be larger than 520cm2.

c. No dose adjustment is required for patients with renal or hepatic impairment.

d. Patches should not be held near eyes or mucous membranes.

e. Qutenza must be applied to intact, non-irritated, dry skin and allowed to remain in place for 30 minutes on the feet, and 60 minutes for all other locations.

8.7 Dosage modifications

Dosage of pregabalin is changed every 3 days. Starting dose will be 150mg per day (75mg in the morning and 75mg in the evening). Based on individual response and tolerability, the dose of pregabalin may be further increased to 225mg after an interval of 3 days, and to 300mg after an additional 3-day interval. Dosage can be further increased to the maximum daily dose of 600mg through dosage increases of 75mg every 3 days. Or can be decide otherwise if in accordance with current clinical practice or patient-specific conditions requiring changes to the dosing schedule.

- The dosage of pregabalin can always be modified upon request by the patient. Reasons to modify the dosage could be occurrence of side effects after increase of daily dose (in most cases dizziness, sedation, peripheral edema, blurred vision or nausea and vomiting). In case of side effects, the daily dose should be reduced in first instance by 75mg. If side effects persist additional reductions in daily dose by 75mg should be performed until side effects have (almost) disappeared. All the dose changes (increase and decrease) should be captured in the patient file and the eCRF. If decrease of the dosage appears, also the reason (side effect) will be documented.
- Adjustment of dosage can be done at home following medical guidance.
- Standard of care will be applied to treat side effects.
- Intake of medication can at any time be stopped by the patient if the patient suffers from in his/her opinion unacceptable side effects (no need for tapering down the medication dose).

If systemic treatment is stopped by the patient or the treating physician due to side effects then there is a possibility to switch to another systemic anti-neuropathic treatment, gabapentin. Starting daily dose is 600mg (300mg x 2), to be increased by 300mg every three days to a maximum daily dose of 1800mg (dose including down titration can always be modified by the patient). Or can be decide otherwise if in accordance with current

clinical practice or patient-specific conditions requiring changes to the dosing schedule. Gabapentin is provided by the hospital pharmacy in a dose of 300mg preferably in a package containing 200 capsules. All the dose changes (increase and decrease) should be captured in the patient file and the eCRF. If decrease of the dosage appears, also the reason (side effect) will be documented.

There are no dosage modifications for the topical investigational medicinal products. In both cases (lidocaine medicated plaster and capsaicin patch) the **most painful skin area should be completely covered by the patches**. There is no increase in dose over time. However, the number of patches can be decreased over time if reassessment indicates that the amount of plasters needed to cover the painful area can be reduced since painful skin area has decreased in size (shrinkage of the painful skin area).

The skin area of maximal pain should be covered with the lidocaine 5% medicated plasters once daily for up to 12 hours within a 24 hours period (preferably application during the night). Only the number of plasters that are needed for an effective treatment should be used. When needed, the plasters may be cut into smaller sizes with scissors prior to removal of the release liner. In total, **not more than three (3) plasters** should be used at the same time.

The capsaicin 8% patch should be applied to the most painful skin areas. Maximum number of patches is equal to the number needed to cover the painfull area. The surface of this area cannot be larger than 520cm2. The painful area should be determined by the physician and marked on the skin. Qutenza is a single use patch and can be cut to match the size and shape of the treatment area. Qutenza must be applied to intact, non-irritated, dry skin and allowed to remain in place for 30 minutes on the feet, and 60 minutes for all other locations. Treatments with capsaicin patches may be repeated every 90 days, as warranted by the persistence or return of pain.

For both topical interventions the number of patches, location and size of painful skin area will be carefully documented (as this will guide the ordering of study drug).

If topical treatment is stopped by the patient, then there is a possibility to switch to another topical treatment (from lidocaine plaster to capsaicin patch – from capsaicin patch to lidocaine plaster). See section 7.11 for further detail on switch procedure.

8.8 Assessment of compliance

Compliance will be assessed through the completion of a questionnaire on the online platform. On a weekly base the patients will need to provide information concerning the treatment, the dosage and the daily compliance.

Furthermore, drug accountability will be applied in this trial. For pregabalin and lidocaine plaster treatment, delivery dates by the hospital pharmacy can be observed on the ticket on the outside of the box (standard of care in all hospital pharmacies) as well as on the accountability log. Patients will be asked to bring their boxes and empty blisters to be viewed by the investigator during clinical visits. The return accountability will be completed by the physician-investigator or a delegated member of the research team.

- Pregabalin will be given as an oral administration in accordance with the study protocol and under the instruction of the investigator. The patients will be asked to return all unused pregabalin capsules at the next scheduled visit. The

investigator will check whether the patient has taken the medication according to the protocol. Any discrepancies will be documented and explained in the patient file (medical record) as well as in the eCRF (OpenClinica) by the investigator. It is recommended that patients take all doses of pregabalin according to the trial protocol unless dosing is limited by AEs. Patients who interrupt or discontinue pregabalin for no more than two weeks can continue without being removed from the trial. If the respective treatment interval is longer than described previously, a discussion between the local investigator and the sponsor/Chief Investigator will be necessary and documented in the patient file.

- Lidocaine 5% medicated plasters will be administered topically in accordance with the study protocol and under instruction of the investigator. The patients will be asked to return all empty sachets at the next scheduled visit. The investigator will check whether the patient has applied the topical treatment according to the protocol. Any discrepancies will be explained in the eCRF by the investigator. Patients who interrupt or discontinue lidocaine plaster treatment for no more than two weeks can continue with their treatment. If the respective treatment interval is longer than described previously, a discussion between the local investigator and the sponsor/Chief Investigator will be necessary and documented in the patient file.

- Compliance will always be maximal in the capsaicin 8% patches treated patients since these patches are applied while the patient is remaining in the hospital. If a patient does not show up for the scheduled treatment the site will immediately contact the patient by telephone to obtain explanation of no-show. An accountability log will be retained by the hospital pharmacy. Capsaicin patches will be administered topically and in hospital of the investigator under supervision of authorised personnel. Date of administration as well as a statement whether topical administration was done according to protocol and/or whether administration was interrupted will be recorded in the patient file (medical record) as well as in the eCRF (OpenClinica).

9 SAFETY REPORTING

9.1 Recording and reporting of SAEs AND SUSARs

All SAEs occurring from the time of written informed consent and SUSARs occurring from the time of first active treatment until 14 days post cessation of trial treatment must be recorded on the SAE Form and mailed to the Sponsor within 24 hours of the research staff learning of its occurrence. Any SAEs experienced after a 30-day period after the last study visit should only be reported to the Sponsor if the local investigators suspect a clear causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

For all SAEs and SUSARs the following information will be collected:

- Full details in medical terms and case description, based on CTCAE v4.03
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria – as assessed by local PI or other authorised and delegated physician
- Grading: grade 1 (mild); grade 2 (moderate); grade 3 (severe); grade 4 (life-threatening); Grade 5 (death)
- Causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator – as assessed by local PI or other authorised and delegated physician
- Whether the event would be considered expected or unexpected. – as assessed by local PI or other authorised and delegated physician

If an authorised physician from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Any change of condition or other follow-up information should be mailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Federal agency for medicines and health products (FAMHP). The Sponsor will inform the FAMHP (through notification of the occurred SUSAR using the EudraVigilance system), the EC and the Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales. EudraVigilance supports

the electronic transmission of ICSRs between electronic data interchange (EDI) partners: EMA, national competent authorities (NCAs), marketing authorisation holders (MAHs) and sponsors of clinical trials in the European Economic Area (EEA).

See the following table to see who needs to report what according to European guidelines.

Who	What	Reference
Sponsors of clinical trials Marketing authorisation holders National competent authorities	Reports of suspected unexpected serious adverse reactions (SUSARs) **via safety reports** (ICSRs/acknowledgements)	Directive 2001/20/EC Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3)
Sponsors of clinical trials Marketing authorisation holders	Information on investigational medicinal products **via product reports** (XEVPRMs/acknowledgements)	Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3)

The point where recording / reporting starts in this study protocol will be:

- For SAEs – consent
- For ARs / SARs and SUSARs – administration of the 1st IMP dose

In the case of our low interventional trial with an IMP that has an extensively documented safety profile, only those non-serious ARs that the investigator considers important will be captured, such as sedation, skin irritation, development of blisters on the skin. Pharmacovigilance reporting will occur according to the requirements from FAMHP for medication with a marketing authorisation.

Safety reporting periods for SAEs and SARs (30 days after the last study visit) are equal across all arms of a randomised trial to prevent any bias in reporting.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes. The PIS will include a section explaining this to the participant.

9.2 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness by using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) or delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of specific ARs, all SAEs, SARs and SUSARs according to the trial protocol onto a safety database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committee identified for the trial (Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (FAMHP IN BE) and EC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in

collaboration with the CI and ensuring timely submission to the FAMHP and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, they will periodically review safety data. The role of the TSC is to provide overall supervision for the trial and provide advice through its Chair. The ultimate decision for the continuation of the trial lies with the TSC.

In preparation of the meeting of the Trial Steering Committee a physician, independent to the trial, will assess the causality of the adverse events and reports his/her findings to the TSC.

Trial Management Group (TMG):

The TMG is responsible for the day-to-day running and management of the trial. It holds regular teleconferences and face-to-face meetings.

