PROTOCOL CAPTRANE

Multicenter, open-label, randomized study comparing topical treatment with 8% capsaicin patch (Qutenza) to oral pregabalin in the early management of intercostobrachial neuralgia (ICBN) following primary surgery for breast cancer.

A) CLINICAL TRIAL IDENTIFICATION	
STUDY TITLE	Multicenter, open-label, randomized study comparing topical treatment with 8% capsaicin patch (Qutenza) to oral pregabalin in the early management of intercostobrachial neuralgia (ICBN) following primary surgery for breast cancer.
SHORT TITLE	CAPTRANE
INVESTIGATOR COORDINATOR	Dr Denis Dupoiron
EUDRACT	2018-003559-39
REF ANSM	MEDAECNAT-2018-20-00041
ETHICS COMMITTEE NAME	CPP SUD MEDITERRANEE IV (MONTPELLIER)
REF ETHICS COMMITTEE	18.11.04
N° CLINICAL TRIAL.GOV	NCT03794388

B) STUDY BACKGROUND

Epidemiology of Breast Cancer

Breast cancer is the most common cancer in women in both the European Union and the United States. In France, 54,000 new cases of breast cancer in women were recorded in 2015. Although its incidence has been decreasing over the past decade, breast cancer remains the most frequent malignancy, ahead of colorectal and lung cancer (2). This cancer is far less common in men.

Breast cancer mortality has been declining since the late 1990s. According to data from the French National Cancer Institute, the five- and ten-year net survival rates are high, at 86% and 76% respectively for individuals diagnosed between 1989 and 2004 (2). Breast cancer has therefore become a chronic disease, and patients must learn to live with it as well as with the adverse effects linked either to the disease itself or to the treatments administered.

As highlighted by the third Cancer Plan (Action 8.3: "Improve the management of physical sequelae of cancer treatments") (3), in continuity with the previous Cancer Plan and the fourth National Pain Management Plan (4), pain is a major criterion impacting the quality of life of patients treated for breast cancer.

Neuropathic Pain in Patients with Breast Cancer

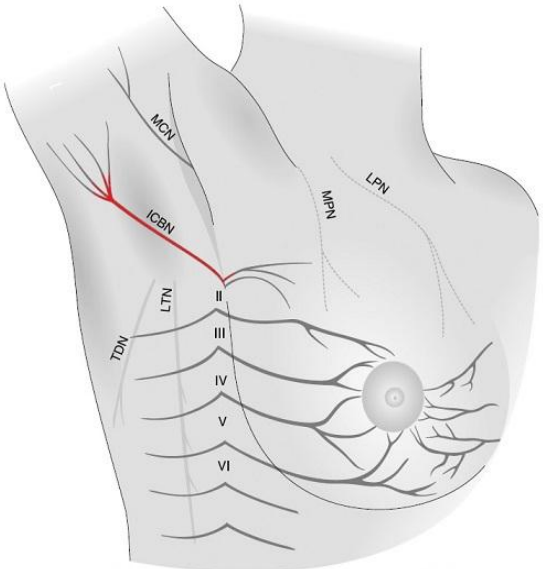
Definitions

Neuropathic pain was defined in 2011 by the International Association for the Study of Pain (IASP) as the direct consequence of a lesion or disease affecting the somatosensory system (5). Nociceptive pain corresponds to a normal—although variably adapted—response of the physiological "alarm system" triggered by a lesion threatening tissue integrity. In contrast, "neuropathic pain is always pathological, as it reflects disturbances and dysfunctions of physiological nociceptive systems" (6). Pain is described as mixed when it includes both neuropathic pain and pain related to nociceptive overload, which is often the case in tumor progression (5).

Etiology of Neuropathic Pain in Patients With Breast Cancer

Breast cancer treatments are divided into locoregional treatments—surgery and radiotherapy—and systemic treatments such as chemotherapy (including targeted therapies) and hormone therapy administered either as adjuvant or neoadjuvant therapy.
Among these treatments, only hormone therapy does not directly induce neuropathic pain, although prolonged administration may lead to nociceptive pain of musculoskeletal origin (7). Chemotherapy can also cause neuropathic pain as part of a sensorimotor peripheral neuropathy, which most often improves after discontinuation of treatment (5). Adjuvant radiotherapy may complement surgery. Irradiation may target the breast, the chest wall in cases of total mastectomy, and possibly regional lymph nodes. The risk of radiation-induced plexopathy exists, although it is less frequent with current radiotherapy techniques (8).
Surgery is often the first treatment for breast cancer. It may be breast-conserving, through partial mastectomy (lumpectomy or quadrantectomy), or non-conserving, through total mastectomy. These procedures are frequently combined with axillary surgery: either axillary lymph node dissection involving removal of 8–10 lymph nodes, or sentinel lymph node biopsy, which consists of identifying and excising the first lymph node(s) draining the breast. Axillary dissection is performed only if the sentinel lymph node is metastatic (9).

<u>Intercostobrachial Neuralgia (ICBN)</u>
Intercostobrachial neuralgia (ICBN), also referred to as Intercostobrachial Neuralgia (10) or Post-Mastectomy Pain Syndrome (PMPS), was first described by Wood in 1978 as “a chronic pain that begins immediately or soon after a mastectomy or lumpectomy and affects the anterior chest, axilla, and/or upper half of the arm.”
These postsurgical pains are related to injury of nerves within the breast region. In particular, the intercostobrachial nerve may be transected, stretched, or compressed during surgery. However, literature reports indicate that nerve injury does not always result in pain.
Furthermore, axillary dissection may lead to upper-limb lymphedema, which can maintain or exacerbate pre-existing intercostobrachial neuralgia. Breast-conserving surgery appears to be associated with a lower risk of ICBN than mastectomy combined with axillary dissection. Postoperative complications, such as hematoma or infection, also seem to increase the incidence of ICBN. Overall prevalence ranges between 32% and 58%, though it varies widely across studies and depends on the pain assessment method used (8).



Innervation of the breast and location of the nerves at risk during breast cancer surgery. ICBN indicates intercostobrachialnerve (sensory only); II-VI, intercostal nerves 2 to 6, lateral cutaneous branches (sensory only); LPN, lateral pectoral nerve (mixed sensory andmotor); LTN, long thoracic nerve (motor only); MCN, medial cutaneous nerve of the arm (sensory only); MPN, medial pectoral nerve (mixed sensory and motor); TDN, thoracodorsal nerve (motor only).
Reg Anesth Pain Med. 2014 Jun in press. Neural Blockade for Persistent Pain After Breast Cancer Surgery. Wijayasinghe N et al

Figure 1: Innervation of the breast and location of nerves at risk during surgery (Reg Anesth Pain Med, 2014, Wijayasinghe N. et al.)

Assessment of Neuropathic Pain

Postoperative neuropathic pain in breast cancer patients is underdiagnosed, both in primary care and in specialized settings. This diagnostic difficulty is attributed to challenges in early recognition and clinical identification of neuropathic pain (11, 12). Diagnosis is based on clinical history and physical examination; no additional tests are required (12).

History-taking helps identify pain characteristics (paresthesia, burning sensations…). Neurological examination should assess for signs suggestive of involvement in a neuroanatomically plausible territory of the peripheral nervous system. This includes negative sensory signs (sensory deficits) as well as positive signs such as hyperalgesia or mechanical allodynia.

Several screening tools can detect neuropathic pain. In France, the most commonly used is the DN4 questionnaire (Douleur Neuropathique en 4 questions), consisting of 10 items covering pain descriptors. It has excellent sensitivity (82.9%) and specificity (90%) (13). The S-LANSS (Self-report Leeds Assessment of Neuropathic Symptoms) is also useful, with sensitivity of 85% and specificity of 80% (14). Other tools (Neuropathic Pain Questionnaire, ID Pain, PainDETECT, Standardized Evaluation) are less convenient for routine practice. The DN4 is currently recognized as the most specific and sensitive scale (8).

Patients do not always report these symptoms. They may fail to associate their pain with the surgery when pain appears weeks or months after the procedure, or they may consider it normal to experience pain at the surgical site (11). These diagnostic challenges delay adequate analgesic management, thereby promoting chronic neuropathic pain.

Treatment of Neuropathic Pain

There is no consensus regarding the management of neuropathic pain in cancer patients. Recommendations for non-cancer-related neuropathic pain are currently applied by extrapolation (11).