9.3 Notification of deaths

All deaths, from written informed consent till 14 days post cessation of trial treatment must be recorded on SAE form and mailed to sponsor of the trial within 24 hours of awareness after the patient has passed away. Also deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported to the sponsor

9.4 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, provide electronic notice to EudraVigilance (fully automated safety and message-processing mechanism using XML-based messaging) and the relevant EC of the measures taken and the circumstances giving rise to those measures.

9.5 The type and duration of the follow-up of subjects after adverse events

Any SUSAR related to the IMP's will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

9.6 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (FAMHP in Belgium), Ethics Committee and Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The primary outcome is the change in EQ-5D-5L from baseline to 6 weeks.

In the paper of Baron et al (2009) they evaluate the short-term effect of 5% lidocaine medicated plaster versus pregabalin on the quality of life.[58] Baron et al. reported 0.12 (0.240) as the mean change (SD) for EQ-5D from baseline to 4 weeks in the 5% lidocaine medicated plaster group compared to 0.04 (0.235) in the pregabalin group or an effect of 0.08. According to Walters and Brazier (2005) the mean minimally important clinical difference (MICD) for the EQ-5D is 0.074 for all patient groups and 0.081 for the back-pain patient group.[59] **We have therefore powered the study around this effect of 0.08.**

Based on these numbers we would need **173 patients per treatment arm** using an independent samples t-test to have 80% power to detect an effect of 0.08 assuming a standard deviation of 0.240 with an alpha of 0.05/2. We are interested in all 3 comparisons, between on one hand the systemic versus the topical treatment options (pregabalin versus capsaicin 8% patch, pregabalin versus lidocaine 5% patch), and on the other hand within the topical treatment options (capsaicin 8% patch versus lidocaine 5% patch - as they imply a considerable difference in cost). Given the fact that each group will be used twice in the comparisons we corrected the significance level with a factor 2 to keep the overall type I error at 5%.

In Haanpää et al.[36] and Baron et al. patient completion rates for the follow-up of 90% and 96% respectively are reported which seems - bearing in mind that the burden on the patients in follow-up assessments is extremely low in the proposed pragmatic trial - realistic to us. However, in the systemic treatment arm drop-out from the study medication will be considerable (due to side effects). Indeed, in Baron et al. 39 of 153 patients (25.5%) of the pregabalin group discontinued the study medication and Haanpää et al. reports 41 out of 277 (14.8%) of the pregabalin arm withdrawing from the study medication. If we combine the two studies, we get 80 out of 430 or 18.6% drop out rate. For capsaicin 8% patch the withdrawal from study medication was 6 out of 282 (2.1%) and for lidocaine 5% plaster 9 out of 155 (5.8%) withdrew. Hence, we anticipated an average drop-out rate between 5.8% and 18.6% of 12% for each treatment arm which implies 197 patients per treatment group. In total, we would need to randomize **591 patients** in a 1:1:1 way to the 3 treatment arms.

10.2 Planned recruitment rate

The number of recruiting centers is 13 all of them officially recognized multidisciplinary pain centers (MPC). In general, each of the participating pain centers have indicated that they see at least 50 new patients suffering from NP on a monthly basis, and more than 500 on a yearly basis. Since more than 60% of these patients actually suffer from LNP and are eligible to participate in the study, this means that each center will be able to identify at least 30 possible patients on a monthly basis. Assuming a consent rate of 90% of which 5% will be screening failures we end up with 25 patients. Even in the worst case scenario where we should be able to include 3 to 5 patients every month during the recruitment period, this means that at least 45 new patients will be included nationwide

on a monthly basis in the study protocol.

It is therefore anticipated that we will be able to include the total number of patients (591 patients) in a time frame of maximum 18 months.

Currently there are no competing clinical studies ongoing nor planned in Belgium on the subject of topical treatment of LNP. In addition, currently there are no ongoing trials on the subject of NP in Belgium so there will be no risk of competing trials during our study period.

It will be of great importance that participating pain centers activate their network with surrounding hospitals, rehab centers and ambulatory centers to achieve high referral rates of patients recently diagnosed with LNP. Finally, primary care physicians will also be notified of this study to optimize referral.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

- Compare primary outcome quality of life (EQ-5D-5L) at baseline between the treatment arms. Means and standard deviations per treatment group will be reported.
- Compare pain, mood, sleep and functional status at baseline between the treatment arms using the different questionnaires (PI-NRS, Sleep-NRS, HADS, ISI, Utrecht Work Engagement Scale-9, Interference BPI and WPAI). Means and standard deviations per treatment group will be reported.
- Compare gender, level of education and family situation between the treatment arms. Proportions per treatment group will be reported.
- Compare the 3 stratifying variables hyperalgesia/allodynia (absent or not), spontaneous positive sensory phenomena (such as dysesthesia) (absent or not) and duration of pain (less than or more than 3 months) between the treatment arms. Proportions per treatment group will be reported.
- A consort flow diagram will be produced to get an overview of the number of patients available at each stage: eligibility, randomisation, allocation, discontinuation and follow-up.

10.3.2 Primary outcome analysis

The primary outcome EQ-5D-5L at 6 weeks will be compared between the 3 treatment arms in first instance using a linear regression model with treatment as a predictor and correction for quality of life at baseline. All patients in the study will be used in an intention-to-treat (ITT) analysis.

Patients who withdraw from the study medication are offered a different treatment option of topical or systemic treatment respectively. Following standard care practice patients on the pregabalin arm will be offered an alternative systemic drug (gabapentin) and patients on the topical arm will be offered a different topical drug (failing treatment with lidocaine 5% medicated plasters will be treated with capsaicin patches and otherwise) Cross-over between topical and systemic treatment is not allowed to maximally preserve the treatment

effect between the two methods. Non-compliers and withdrawals are followed up according to the protocol. Their data will be collected in the same way as for the adherers and in the analysis they will be considered in the initially randomised treatment arm.

10.3.3 Secondary outcome analysis

- Different sensitivity analyses will be done to evaluate the treatment effect at 6 weeks. Confounders like the use of rescue medication, the 3 stratifying variables (sensory disturbances such as hyperalgesia/allodynia, spontaneous positive sensory disturbances and duration of pain) and some other known confounders (gender, level of education, family situation) will be added to the linear regression model.

  A linear mixed model using all quality of life measurements over the 26 weeks with subject as random effect will improve the precision on the estimated treatment effect at 6 weeks. This complex model will be expanded by including site as a random effect and possible confounders will also be added to this model as fixed effects. From the linear mixed model the long term profiles of the treatments over the 26 weeks can be determined and using time as a categorical variable in this model will allow different linear evolutions from one time point to another.
- For each patient, an area under the curve including all quality of life measurements will be calculated using the trapezium rule and compared between the different treatment arms using linear regression. The area under the curve can be seen as a summary measure summing up initial treatment response or lack off and the effect of any rescue medication during follow-up.
- A similar analysis will be done for the subgroup of patients who adhered to the protocol in a per protocol analysis.
- Linear regression at 6 and 26 weeks will be performed to compare the pain intensity between the 3 treatment arms. Changes over time will be analyzed using linear mixed effect models.
- The use of rescue medication using MQS-III will be evaluated at 6 and 26 weeks using linear regression. Changes over time will be analyzed using linear mixed effect models.
- The time to worsening will be studied in a time-to event analysis comparing the different treatment arms. Two different events of worsening will be considered:
  - The first time the patient experiences a 30% increase in MQS-III score
    - This implies that patient has either significantly increased the use (number of intakes) of the rescue medication or has started taking analgesics of a higher level (WHO step ladder)
  - The first time the patient has a worsening of the pain in terms of 2 units rise on the pain intensity (numeric rating scale - NRS) scale compared to the previous assessment.
- The percentage of systemic drug-related side effects will be evaluated at 6 and 26 weeks using Chi-square test or Fisher's exact test. The evolution of the percentage of systemic drug-related side effects over time will be analyzed using a generalized linear mixed effects model using the clinical visit data and

the self-reported patient data.

- Discontinuation of study drug or study withdrawal: the percentage of study withdrawal will be compared after 6 and 26 weeks with a Chi-square test or Fisher's exact test whatever is appropriate based on assumptions. The time to discontinuation will also be studied in a time-to event analysis comparing the different treatment arms. The self-reported patient data will be used for this.
- Global perceived effect (GPE), effect on mood (Hospital Anxiety and Depression Scale), quality of sleep (Sleep-NRS and ISI), participation in activities (Utrecht Work Engagement Scale-9), impact of pain on functioning (interference – BPI), and Work Productivity and Activity Impairment (WPAI-Neuropathic Pain) will be compared at 26 weeks using linear regression and over time using linear mixed models.
- Similar to the primary outcome the treatment effect on the secondary outcomes will be estimated in a model with adjustment for confounders and including site as a random effect

10.3.4 Procedure(s) to account for missing or spurious data

Most of the data is collected through the online platform. A deviation of max. 48 hours or 7 days will be allowed for the completion of the different assessments at every time point (weekly versus monthly).

- The proposed linear mixed model allows that subjects have missing values at certain time points as the model uses all available data points per subject. The missing value assumption of the model is Missing At Random which means that missing values can only be dependent on the observed responses which seems a reasonable assumption in this case.