<u>Systemic Treatments</u>

Neuropathic pain responds poorly to conventional analgesics such as paracetamol or non-steroidal anti-inflammatory drugs. Three major therapeutic classes are indicated: tricyclic antidepressants (amitriptyline, imipramine, clomipramine), antiepileptics (pregabalin, gabapentin), and opioids.

Systemic analgesics may be poorly tolerated due to side effects that can compound those of cancer treatments. For example, breast cancer patients receiving hormone therapy may experience menopausal-like symptoms including weight gain. Tricyclic antidepressants and pregabalin can also cause weight gain. According to the 2007 French Health Authority report, weight gain affects 3.5% of patients receiving pregabalin at 600 mg/day (15). Adverse effects from hormone therapy and neuropathic pain management may therefore add up and should be considered when developing the therapeutic strategy.

According to good practice recommendations from the French Society for the Study and Treatment of Pain, the choice of treatment depends on clinical context, comorbidities, safety profile, and cost (lower for tricyclic antidepressants) (16).

<u>Topical Treatments</u>

Systemic treatments may be combined with topical therapies such as lidocaine or capsaicin patches.

5% Lidocaine Plasters (VERSATIS®)

Lidocaine 5% plasters (VERSATIS®) received a European marketing authorization in 2007 for the treatment of post-herpetic neuralgia in patients with mechanical allodynia. The topical formulation is useful when systemic treatments are contraindicated. Tolerance is excellent, with minimal adverse effects compared to systemic treatments (17).

8% Capsaicin Patches (QUTENZA®)

Capsaicin 8% patches (QUTENZA®), marketed in France since 2011, are an innovative treatment for localized postsurgical neuropathic pain. Capsaicin is an agonist of the transient receptor potential vanilloid 1 (TRPV1) channel. It is indicated for the treatment of peripheral neuropathic pain in adults, alone or in combination with

other analgesics (1). The patch is applied to the most painful intact skin areas for 60–90 minutes, up to four patches simultaneously. Applications may be repeated every 90 days if needed. Application must be performed by a physician or healthcare professional in a hospital setting. Its major advantage lies in its low rate of adverse effects (10%), mostly mild erythema, burning sensations, or pruritus at the application site (1). Furthermore, the effect is long-lasting. Recent studies have demonstrated the superiority of capsaicin over pregabalin in treating allodynia in peripheral neuropathic pain (18).

Chronic Neuropathic Pain After Breast Surgery for Breast Cancer

Chronic Postsurgical Neuropathic Pain: A Frequent Symptom

The prevalence of chronic pain after breast cancer is estimated at 47% in a study by Gartner involving 3,254 patients in Denmark in 2009 (19). Other studies have assessed the incidence of chronic neuropathic pain after breast surgery, but most lack sufficient power for generalization to all breast cancer patients.

Risk Factors for Chronic Neuropathic Pain After Breast Cancer Surgery

Several risk factors for chronicization have been identified in the literature. Among them, younger age—≤49 years in Mejdahl's Danish study (12) and 18–39 years in Gartner's study (19)—is associated with higher risk. Breast cancer in younger patients is often more aggressive, warranting more intensive treatments (19, 20). Conversely, age >70 years appears protective and is associated with fewer chronic postsurgical pain symptoms (21).

Axillary lymph node dissection is the second unanimously recognized risk factor, due to the risk of intercostobrachial nerve injury. According to Gartner, the risk of developing neuropathic pain is higher after axillary dissection than after sentinel lymph node biopsy (19). Additional risk factors include adjuvant chemotherapy, adjuvant radiotherapy, and preexisting chronic pain conditions such as chronic low back pain, osteoarthritis, or fibromyalgia (19, 20).

The presence of early neuropathic pain symptoms is also a predictor of chronic neuropathic pain (22). Finally, depression, psychological vulnerability, and stress are the psychological factors most strongly associated with chronic postsurgical pain (23).

Consequences of Pain Chronicization

Moderate-to-severe neuropathic pain correlates strongly with reduced quality of life (24). Although no specific studies have evaluated the economic impact of chronic pain after breast surgery, reduced quality of life is a key driver of the overall financial burden of breast cancer (25, 26).

Importance of Early and Appropriate Management

Early diagnosis, assessment, and management of neuropathic pain are essential to prevent chronicization, improve the quality of life of breast cancer surgery patients, and facilitate faster return to work. Early neuropathic pain management may also reduce societal costs, particularly for national health insurance systems.

References

1. HAS. Synthèse d'avis de la commission de transparence – QUTENZA (capsaïcine, antalgique local en patch. http://wwwhas-santefr/portail/upload/docs/application/pdf/2011-04/synthese_davis_qutenza_-_ct-8291pdf 2011.
2. Unicancer. Epidémiologie du cancer du sein. Les cancers en France. 2014:55. PubMed PMID: http://www.unicancer.fr/sites/default/files/Les%20cancers%20en%20France%20%20Edition%202014%20-%20V5.pdf
3. Fioraso MTeG. guérir et prévenir les cancers : donnons les mêmes chances à tous, partout en France. Plan cancer 2014 – 2019 2014.
4. Santé Mdasedl. Avis du 17.09.2013 sur le projet programme national douleur (20143 – 2017). Journal officiel. 2013. PubMed PMID:
http://socialsante.gouv.fr/IMG/pdf/avis_proj_prog_douleur_1709_env_av_260913_rel_jol.pdf

5. Jensen TS, Baron R, Haanpaa M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain. 2011 Oct;152(10):2204-5. PubMed PMID: 21764514. Epub 2011/07/19.
6. Bouhassira D. [Definition and classification of neuropathic pain]. Presse Med. 2008 Feb;37(2 Pt 2):311-4. PubMed PMID: 18191365. Epub 2008/01/15. Definition et classification des douleurs neuropathiques.
7. Sheridan D, Foo I, O'Shea H, Gillanders D, Williams L, Fallon M, et al. Long-term follow-up of pain and emotional characteristics of women after surgery for breast cancer. J Pain Symptom Manage. 2012 Oct;44(4):608-14. PubMed PMID: 22743155. Epub 2012/06/30.
8. Ilhan E, Chee E, Hush J, Moloney N. The prevalence of neuropathic pain is high after treatment for breast cancer: a systematic review. Pain. 2017 Nov;158(11):2082-91. PubMed PMID: 28797014. Epub 2017/08/11.
9. Caudle AS, Bedrosian I, Milton DR, DeSnyder SM, Kuerer HM, Hunt KK, et al. Use of Sentinel Lymph Node Dissection After Neoadjuvant Chemotherapy in Patients with Node-Positive Breast Cancer at Diagnosis: Practice Patterns of American Society of Breast Surgeons Members. Ann Surg Oncol. 2017 Oct;24(10):2925-34. PubMed PMID: 28766207. Epub 2017/08/03.
10. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain. 2003 Jul;104(1-2):1-13. PubMed PMID: 12855309. Epub 2003/07/12.
11. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. Pain. 2012 Feb;153(2):359-65. PubMed PMID: 22115921. Epub 2011/11/26.
12. Mejdahl MK, Andersen KG, Gartner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. BMJ. 2013 Apr 11;346:f1865. PubMed PMID: 23580693. Epub 2013/04/13.
13. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005 Mar;114(1-2):29-36. PubMed PMID: 15733628. Epub 2005/03/01.
14. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001 May;92(1-2):147-57. PubMed PMID: 11323136. Epub 2001/04/27.
15. HAS. Quelle place pour la prégabaline dans les douleurs neuropathiques ,. http://wwwrespelorg/fileadmin/telechargements/fiche_bum_lyrica__082007pdf. 2007.
16. Martinez V AN, Bouhassira D, Lantéri- Minet M. Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecine ambulatoire. Douleurs. 2010;11:3 – 21
17. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin. 2009 Jul;25(7):1663-76. PubMed PMID: 19485723. Epub 2009/06/03.
18. Cruccu G, Nurmikko TJ, Ernault E, Riaz FK, McBride WT, Haanpaa M. Superiority of capsaicin 8% patch versus oral pregabalin on dynamic mechanical allodynia in patients with peripheral neuropathic pain. Eur J Pain. 2017 Dec 1. PubMed PMID: 29194851. Epub 2017/12/02.
19. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA. 2009 Nov 11;302(18):1985-92. PubMed PMID: 19903919. Epub 2009/11/12.
20. Schou Bredal I, Smeby NA, Ottesen S, Warncke T, Schlichting E. Chronic pain in breast cancer survivors: comparison of psychosocial, surgical, and medical characteristics between survivors with and without pain. J Pain Symptom Manage. 2014 Nov;48(5):852-62. PubMed PMID: 24703940. Epub 2014/04/08.
21. Macdonald L, Bruce J, Scott NW, Smith WC, Chambers WA. Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. Br J Cancer. 2005 Jan 31;92(2):225-30. PubMed PMID: 15655557. Pubmed Central PMCID: PMC2361843. Epub 2005/01/19.
22. Martinez V, Baudic S, Fletcher D. [Chronic postsurgical pain]. Ann Fr Anesth Reanim. 2013 Jun;32(6):422-35. PubMed PMID: 23747211. Epub 2013/06/12. Douleurs chroniques postchirurgicales.