The study coordinator follows up on the missing data and records any reasons for missing data in patient file (medical record) and the eCRF (OpenClinica).

10.3.5 Other statistical considerations

- An important exploratory goal of this study is to design a profile of the patient-selective sensory phenotypes suitable for both topical treatment options. We will use the 3 stratifying variables as specified in our stratified randomisation (hyperalgesia/allodynia, dysesthesia, duration of pain) and test for a significant interaction between the treatment and the stratifying factor to see if the treatment effect is modified by this factor.

10.4 Data collection for economic evaluation

The burden of neuropathic pain seems to be related to the complexity of neuropathic symptoms (e.g. allodynia), poor outcomes and difficult treatment decisions. Evidence suggests that herpes zoster and peripheral nerve traumas are the most frequent causes of peripheral neuropathic pain, whereas stroke, multiple sclerosis and spinal cord injury are the major causes of central neuropathic pain. The negative impact upon functioning and quality of life is profound. Studies have demonstrated that neuropathic pain is more severe than non-neuropathic pain. Previous research has shown that NP can be

interfering with sleep, functioning, and emotional well-being.[60-63] It was shown in US patients suffering from painful peripheral neuropathy with small fiber involvement that they experience moderate to severe pain, which negatively impacts health status, function and productivity and leads to substantial direct and indirect costs.[64] In a study in patients suffering from post-traumatic/post-surgical NP it was shown that these patients reported high pain scores, which were associated with poor health utility, sleep, mood and function, as well as high health care resource utilisation and costs. The impact on quality of life and costs attributable to these NP conditions suggest an unmet need and the potential benefits of more effective management of NP.[65]

The most commonly used HRQOL (Health-related quality of life) instruments are general, whereas others have been designed specifically for those with neuropathic pain. Meyer•Rosberg and col• leagues validated both the 36•Item Short Form Health Survey (SF•36) and the Nottingham Health Profile (NHP) in the assessment of HRQOL in neuropathic pain related to peripheral nerve or nerve root lesions in patients attending multidisciplinary pain clinics.[66] The scores of all eight dimensions (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health) in the SF•36 were significantly lower in those with neuropathic pain than in the general population, which is in line with another study.[67] Employment status was reduced in more than 52% of these patients.

The onset of neuropathy in patients with diabetes mellitus has been shown to significantly decrease all aspects of quality of life.[68] If diabetic polyneuropathy is accompanied by pain, both physical and mental components of quality of life are further affected.[69] A recent study also showed that both EuroQol five dimensions (EQ•5D) and Short Form•6 dimension (SF•6D) questionnaires can discriminate between chronic pain with or without neuropathic pain.[14] Furthermore, the role of psychological factors in impairing quality of life in neuropathic pain has been analyzed, showing, for example, that pain catastrophizing was associated with decreased HRQOL.[70] The SF•36 and the EQ•5D have been the most commonly used instruments in clinical trials to assess the efficacy of treatments, such as gabapentin in postherpetic neuralgia[71], diabetic polyneuropathy[72] and neuropathic pain due to peripheral nerve injury[67]; the efficacy of duloxetine in diabetic peripheral neuropathy[73]; and the efficacy of spinal cord stimulation in diabetic polyneuropathy.[74] Finally, it should be mentioned that it has been shown that the EQ-5D seem to have higher construct validity and responsiveness than the SD-6D in patients with chronic pain.[75]

The primary outcome measurement of the proposed study protocol is a measurement of the overall quality of life of these patients suffering from LNP. Current first line (oral) treatment options often result in systemic side effects, decreasing the quality of life of the patients and negatively impact treatment adherence. Significantly decreasing these side effects (by using topical treatment options) will immediately result in a positive impact on QoL of these patients. Positive impact on QoL of patients suffering from LNP will have immediate positive impacts on activities of daily living (e.g. gait, ADLs), will increase and normalize their participation in normal socio-economic activities as well as their employment status. Significantly decreasing the incidence and severity of side effects will enable patients to decrease the number of doctor visits, decrease their medical needs (e.g. physiotherapy, cognitive behavioral support, relaxation), decrease the medical shopping (which is towering in these patients), and decrease the duration of sick leave. In addition, a rapid resolution of the neuropathic pain problem without side effects will also positively impact the use of concomitant medication such as benzodiazepines (great abuse of such drugs in this patient population).[76]Finally, it should be mentioned that some

scientific evidence exists indicating that the painful skin area is actually shrinking during the course of the topical treatment (see above). This means that for example the allodynic area will decrease in size during the course of the topical treatment, something that has never been described with any systemic anti-neuropathic therapy. Allodynia is often a prominent feature of LNP, and is usually considered to be one of the most distressing and debilitating symptoms of PHN. Therefore, one contributory factor to the improved QoL scores is likely to be the reduction in the area of allodynia - typically more than 50% - produced by treatment with the lidocaine or capsaicin patch. Reducing the painful area, which can increase tolerance of bathing and contact with clothing, is therefore a justifiable treatment goal for this medication. When the painful area is on the sole of the foot—limiting mobility—or on the palm of the hand, this advantage of the topical route over systemic medications assumes even greater importance. Based on the above-mentioned arguments it is obvious that ***timely implementation (as soon as possible after diagnosis of LNP) of topical treatments can result in significant savings both in the short-term as in the long-term****. Recently, a Scottish study stated that capsaicin 8% patch is cost-effective treatment option compared with dose-optimized pregabalin in patients with peripheral NP who have failed one or more previous systemic treatments.*[77]

Complexities in the NP care pathway make the condition difficult to manage and difficult to capture in cost-effectiveness models.[78] The authors of this recent review state that to improve future economic modeling in NP, further research is suggested into the effect of multiple lines of treatment and treatment failure upon patient outcomes and subsequent treatment effectiveness; the impact of treatment-emergent adverse events upon patient outcomes; and consistent and appropriate pain measures to inform models. The authors further encourage transparent reporting of inputs used to inform cost-effectiveness models, with robust, comprehensive and clear uncertainty analysis and, where feasible, open-source modeling is encouraged.

10.5 Methodology

The study will possibly include a cost-utility analysis of the topical treatment options compared to standard oral therapeutic approaches (this will be decided after termination of the study and presentation of the findings). This analysis will use cohort simulation based on a Markov model that will be constructed to evaluate the cost- effectiveness of topical lidocaine and capsaicin for the treatment of LNP conditions. Analysis will be performed using a 12-month time horizon from both the payer and societal perspectives, with the latter including indirect costs associated with work productivity and activity impairment that will also be evaluated as a cost component. The model will compare topical treatment to oral systemic treatment by extrapolating effectiveness data for each of the 3 arms in this protocol. Patient-reported outcomes assessments that will be included and incorporated into the economic model will include a numeric rating scale (NRS) for pain severity and sleep quality and the five-level EuroQol health status measure (EQ-5D-5L). Responses on the EQ-5D-5L will be converted to one-dimensional QOL scores using the value set to estimate quality-adjusted life-years (QALYs), which is the unit of incremental cost-effectiveness. The Markov model will follow transition states among severity of no/mild, moderate and severe pain. The pain level at week 26 (end of study protocol) will be extrapolated to 1 year. Resource utilisation in the model, and thus cost inputs, will be estimated through a survey completed by physicians, providing information on treatment of LNP based on longitudinal pain severity transition patterns assuming either moderate or severe pain as the initial pain category. Direct medical costs will be based on resource utilisation and medication use reported by the patients and physicians

(online platform – next generation PELICAN@Home platform). Drug acquisition costs are based on real-world doses observed in previous studies and protocols (see table underneath for medication cost per day).

***Table*: Medications cost per day (maximum) – 3 treatment groups in study protocol**

Lidocaine 5% medicated plaster - VERSATIS	3.28€ per plaster	Up to 3 plasters per day per patient, during 24 weeks	Maximum cost of 9.84€ per day
Capsaicin 8% patch - QUTENZA	308.52€ per patch	Budget 1: Up to 4 patches per patient, max. of 3 applications in each patient (every 90 days)	Maximum cost of 14.70€ per day
	154.26€ per patch	Budget 2: if reimbursement by RIZIV/INAMI; Up to 4 patches per patient, max. of 3 applications in each patient (every 90 days)	Maximum cost of 7.35€ per day (reimbursement category C)
Pregabalin 75mg - LYRICA	0.06€ per 75mg	Up to 8 capsules per day per patient, during 24 weeks	Maximum cost of 0.48€ per day
Gabapentin 300mg – EG	0.05€ per 300 mg	Up to 7 capsules per day per patient, during 24 weeks	Maximum cost of 0.30€ per day

The costs detailed in this table are based on the current reimbursement policies and do not take into account eventual reimbursement by RIZIV/INAMI for the patients participating in this trial.

Indirect costs associated with lost productivity at work will be calculated using the method of Lofland et al.[79], based on the Work Productivity and Activity Impairment (WPAI) scale for special health problems.[80,81] In this protocol the WPAI scale for Neuropathic Pain will be applied (v2.2 – Belgium with validated Dutch and French translations available). Productivity will be defined as a percentage from 0% to 100% and mapped to pain scores such that for each point change in pain score, the change in lost productivity can be estimated. Costs will be estimated on mean monthly income in Belgium.