23. Hinrichs-Rocker A, Schulz K, Jarvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. Eur J Pain. 2009 Aug;13(7):719-30. PubMed PMID: 18952472. Epub 2008/10/28.
24. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology. 2007 Apr 10;68(15):1178-82. PubMed PMID: 17420400. Epub 2007/04/11.
25. Gordon L, Scuffham P, Hayes S, Newman B. Exploring the economic impact of breast cancers during the 18 months following diagnosis. Psychooncology. 2007 Dec;16(12):1130-9. PubMed PMID: 17345557. Epub 2007/03/09.
26. Fenn KM, Evans SB, McCorkle R, DiGiovanna MP, Pusztai L, Sanft T, et al. Impact of financial burden of cancer on survivors' quality of life. J Oncol Pract. 2014 Sep;10(5):332-8. PubMed PMID: 24865220. Epub 2014/05/29.

C) STUDY INFORMATION

INDICATION	The study population consists of patients with breast cancer who have undergone surgical treatment and who present with intercostobrachial neuralgia (ICBN) diagnosed within 3 to 12 months after surgery
METHODOLOGY	Randomized, prospective, national multicentre, phase III

Primary Objective and Endpoint

Primary objective	Endpoint	Evaluation time
The primary objective is to demonstrate the non-inferiority of an early management strategy using 8% capsaicin topical treatment compared with standard oral pregabalin therapy on the evolution of ICBN at 2 months after randomization in patients who have undergone surgical excision for breast cancer.	Neuropathic pain intensity is assessed using the 11-point Numerical Rating Scale (0–10). Pain intensities over the preceding 24 hours (night, evening, afternoon, morning) will be collected. The highest pain intensity reported over the past 24 hours will be used for analysis to address the primary objective. The change in pain intensity is measured between randomization (T0) and the evaluation visit at Month 2 (T2)	2 months

SECONDARY OBJECTIVES AND ENDPOINTS

Secondary objectives	Endpoints	Evaluation time
If non-inferiority is demonstrated: to compare the efficacy of an early management strategy using 8% capsaicin topical treatment with that of standard oral pregabalin therapy on the evolution of ICBN after 2 months of treatment in patients who have undergone surgical excision for breast cancer.	The 11-point Numerical Rating Scale (NRS) for pain is collected at randomization (T0) and at Month 2 (T2) (see primary endpoint).	2 months
To compare the efficacy of an early management strategy using 8% capsaicin topical treatment (experimental arm) versus standard pregabalin therapy (control arm) on the evolution of ICBN after 6 months of treatment in patients who have undergone surgical excision for breast cancer.	The 11-point Numerical Rating Scale for pain is also collected at Month 6 (T6).	6 months
To compare patient-reported functional changes (activities, symptoms, emotions,	The PGIC, QLQ-C30, QLQ-BR23, and EQ-5D questionnaires are administered at T0, T2, and	6 months

and quality of life) between the two arms after 2 and 6 months of treatment.	T6 to assess functional changes and patient-reported quality-of-life outcomes in both treatment arms.	
To compare the reduction of the painful area between the two arms after 2 and 6 months of treatment.	The painful area is measured using pain mapping at baseline (T0), and after 2 months (T2) and 6 months (T6) of treatment. The surface area corresponds to the zone enclosed within the drawn boundaries of the painful region (centralized review).	2 months
To assess the safety profile of each treatment by collecting adverse events in each study arm.	Treatment tolerability will be assessed based on the number of patients experiencing at least one adverse event of grade ≥ 2 according to CTCAE v5.	6 months
To compare weight change between the two arms after 6 months of treatment.	Weight is collected at T0, T2, and T6.	6 months
In the capsaicin arm only, to estimate the proportion of patients for whom a single application was sufficient.	In the capsaicin arm, the number of applications and the total number of patches received by each patient during the 6-month period will also be recorded.	6 months
To assess the impact of anxiety and depression on treatment response for ICBN after breast cancer surgery.	The HADS questionnaire is collected at baseline, T2, and T6.	6 months
To evaluate the impact of pain duration prior to treatment initiation on therapeutic response.	Treatment effect will be assessed at 2 and 6 months using the 11-point NRS in both arms. Pain duration prior to initiation of treatment is self-reported, expressed in months, and collected at baseline	6 months

INCLUSION CRITERIA	1) Male or female patient who has undergone first-line surgical treatment for breast cancer, regardless of the type of surgery. 2) Age ≥ 18 years. 3) Healthy and non-irritated skin over the painful areas to be treated. 4) Neuropathic pain of the breast and/or axillary region consistent with intercostobrachial neuralgia, with a DN4 score ≥ 4, diagnosed between 3 and 12 months after surgery. 5) Written informed consent obtained and signed by the patient. 6) Adult patient covered by a national health insurance scheme.
NON-INCLUSION CRITERIA	1) Specific contraindications to the study treatments: a. Pregabalin: hypersensitivity to the active substance or any excipient. b. Capsaicin: hypersensitivity to the active substance or any excipient. 2) Patient with diabetes. 3) Prior treatment with capsaicin or pregabalin between surgery and study inclusion. 4) Ongoing opioid treatment > 80 mg/day of morphine or equivalent at the time of inclusion. 5) Topical pain treatment within 7 days prior to inclusion. 6) Uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 90 mmHg) or recent history of cardiovascular events (stroke, myocardial infarction, pulmonary embolism). 7) Patient with chronic kidney failure. 8) Pregnant or breastfeeding women, or women who may become pregnant.

	9) Individuals deprived of liberty or under legal protection (including guardianship or curatorship). 10) Inability to comply with the study's medical follow-up.

E) INVESTIGATIONAL TREATMENT DESCRIPTION

Active Ingredient (INN)	Brand Name	Pharmaceutical Form	Route of Administration	Dose per Administration
Capsaicin	QUTENZA	Cutaneous patches	Topical	640 micrograms of capsaicin per cm^2 Patch size: 280 cm^2
Pregabalin	LYRICA	Capsule	Oral	50 mg to 600 mg

Therapeutic schema

The screening period extends from 3 months before surgery to 12 months after breast cancer surgery. Patients who agree to participate are scheduled for a screening visit between 3 and 12 months post-surgery. If they present with ICBN, defined by a DN4 score ≥ 4, they will be included and randomized to receive either pregabalin (standard treatment) or topical capsaicin patch (experimental treatment), both of which are indicated for the management of peripheral neuropathic pain.
Pregabalin will be initiated with a gradual titration to reach a dose of 600 mg/day in two divided doses, depending on patient tolerability.
Capsaicin patches will be applied in a hospital setting to the painful area for 1 hour, with applications scheduled every 90 days.
All patients will undergo assessments at T0 (± 7 days) and T6 (± 7 days) regarding pain evolution (intensity and area), treatment tolerability, and quality of life.
The end of treatment and study follow-up is planned at the final pain-evaluation visit (T6).

F) STATISTICAL CONSIDERATIONS

SAMPLE SIZE DETERMINATION	Statistical analyses will be performed using R software. **A total of 772 patients** will be included, allocated into two balanced groups. Sample size calculation An interim analysis is planned once 300 patients have been included (minimum 150 per arm), based on the primary endpoint. Alpha allocation: - 0.005 for the interim analysis - 0.045 for the final analysis Assumptions for calculating the required sample size: - At baseline, the standard deviation of NRS pain score is estimated at 2.0. - The expected mean difference in NRS (Capsaicin – Pregabalin) is 0. - The non-inferiority margin is set at +0.4 points on the NRS. - One-sided alpha risk: 4.5%. - Statistical power: 80%. Under these assumptions, 322 patients per arm are required (644 total). Considering a 20% rate of non-evaluable patients at 6 months, the total required sample size is 772 patients (386 per arm).