QALYs

For calculation of the cost-utility, estimates of QOL scores for determination of QALYs were based on regression equations with the pain NRS scores, age, and sex as independent variables. These values, estimated individually for males and females, were then weighted and averaged by sex ratio and average age to derive weighted averages for each NRS score.

Cost-utility

Based on QALY and costs, the incremental cost-utility ratio (ICUR) will be calculated to evaluate the cost-utility of topical treatments. Sensitivity analyses will be performed to account for uncertainties in the data sources and assumptions, and to confirm the robustness of the ICURs estimated in the base case.

11 DATA HANDLING

11.1 Data collection tools and source document identification

There are two primary sources for the trial data. For clinical findings, observations, laboratory data, etc., the participating site's (electronic) medical record will be used as a primary source. For questionnaires completed by the participants, the **PELICAN@Home platform or paper questionnaires** will be the primary source.

In order to allow Source Data Verification of the medical record primary source, each participating site will be requested by the Sponsor to complete, before FPFV in the site, an Electronic Medical Record/Source Data Questionnaire. In this questionnaire, sites will confirm the presence of documentation related to validation of the electronic medical record or other records or questionnaires used as the primary source of trial data. If the participating site is able to provide a System Validation Certificate, a copy will be sent to the Sponsor and stored in the Investigator Site File. This questionnaire will request details concerning (at least) the following topics:

- System validation
- Electronic signature
- System access for monitors, auditors, and inspectors
- Copying, printing, and scanning
- Backup and archiving

In order to assess the validity of the data collected in the PELICAN@Home platform, third party BeWell Innovations will be asked to issue documentation related to storage of source data, system validation, backup, archiving, before FPFV in the trial and at the request of the Sponsor. BeWell Innovations will update the documentation and communicate with the Sponsor in case of any fundamental changes or data breaches. The Sponsor and BeWell Innovations will agree on timings and format of the release of source data to the sponsor/CI. A copy of the source data of all patients in PELICAN@Home included at a specific site will be provided to the local investigator.

An electronic case report form (eCRF) system – i.e. OpenClinica Community Edition – will be used by all participating sites to collect the individual patient data required by the trial protocol. It will include data from the (electronic) medical record(s) (primary source 1) and from the PELICAN@Home platform (primary source 2). The eCRF data will be used to perform the statistical analyses for the trial, as described in Section 10.3.

The Sponsor will provide functional training for designing eCRFs in and extracting data from OpenClinica for (at least) the Chief Investigator, the Trial Coordinator, and the Data Manager. The Sponsor will provide data entry training sessions for the participating centers. The training sessions will be repeated if necessary (e.g. new version, delayed data entry, …) The Sponsor designates the Chief Investigator and the statistician to validate the designed eCRFs to ensure that the data points required for statistical analysis for the trial are included and no redundant or secondary data is being collected. Validation of the designed eCRFs is done by means of a paper print with wet signature by both Chief Investigator and statistician. In case of changes in the design of the eCRFs, the validation

is repeated. Full audit trail of data collected is available in OpenClinica. The Chief Investigator, Trial Coordinator, Data Manager, monitors, and auditors will receive access to the audit log in OpenClinica. Data extraction can be performed by the designated people at fixed times.

The eCRF system will not be used as a primary source of data.

11.2 Data handling and record keeping

The **PELICAN@Home platform** (developed by the Antwerp University Hospital in cooperation with BeWell Innovations) – a primary source – is hosted on servers within the central server facility at the Antwerp University Hospital (Sponsor's location). The use of this platform has become routine standard care since the platform is used nationwide for other (pharmacological and invasive) therapeutic options for severe chronic pain conditions in all acute Belgian hospitals. This nationwide access to the online platform was fully implemented by February 1st 2018.

All trial data will be gathered in OpenClinica (Community Edition), an open-source web-based electronic Case Report Form (eCRF) system. The Sponsor hosts OpenClinica version 3.13 on two virtual servers – one for the initial testing of the eCRFs and one for the collection of trial data in production. These virtual servers are hosted in the central server facility at the Antwerp University Hospital (Sponsor's location). The trial data are backed up on a daily basis and stored in a Data Domain (Dell EMC Data Domain) at the Sponsor's location to enable disaster recovery with a maximum loss of 1 day of trial data. The Sponsor's IT project lead who supports OpenClinica is certified to provide basic and advanced training in OpenClinica version 3.13 to end users. Since the eCRF data are stored at the Sponsor's location, no data storage needs to be foreseen with the participating sites.

PELICAN@Home and paper questionnaires data will be integrated into OpenClinica.

In the eCRF, the trial participants will be coded by their unique enrolment ID.

The sponsor will be responsible for data analysis after the monitoring has been concluded.

11.3 PELICAN@Home digital platform

The PELICAN@Home system is made up of several components that ensure a detailed and optimal flow between patient and healthcare provider. The PELICAN@Home system consists of:

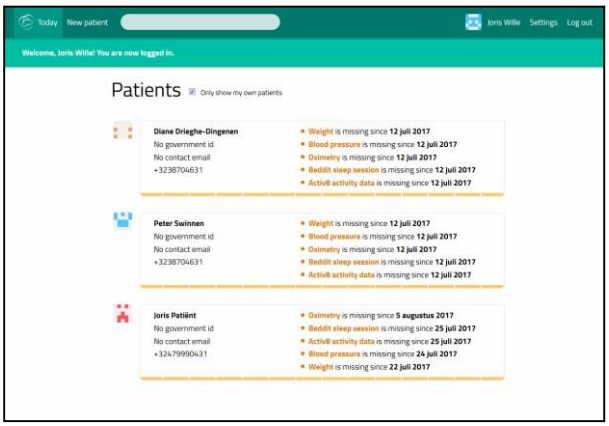
- PELICAN@Home web-based platform (https://pelican.uza.be)

The combination of these components makes PELICAN@Home very flexible and easy to use, allowing the patient to be informed automatically at the right times without much effort. The system is available in Dutch and French (French version can also contain German questionnaires in order to facilitate the completion of the validated questionnaires by German-speaking patients).

11.3.1 PELICAN@Home digital platform

The installation of the platform is performed on the UZA's server infrastructure, ensuring 100% privacy of the data.

The follow-up of a patient within the PELICAN@Home system, is easy to configure within the web-based platform. The healthcare provider can follow-up all his/her patients. The sequence within the patient list, provided within the dashboard, shows the patients who require most attention at the top of this list.



The configuration of the platform is based on:

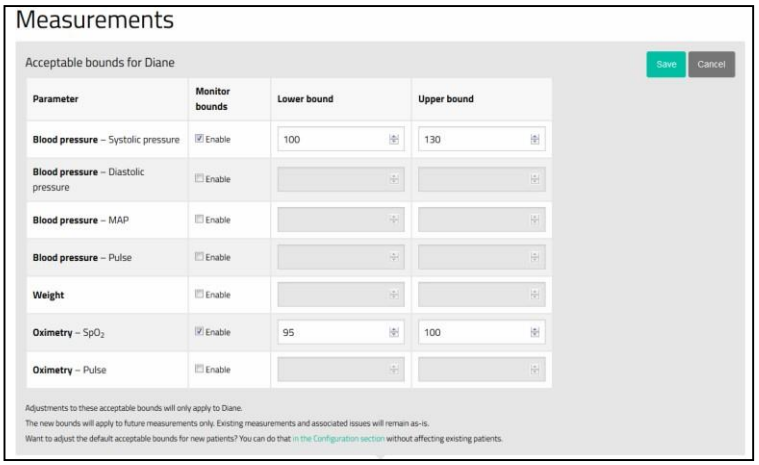
- Management of healthcare providers and administration, who have access to the platform, through the admin account.
- Management of preset parameters that are automatically used when a new patient is created. This results into an optimal follow-up of the patient based on these parameters.
- Management of the questionnaire module. These are either validated questionnaires entered by the admin with the option to obtain validated outcome. The patient can answer a questionnaire, via the web-based platform, after which the outcome appears in his file.
- Management of predefined notifications
- Configure a decision-tree structure.

A patient in the PELICAN@Home platform is always linked to a unique box code that the patient needs to use for the PELICAN@Home. This creates a direct link with the server on which the data of this patient is located. The physical location of this server is Intramuros at the UZA (sponsor of this trial), ensuring that privacy is fully guaranteed.

Within the setup of a patient, the task package for that patient can be configured, among which

- Measurement of medical parameters by the patient, in his or her home environment (intensity of pain, sleep quality, occurrence of side effects, MQS-III score, etc…)
- Compilation of validated questionnaires to be completed by the patient at specific times.
- Automatic trigger of an action when an outcome is out of bounds. A

questionnaire and/or measurement can be linked to the result of another measurement/outcome.

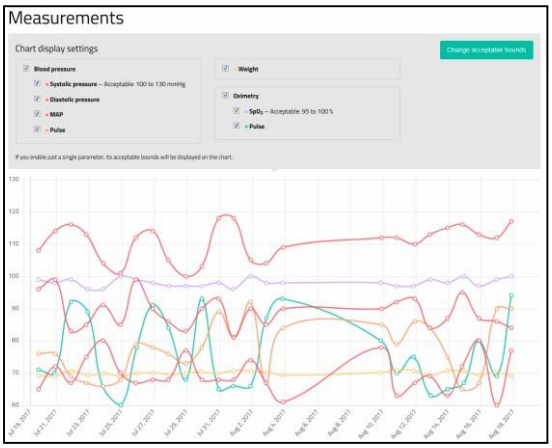


The follow-up of a patient can be partially automated within the PELICAN@Home system. The patient / group settings make the list of these patients in the dashboard already more transparent. The next step in the follow-up is to consult a patient's details.