DESCRIPTION OF ANALYSIS SETS	**Description of planned statistical methods** A descriptive analysis of the study sample will be performed. Data will be presented as follows: • Qualitative variables: expressed as percentages. • Quantitative variables:expressed as mean and standard deviation, or median and range, depending on the distribution. Comparisons will be performed as follows: • Qualitative variables: using the Chi-square test or Fisher's exact test when appropriate. Quantitative variables: using Student's t-test or a non-parametric test (Wilcoxon test) depending on distribution and normality assumptions. **Definition of Analysis Populations** • The ITT population includes all randomized patients in the CAPTRANE study. Patients are analyzed according to the treatment arm to which they were randomized, regardless of the treatment actually received. • Modified Intention-to-Treat Population (mITT) • The mITT population includes all randomized patients who received at least one administration of study treatment; i.e., excluding patients withdrawn prematurely or incorrectly included before receiving treatment. Patients are analyzed according to their allocated arm, regardless of treatment actually received. • Per-Protocol Population (PP) • The PP population includes all randomized patients who received the allocated treatment according to the protocol. Patients who received any treatment other than that assigned are excluded from the analysis. • If non-inferiority is demonstrated at the pre-specified 0.4 threshold (primary endpoint in the PP population), a Student's t-test will be used to compare the mean 24-hour maximum NRS pain scores at T2 (2 months after randomization) between the capsaicin and pregabalin arms, in the mITT population. • Mean 24-hour NRS scores at T6 will be compared between arms using a Student's t-test. • The percentage of patients with at least a "notable improvement" (PGIC score ≥ 5) will be compared between arms using a Chi-square test. • Reduction in painful area will be expressed as a percentage relative to baseline. • Differences in painful area between T2–T0 and T6–T2 will be compared using a Student's t-test. • All grade ≥ 2 adverse events will be described by category and by treatment arm. • The number of patients experiencing at least one grade ≥ 2 toxicity event will be compared using a Chi-square test. • The percentage of patients with ≥5% weight gain will be compared between arms using a Chi-square test. • A subgroup analysis of NRS pain scores at T2 and T6 will be performed among patients with probable anxiety disorder and those with probable depressive disorder according to baseline HADS scores. • A multivariable linear regression model will be used to estimate the impact of pain duration before inclusion (expressed in months) on pain intensity at T2 and T6 (NRS), adjusted for:

	- baseline NRS pain score, - treatment arm. <u>Statistical stopping rules</u> An interim analysis will be conducted after inclusion of 150 patients per arm based on the primary endpoint (NRS at T6). If a statistically significant difference in efficacy is observed at alpha = 0.005, the study will be stopped for efficacy, regardless of which treatment demonstrates superiority. <u>Handling of missing, unused, or invalid data</u> Missing data for the numerical pain scale (NRS), painful area, and PGIC will not be imputed. The proportion of missing data will be compared between arms using a Chi-square test. Baseline characteristics of patients with missing data will also be compared. Missing data for quality-of-life questionnaires (QLQ-C30, QLQ-BR23, EQ-5D) may be imputed according to EORTC manual recommendations. <u>Management of amendments to the analysis plan</u> Modifications to the statistical analysis plan may be proposed by the data monitoring committee (interim analysis, statistical tests, adverse event review, secondary objectives) if justified by emerging literature. Protocol deviations will be identified and quantified. <u>Randomisation</u> Patients with a positive DN4 score will be randomized directly through the eCRF to be allocated to one of the following treatment arms: - Arm A (experimental): CAPSAICIN (patch), application of capsaicin patches to the painful area for 1 hour, with applications repeated every 3 months. - Arm B (standard): PREGABALIN (oral), oral pregabalin with progressive dose escalation. Validation of the randomization will automatically generate a confirmation email specifying the treatment arm allocated to the patient. Randomization will be performed using balanced block allocation, stratified according to the following factors: - Study center - Pain intensity on the numerical rating scale (≥ 5) - Age (≥ 65 years) - HADS score (Incomplete, ≤ 18, > 18) - Pain duration (< 3 months or ≥ 3 months)

G) STUDY CALENDAR	
DURATION OF INCLUSION PERIOD	36 months
TREATMENT DURATION	6 months
POST TREATMENT FOLLOW UP	6 months
STUDY COMPLETION DURATION (INCLUDING FU PERIOD)	42 months