Multiple parameters can be checked in here:

- Measurements added by the patient directly and without further action by the patient to his / her file:
  - Pain Intensity
  - Sleep Quality
  - Side effects (occurrence and intensity of symptoms)
  - Activity (lay down, standing, walking, running, cycling)
- Results for PROM/PREM of validated questionnaires (MPI-DV, HAD scale, etc.).
- Overview of drug use. For pain medication, a validated score is calculated based on the MQS-III medication score.
- List of requested data of missing data (Patient who did not perform the measurement)

The patient can receive messages in function of missing parameters. Thanks to these automatic notifications, the follow-up of a patient with a lower "therapeutic compliance" is improved.



11.4 Access to Data

When requested, monitors, auditors and inspections will be granted direct access to the eCRF system and to the primary data sources.

11.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures they are readily available upon authorities' request. Documents for this study will be archived for 25 years, through an external partner (Merak, http://www.merak.be).

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12 MONITORING, AUDIT & INSPECTION

Before study initiation, at a site initiation visit a representative from the sponsor will review the protocol and data capture requirements (i.e. eCRFs) with the local investigators and their staff. During the study, field monitors employed by the sponsor (belonging to the CTC) will employ several methods of ensuring protocol and Good Clinical Practice compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture and data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that study treatment is being dispensed and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by the centralized Sponsor research associate (CRA).

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigators must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to a study-specific monitoring plan. This monitoring plan will be approved by CI. Themonitoring visits including site initiation visit and close out visit will be performed at each site. There will be a monitoring visit every 6 weeks. If there is no on-site monitoring visit, a remote monitoring visit will be performed according to the monitoring plan. Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring report. If necessary, an amendment of the monitoring plan will be drawn up and approved again by CI

If study sites (pain centers) do not register patients or stop enrolment, no regular monitoring visit will be planned. In the case of long-term absence (more than 2 months) of research activities, the monitor will ensure the research team is adequately trained when the research activity is restarted.

No information about the identity of the patients will be disclosed in source documents.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Ethics Committee (EC) review & reports

- Relevant documents will be sought from the leading EC UZA/UA and any local EC from subsites;
- Substantial amendments that require review by EC will not be implemented until the leading EC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the FAMHP before they can be implemented in practice at sites);
- All correspondence with the EC will be retained in the Trial Master File/Investigator Site File;
- An annual progress report (APR) will be submitted to the leading EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended;
- It is the Chief Investigator's responsibility to produce the annual reports as required;
- The Chief Investigator will notify the EC of the end of the study;
- Local PI's will notify their local EC by close out;
- If the study is ended prematurely, the Chief Investigator will notify the EC, including the reasons for the premature termination;
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the EC.

13.2 Peer review

The proposed protocol has been reviewed and discussed on several occasions (before submission of each update of summary and before submission of full proposal) by the board of the Belgian Pain Society (BPS). As such, an independent and proportionate peer review could be guaranteed. In addition, after submission of final summary this proposal was sent to all candidate centers for further review, commenting and discussion. The current version of the full proposal is therefore based on the comments expressed by the candidate centers. In addition, this proposal was discussed with two international experts on the subject of neuropathic pain.

Peer review has been independent, expert, and proportionate:

1. Independent: Five individual experts, members of the BPS board, did review the study. These reviewers are external to the investigators' host institution (UZA) and are not involved in the study in any way.
2. Expert: The above-mentioned reviewers have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol and have the expertise to assess the methodological aspects of the study.
3. Proportionate: Peer review is considered to be commensurate with the size and complexity of the study. This multicenter study requested a higher level of peer review (more reviewers with broader expertise and often independent review committee or board), and international peer review.

13.3 Public and Patient Involvement

In the last couple of years, the Belgian Pain Society (BPS) has frequently organized discussion rounds with patient groups in order to establish the research priorities from the patients' perspective. Patient representatives were actively involved in the different stages of the research proposal, as this has been so on previous occasions (submission for grants at a Belgian and international level). More in detail, patient involvement was included in the outlining of research topics, assessment of the design. In the future patient organisations will be actively involved in the carrying out of the research project. It should be stressed that previous users of the online platform have been actively recruited to serve as counsellor for the further development of the platform. By this interaction the outline and content as well as the accessibility of the platform have been updated regularly in order to increase the compliance of the users to the provided interactive register.

In which aspects of the research process patients and users have actively involved, or will involve, patients, service users, and/or their careers, or members of the public in particular;

- Design of the research: discussion
- Management of the research
- Undertaking the research
- Dissemination of findings

13.4 Regulatory Compliance

The trial conduct will comply with any and all applicable laws and local requirements, including but not limited to

- the International Conference on Harmonisation Guidelines (ICH Guidelines),
- the European Directive No 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products,
- the European Regulation No 536/2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC, and
- the Belgian law of May 7th 2004 regarding experiments on the human person and any relevant amendments

In accordance with the aforesaid applicable laws, regulations and guidelines, the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the EC, and the FAMPH.

13.5 Protocol compliance

The trial will be carried out in full compliance with the final version of the protocol. No deviations nor waivers to the selection criteria or protocol procedures will be allowed at

any time by the sponsor in one of the participating multidisciplinary pain centers.

All protocol deviations that occur during the protocol which are related to a patient will be documented in the patient file (medical record) and eCRF (OpenClinica). The eCRF deviation log will capture the deviation description, deviation type, deviation date, date identified, relation to adverse event and influence on intake study medication. If a protocol deviation is related to more than one patient this deviation must be recorded in the eCRF of each patient. General protocol deviations will be recorded on a paper protocol deviation log and will be present in ISF and TMF. A protocol deviation with impact on the process of informed consent, serious adverse event reporting and trial medication administration, will initiate a retraining by the sponsor appointed monitor of at least the principal investigator as well as the main study coordinator. This training will need to be documented on the protocol training log.

Other protocol deviations will be documented on the eCRF log form. If the same protocol deviation re-appears three times within the same trial site, a protocol retraining (with special attention to the deviation process) of at least the principal investigator will be performed by the monitor.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A serious breach is defined as a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial.

A serious breach to GCP and/or protocol will be communicated immediately to the chief investigator by phone, with confirmation by e-mail later on. The eCRF deviation log will be updated by the serious breach within 3 working days.

The sponsor will notify the licensing authority in writing of the serious breach to GCP and/or protocol within 7 working days of becoming aware of that breach.

13.7 Data protection and patient confidentiality

Patient confidentiality must be maintained at all instances and the trial will be compliant with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The PI of the sponsor has NO competing interest with respect to this trial. The design of the trial, nor its conduct of reporting will be influenced by any competing commercial interest.

Information regarding financial and other competing interests will be gathered from the investigators and co-investigators of all of the participating multidisciplinary pain centers as soon as these centers have been identified. These disclosures from the individual centers will be documented in ISF and TMF. These disclosures should reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

13.9 Indemnity

In accordance with the Belgian law relating to experiments in humans dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a participant and linked directly or indirectly to the participation to the study, and in order to provide compensation therefore the Sponsor has undersigned a sufficient insurance policy with AMMA, Kunstlaan 39/1, 1000 Brussel, policy n° 1887617.

The Study Partner, any participating site and any Investigator (whether or not through the participating site to which he/she is affiliated) must have and maintain in full force and effect during the term of the study (and following termination of the study to cover any claims arising from the study) adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability, and (iii) other possible damages resulting from the study, each such insurance coverage in amounts appropriate to the conduct of its tasks and responsibilities in the study.

13.10 Access to the final trial dataset

PELICAN Policy on data sharing

“PELICAN Database” shall mean the database containing all Results resulting from or relating to the Study conducted; and “PELICAN Data” shall mean any data contained in the PELICAN Database.

The PELICAN Database will be a valuable resource for further research beyond the Study which we would wish to encourage. The PELICAN Database has been facilitated by public funding.

Hence, it is not only from a desire to facilitate research to improve the care of neuropathic pain patients but also from a moral obligation to the community to ensure the most optimal

return on invested funding, that the Study Sites support the concept of data sharing. With the aim to ensure an optimal use of the PELICAN Data and to prevent possible misuse, this policy for data sharing as well as for publication and publication credits for those who use PELICAN Data has been established.

This policy further aims to encourage academic productivity and to provide a mechanism for tracking and archiving PELICAN Data requests, intended analyses and publications related to and resulting from the PELICAN Data.

1. Staging of access

This policy contains a staged access to the PELICAN Data in order to optimize their reliability and to guarantee their best use.

Prior to completion, closure and checking of the PELICAN Database, access to the PELICAN Database by third parties other than those contributing data to the PELICAN Database or under clause 9.2.1 of the draft KCE Agreement should only be allowed by the Trial Steering Committee under carefully controlled circumstances, as outlined in section 2 below.

2. Data sharing with the Consortium

In order to facilitate best use of the PELICAN Data within the Project and to streamline analyses and reporting during the PELICAN Study phase, the following general rules are agreed upon:

- The initial and additional analysis of PELICAN Data will be coordinated by the Trial Steering Committee in collaboration with the Parties involved.
- Research questions that are not specified in the Protocol can be addressed following notification to and approval by the Trial Steering Committee in accordance with the procedure set forth in section (3) below.
- Analysis and reporting of PELICAN Data obtained by a single Party or a single third party will be discouraged prior to completion of the full analysis of the PELICAN Database, unless it forms part of the ongoing Study.

3. Data sharing and data requests outside the scope of the PELICAN Study

The expectation of UZA is that de-identified PELICAN Data can be made available to the general scientific community within a relatively short time frame after closing and checking of the PELICAN Database.

Users will complete an application form and data use agreement. The application will be reviewed by the Trial Steering Committee with regard to feasibility and confidentiality. The feasibility will be assessed in discussion with the PI of the collaborating sites. When the application is approved by the Trial Steering Committee, the applicant will be requested to sign a data use agreement and will then be provided access to the required PELICAN Data. Such data use agreement shall be countersigned by UZA as Sponsor.

It is not expected that Parties of the PELICAN Consortium will automatically be assigned authorship on any publications that emerge from such use of the PELICAN Data.

However, where the cohort collection and characterization represent a key part of the analysis, or members of the PELICAN Consortium contribute materially to the science underpinning published abstracts or manuscripts, they should be cited as authors on these publications.

Information required from applicants

Applicants will be required to provide the following information:

- Name
- Address and contact information
- Academic affiliation (if any) or institution/company name
- Proposed analysis with a named lead investigator on each analysis. Submission of an analysis plan is aimed to avoid redundant topics.
- Certification to each point of the data use agreement

Applicants will receive annual requests to update the application information and to provide a report on progress and publication. Non-compliance with the required updates will result in a prohibition to further access PELICAN Data.

Applicants who move to another institution, are required to notify PELICAN Trial Steering Committee in writing within 30 days regarding disposition of the PELICAN Data. If the applicant plans to continue work on the PELICAN Data at his/her new institution, updated contact information including identification of any other new users and execution of a new data use agreement is required. If the PELICAN Data remain at the initial requesting organisation then the applicant must designate who is responsible for the files and ensure that he/she signs a copy of the data use agreements and submits this to the Clinical Trial Unit of UZA.

Data use agreement PELICAN Database

The Trial Steering Committee shall finally decide on the terms of the Data Use Agreement, which shall substantially be as follows:

I request access to the PELICAN Database, for the purpose of scientific investigation, teaching or the planning of clinical research studies in the field of neuropathic pain and agree to the following terms:

1. I will receive access to de-identified data and confirm that use of the data will be restricted for purposes outlined in the submitted analysis plan.
2. I will not attempt to establish the identity of, or attempt to contact any of the individuals, whose data are contained in the PELICAN Database.
3. I will not further disclose these data beyond the uses outlined in this agreement and my data use application and understand that redistribution of data in any manner is prohibited.
4. I will require anyone on my team who utilizes these data, or anyone with

whom I share these data to comply with this data use agreement.

5. I will accurately provide the requested information for persons who will use these data and the analyses that are planned on these data.
6. I will respond promptly and accurately to annual requests to update this information.
7. I will comply with any rules and regulations imposed by my institution and its institutional review board in requesting these data.
8. I will ensure that investigators who utilize PELICAN Data use appropriate administrative, physical and technical safeguards to prevent use or disclosure of the data other than as provided for by this agreement.
9. In the event any undesired disclosure may occur I will report to UZA any use or disclosure of the data not provided for by this agreement of which I become aware within 24 hours of becoming aware of such use or disclosure and will take all reasonable measures to avoid further disclosures and to mitigate the effect of the undesired disclosure already occurred.
10. I agree to notify the PELICAN Trial Steering Committee in case I should move to another institution. In case the analysis will be continued at my new institution, I will provide the PELICAN Trial Steering Committee with updated contact information that includes identification of any other new users and a data use agreement executed by my new institution. If the data remain at the initial requesting organisation I will inform the PELICAN Trial Steering Committee who will become responsible for the files and ensure that he/she submits a signed copy of the agreement.

If I publish abstracts, using data from the PELICAN Database, I agree to the following:

11. I will cite PELICAN as the source of data and the PELICAN funding sources in the abstract as space allows.
12. Acknowledgement of PELICAN will not be cited in the authorship line of the abstract.
13. I will submit abstract by email to the PELICAN Trial Steering Committee If I publish manuscripts, using data from PELICAN, I agree to the following:
14. I will acknowledge the source of the data using language similar to the following: Data used in preparation of this manuscript were obtained from the PELICAN Consortium. The collation of the PELICAN Database was funded by the Belgian Health Care Knowledge Centre (KCE Trials programme).
15. I will submit all manuscripts to the PELICAN Trial Steering Committee prior to submitting to a journal.

This review will not be a scientific review but is intended to ensure that items 11-14 are correctly implemented. The PELICAN Trial Steering Committee will maintain confidentiality of the manuscript and will complete its review within 2 weeks.

It is not expected that members of the PELICAN Study Sites will automatically be assigned authorship on any publications that emerge from such use of the data. However, where the Consortium Agreement cohort collection and characterisation represent a key part of

the analysis, or members of the PELICAN Study Sites contribute materially to the science underpinning published abstracts or manuscripts, they should be cited as authors on these publications.

General terms

The PELICAN Database is experimental in nature and is provided without any warranties, expressed or implied, including any warranty of merchantability or fitness for a particular purpose. Antwerp University Hospital for itself and on behalf of any other PELICAN Study Sites make no representation and provide no warranty that the use of the material will not infringe any patent or other proprietary right.

To the extent allowable under applicable laws, my organisation agrees to indemnify, defend and hold harmless Antwerp University Hospital, its officers, staff, representatives and agents and all PELICAN investigators against all damages, expenses (including without limitation legal expenses), claims, demands, suits or other actions arising from organisation acceptance, use and disposal of the material.

This agreement is not assignable.

I understand that failure to abide by this agreement will result in termination of my access to the PELICAN Data and may lead to liability.

4. Access following completion of the Project

The preferred arrangement would be for UZA to seek additional independent funding to maintain the PELICAN Database after completion of the Study as an independent resource with access procedures as set out above. In the event that such funding could not be identified and continued access to the PELICAN Database can only be assured by making the PELICAN Database publicly available, the Trial Steering Committee may decide to make the de-identified PELICAN Data contained in the PELICAN Database publicly available.

14 DISSEMINATION POLICY

14.1 Dissemination policy

Upon study completion and finalization of the study report, the study results will be disseminated as soon as possible by disclosing them to the public by appropriate means, including scientific publications.

The final study report and any other dissemination of results of the study will be made available for review and comment by KCE before their dissemination as required by the agreement between UZA and KCE.

UZA shall assure that any dissemination is scientifically correct, objective and unbiased.

UZA will not, and will use its best efforts to ensure that the Study sites shall not, independently publish or disclose any results of the study before publication of the main multicenter publication.

UZA shall ensure that any dissemination shall acknowledge KCE's financial support and carry a disclaimer as KCE may require.

UZA will ensure open access to all peer-reviewed scientific publications relating to the results.

14.2 Authorship eligibility guidelines and any intended use of professional writers

For the publication resulting from this trial no professional medical writers will be hired. In general, a group authorship will be applied, after individual mentioning of the first five authors. The following general criteria will be applied with respect to authorship:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria will be acknowledged. All individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

The individuals who conduct the work are responsible for identifying who meets these criteria and ideally should do so when planning the work, making modifications as appropriate as the work progresses. It is the collective responsibility of the authors, not the

journal to which the work is submitted, to determine that all people named as authors meet all four criteria; it is not the role of journal editors to determine who qualifies or does not qualify for authorship or to arbitrate authorship conflicts. If agreement cannot be reached about who qualifies for authorship, the institution(s) where the work was performed, not the journal editor, should be asked to investigate. If authors request removal or addition of an author after manuscript submission or publication, journal editors should seek an explanation and signed statement of agreement for the requested change from all listed authors and from the author to be removed or added.

The corresponding author is the one individual who takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process, and typically ensures that all the journal's administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and gathering conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more co-authors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication.

For this trial resulting publications will apply **large multi-author groups** designate authorship by a group name (**PELICAN study group**), with or without the names of individuals. When submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists, and clearly identify the group members who can take credit and responsibility for the work as authors. The by-line of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the by-line. If the by-line includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the by-line clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.

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APPENDICES

APPENDIX 1. AUTHORISATION OF PARTICIPATING SITES

Appendix 1.1. Required documentation

Before initiating a participating site, the following documents are requested:

- CV Principal Investigator
- Final feasibility report
- Contact details and delivery address of local hospital pharmacy

Appendix 1.2. Procedure for initiating/opening a new site

Before a site is activated, at a site initiation visit or at an investigator's meeting, a representative of the sponsor will review the protocol and data capture requirements (i.e. eCRFs), with the local investigators and their staff.

During the study, the sponsor employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor of the sponsor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that study treatment is being dispensed, and accounted for according to specifications. Key study personnel must be available to assist the sponsors' field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a logging into the online platform and by accessing the eCRF data of each center.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other relevant tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (another signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. See the monitoring plan for detailed discussion of what will be included in the overall monitoring plan of the participating centres.

Appendix 1.3. Principal Investigator responsibilities

The following requirements are expected from the principal investigator (PI):

- Attendance at the initiation meetings;
- Availability for teleconferences, in order to solve practical problems, answer

questions regarding inclusion and exclusion criteria and discuss specific items with regard to the completion of the trial;

- Ensuring that the ISF is accurately maintained;
- Ensure proper training of the nursing staff applying the topical treatment with capsaicin.

APPENDIX 2. SAFETY REPORTING DEFINITIONS

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Operational definitions for (S)AEs

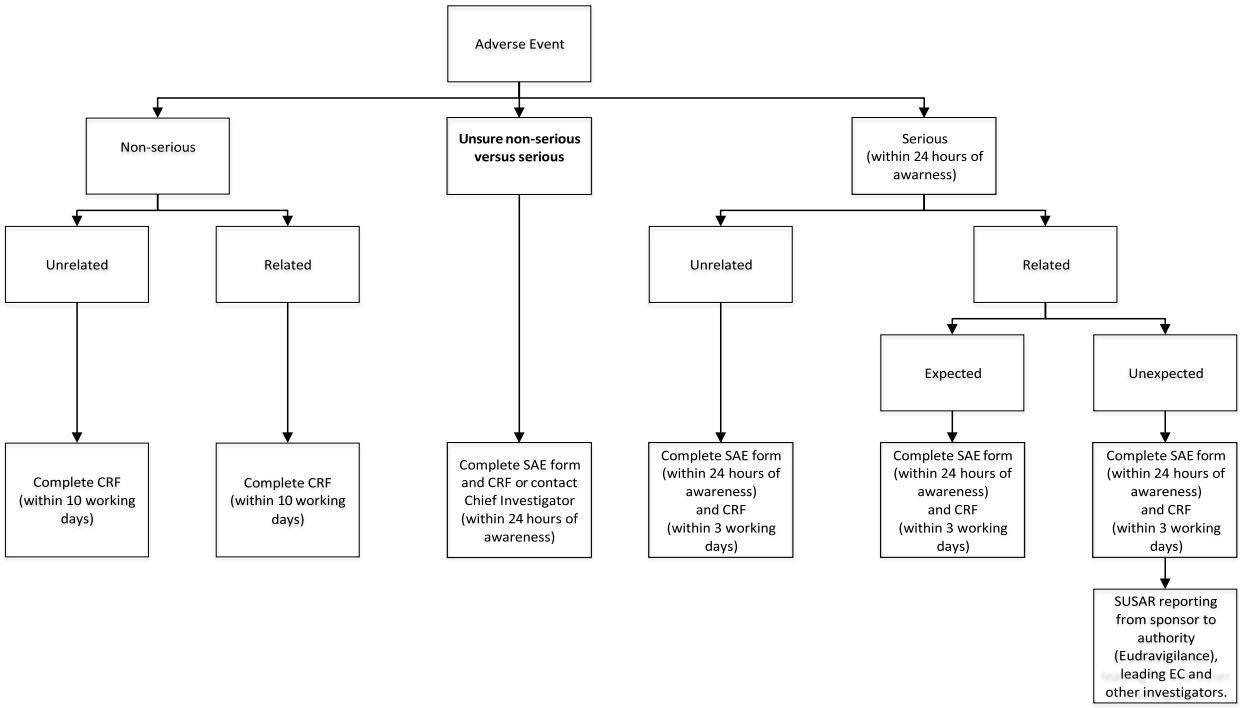
In the OpenClinica eCRF system, (S)AE forms will be designed and made available to all participating sites. Data extraction from OpenClinica can be restricted to only include the reported (S)AEs. Participating sites will need to report SAEs to the Sponsor via mail within 24 hours of awareness and AEs through OpenClinica within 10 days of awareness.

In all cases AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor; these may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation. Where certain AEs are not required to be reported to the Sponsor, these should still be recorded in the participant's medical records. Clear guidance in the protocol should state where this is the case (see appendix 3 for further details).

Since all IMPs being used are licensed, the latest SmPC will be used in this protocol.

The IMP reference documentation that is used for pharmacovigilance purposes is used to assess the causality and expectedness of events and will be checked by the Sponsor for changes on the anniversary of the Clinical Trial Authorisation. A statement will be included in the protocol describing which document is approved for use within the trial for pharmacovigilance monitoring (most current SmPC of the different IMP's used in this trial).

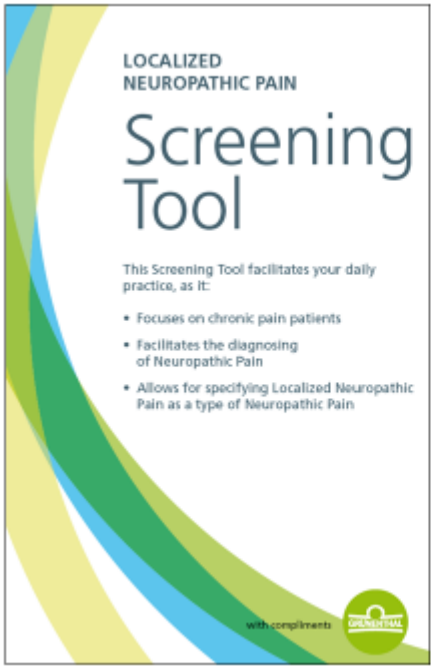
APPENDIX 3. SAFETY REPORTING FLOW CHART



APPENDIX 4. AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
/	1.0	November 27, 2017	Guy Hans	1st version of the full protocol
/	2.0	September 27, 2018	Guy Hans	Updated version signed by KCE
1	3.0	February 20, 2019	Guy Hans	Updated version wave 2
2	4.0	May 21, 2019	Guy Hans	Change eligibility criteria
3	5.0	January 21, 2020	Guy Hans	c

APPENDIX 5. LNP screening tool for GPs

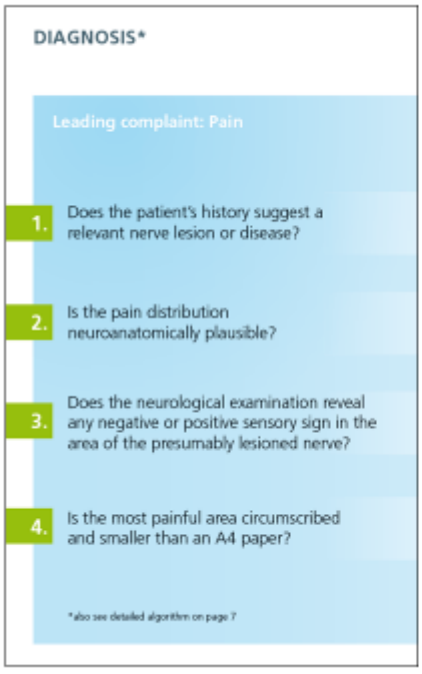


Gelokaliseerde Neuropathische Pijn

Screeningsinstrument

Dit screeningsinstrument helpt u in uw dagdagelijkse praktijk:

- Het is gericht op chronische pijnpatiënten
- Het vereenvoudigt de diagnose van neuropathische pijn
- Het laat een specifieke typering van gelokaliseerde neuropathische pijn toe als een subtype van neuropathische pijn

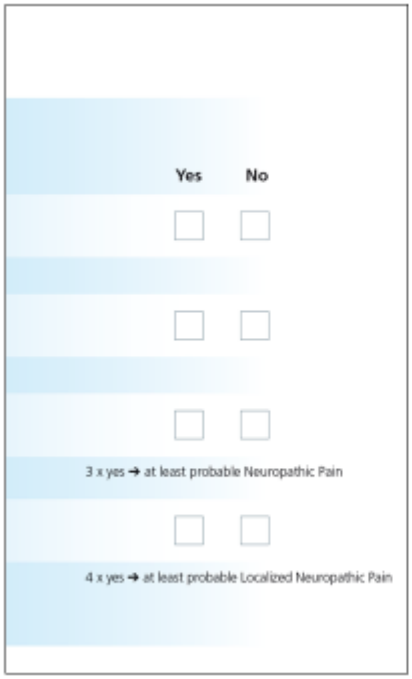


Diagnose*

Voornaamste klacht: Pijn

1. Laat de medische voorgeschiedenis van de patiënt u vermoeden dat er een relevante beschadiging of aantasting van een zenuw aanwezig is?
2. Is de neuroanatomische distributie van de pijnklachten aannemelijk?
3. Duidt het neurologisch onderzoek op de aanwezigheid van een negatief of positief sensorieel symptoom in het dermatoom van de vermoedelijk aangetaste zenuw?
4. Kan de meest pijnlijke huidzone eenduidig afgelijnd worden en is deze zone kleiner dan een A4-blad?

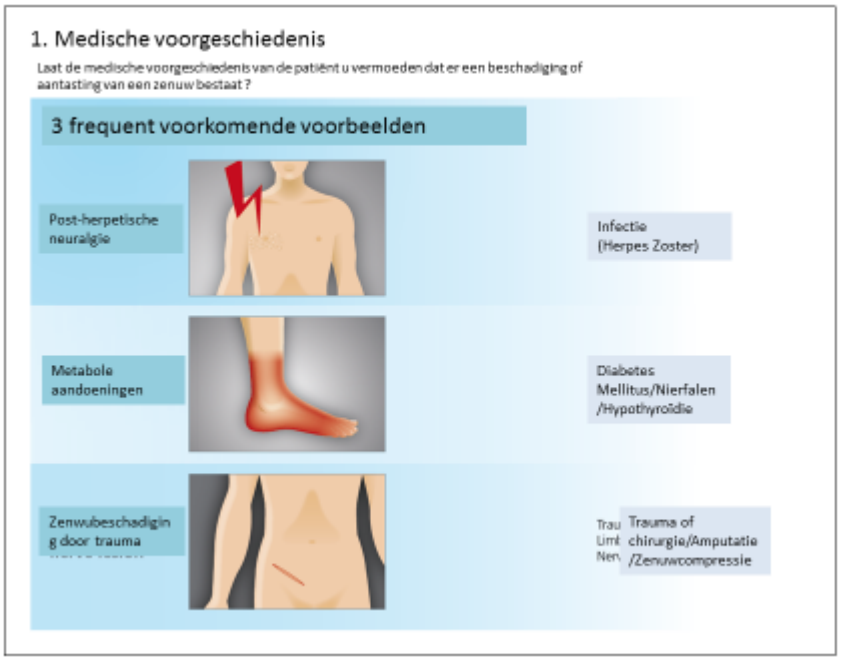
*Zie ook gedetailleerd algoritme op pagina 7



Ja Neen

3 x ja -> neuropathische pijn is op zijn minst waarschijnlijk

4x ja -> gelokaliseerde neuropathische pijn is op zijn minst waarschijnlijk

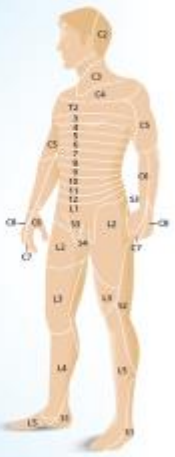


2. Anatomie

Is de neuroanatomische districutie van de pijnklachten aannemelijk?

Pijnlijke symptomen en gevoelsstoornissen

Bezenuwingsgebieden van perifere zenuwen



Dermatomen

3. Sensorieel onderzoek

Duidt het neurologisch onderzoek op de aanwezigheid van een negatief of positief symptoom in het dermatoom van de vermoedelijk aangetaste zenuw?

Aanraking
Wattenstaafje

Speldenprik
Veiligheidsspeld
Tandenstoker

Vibratie
Stemvork 128 Hz

Koude/Warmte
Flesje NaCl in de koelkast/proefbuis met warm of koud water/metalen object (vb. reflex hamer of stethoscoop)

Druk
Injectiespuit/potlood
Monofilament

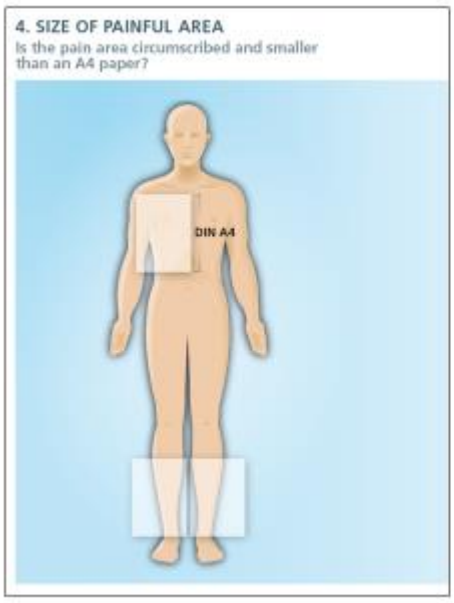
Begin het onderzoek in een gebied dat ver verwijderd is van de pijnlijke huidzones (vb. hand bij pijn/symptomen in de voet en het contralateraal lidmaat bij unilaterale klachten)

Testgebied = meest pijnlijke huidzone zoals aangegeven door de patiënt (indien <A4 = gelokaliseerde pijn)

Herhaal elke stimulatie 3 maal

Interpreteer de respons als normaal, afgenomen of toegenomen (kwanitatieve respons)

Vraag de patiënt onmiddellijk na de 3e stimulatie om de pijn te evalueren aan de hand van een 4-punten pijnschaal
0= geen pijn en/of ongemak
1= oncomfortabel maar draaglijk
2= pijnlijk
3= extreem pijnlijk, patiënt kan dit niet verdragen



4. Grootte van pijnlijk gebied

Kan de meest pijnlijke huidzone eenduidig afgelijnd worden en is deze pijnlijke zone kleiner dan een A4-blad?

FURTHER ETIOLOGICAL TESTS MAY BE CONSIDERED

In case of a progressing disease, please refer immediately to a specialist without waiting for laboratory test or images.

Consider previous medical treatments as possible etiologies for NP:

- Radiotherapy
- Chemotherapy
- Surgery/Trauma
- Others, such as antibiotics

Consider individual aspects of your patient:

Overview of Lab tests:

- Blood glucose level (+/- HbA1c)
- Glucose tolerance test
- Creatinine
- Thyroid hormones
- HIV serology
- Inflammatory parameters
- Liver enzymes
- Urea
- Others

Other tests: consider referral to specialist, imaging and neurophysiological tests:

- Ultrasound
- Rx (LBP)
- MRI
- EMG & nerve studies

For treatment options please, refer to the local guidelines.

Bijkomend onderzoek kan worden overwogen

Opgelet: In het geval van een progressieve aandoening, gelieve **onmiddellijk** door te verwijzen naar een specialist en de resultaten van technische onderzoeken niet af te wachten.

Overzicht laboratoriumonderzoeken:

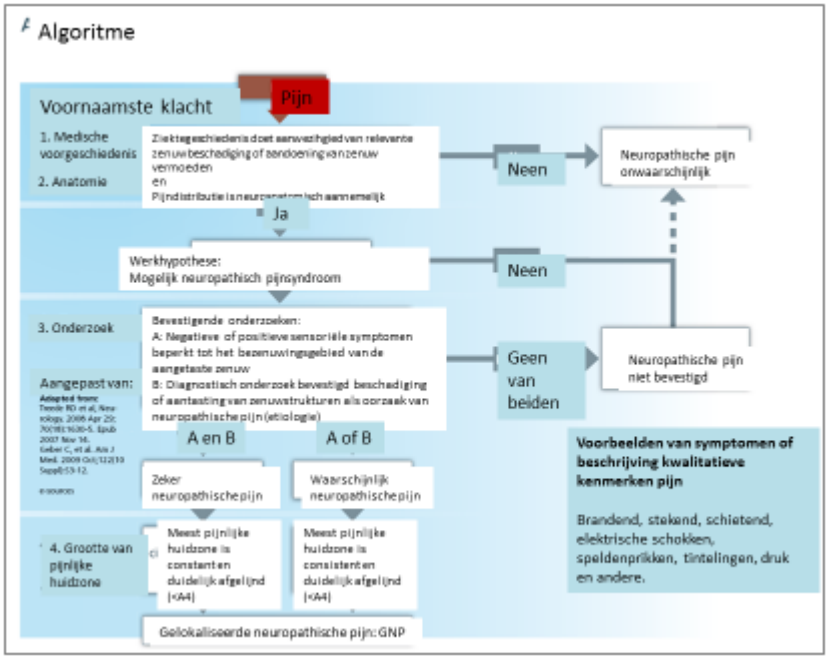
- Bloedglucose (+/- HbA1c)
- Glucosetolerantie
- Creatinine
- Schildklierhormonen
- HIV serologie
- Inflammatoire parameters
- Leverenzymen
- Ureum
- Andere

Andere onderzoeken:

- Echografie
- Rx (lage rugpijn)
- MRI
- EMG & zenuwgeleidingsonderzoeken

Overweeg medische behandelingen uit het verleden als mogelijke oorzaken voor de neuropathische pijn:

- Radiotherapie
- Chemotherapie
- Chirurgie/trauma
- Andere, zoals antibiotica


Algoritme
Voornaamste klacht
Pijn
1. Medische voorgeschiedenis
2. Anatomie
Ziektegeschiedenis doet aanwezigheid van relevante zenuwbeschediging of aandoening aan zenuw vermoeden
en
Pijndistributie is neuroanatomisch aannemelijk
Neen
Neuropathische pijn onwaarschijnlijk
Ja
Werkhypothese:
Mogelijk neuropathisch pijnsyndroom
Neen
3. Onderzoek
Bevestigende onderzoeken:
A: Negatieve of positieve sensoriële symptomen beperkt tot het bezenuwingsgebied van de aangetaste zenuw
B: Diagnostisch onderzoek bevestigd beschadiging of aantasting van zenuwstructuren als oorzaak van neuropathische pijn (etiologie)
Geen van beiden
Neuropathische pijn niet bevestigd
Aangepast van:
A en B
A of B
Zeker neuropathische pijn
Waarschijnlijk neuropathische pijn
Voorbeelden van symptomen of beschrijving kwalitatieve kenmerken pijn
Brandend, stekend, schietend, elektrische schokken, speldenprikken, tintelingen, druk en andere.
4. Grootte van pijnlijke huidzone
Meest pijnlijke huidzone is constant en duidelijk afgelijnd (<A4)
Meest pijnlijke huidzone is consistent en duidelijk afgelijnd (<A4)
Gelokaliseerde neuropathische pijn: GNP