Protocol T2001-01

***Protocol (initial) Version 1.0 and date**: 16-Jan-2014*

***Protocol Amendment Version 2.0 date:** 24-Nov-14*

Protocol Title:
An Observational Study to Collect Data Characterizing Analgesia in Patients Suffering from Bone Metastasis induced Pain

Sponsor:
Tools4Patient
Rue Auguste Piccard, 48
6041 Gosselies
Belgium

EUDRACT number: 2013-005331-24

Study Conduct Compliance Statement
This study will be conducted in compliance with the protocol, in accordance with the Good Clinical Practice (GCP) standards and the ethical principles that have their origin in the Declaration of Helsinki, as well as with all currently applicable laws and regulations of the country where the study will be conducted. This material is confidential and is the property of Tools4Patient. Do not disclose or use except as authorized.

Agreement on Protocol – Signature Page

Protocol Version Number: 2.0

Protocol Version Date: 24-Nov-2014

By signing below, I hereby confirm that I have read, discussed and understood the protocol T2001-01 version 2.0, 24-Nov-2014 and the background information concerning the study. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Investigator		**Sponsor**	
Name		Name:	
Title:		Title:	
Date:		Date:	
Signature:		Signature	

1. SYNOPSIS

Title	An Observational Study to Collect Data Characterizing Analgesia in Patients Suffering from Bone Metastasis induced Pain.
Type of Study	Multicentre, observational study.
Study Duration	From screening to end of study, the study duration for each patient will be of a minimum of 5 weeks and a maximum of 12 weeks.
Number of Planned Patients	Up to 180 patients diagnosed with bone metastasis suffering from pain will be enrolled into the study to have up to approximately 140 completers.
Objective	To define predictive factors of pain management/treatments efficacy in cancer patients with bone metastasis suffering from pain (or Cancer-Induced Bone Pain (CIBP)), based on individual patient disease, therapy history and personality traits.
Study Design	The study is an observational, multicentre clinical study that will be conducted in patients with CIBP requiring an analgesic treatment. Up to 180 patients will be enrolled and followed during a period from 4 to 10 weeks of observation. All patients will continue to receive their cancer therapeutic treatments and will be treated for pain relief exactly as they would normally be by the Investigator based on patient needs and clinician practice. During their regular visits to the Investigator, patients will complete questionnaires and Clinical Pain Assessments (CPAs).
Main Diagnosis and Inclusion Criteria	• Are men or women of at least 18 years of age. • Patients with bone tumors or bone metastasis from any primary cancer origin that are supported by histological or radiological investigations. • Patients having been or being treated for their bone metastasis and/or their primary cancer. • Patients who require analgesic treatment for unsatisfactory pain relief. • Patients will be required to have a score of at least 4 on the weekly average pain score (WAPS) over the week preceding enrolment.
Main Exclusion Criteria	• Patients having poor nutritional status or with unstable condition or who could be rapidly deteriorating in such a way that they would not be able to complete the study. • Patients having had a major surgery within 28 days prior to signing ICD or planning to have a major surgery during the study. • Life expectancy < 3 months according to Investigator judgment. • Patients with a current or recent history unrelated to their cancer condition, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease which would interfere with the patient's participation in the study • Patients having at screening a Karnofsky performance status below 70% /or World Health Organization (WHO) score (Eastern Cooperative Oncology Group (ECOG)/Zubrod score) above 1.
Investigational Product	Not applicable
Planned duration of observation	From 4 to 10 weeks
Randomization	Not applicable
Studied procedures	
Safety data collection:	There will be no safety data collection per se as it is not an interventional study, nevertheless the following information will be collected to describe pre-existing patient condition: relevant medical and primary disease history; primary disease treatment history; analgesic treatment history, if available, up to one month prior to study entry; abbreviated physical examination; symptoms related to analgesic treatment; most recent safety laboratory data if available, up to one month preceding screening visit and/or ongoing laboratory safety

	analysis and urine analysis, if available, performed as part of patient management by the Investigator.
Questionnaires:	Related to patient's personality such as Multidimensional Health Locus of Control Scale (MHLCS), Hospital Anxiety and Depression Scale (HADS), Revised Life Orientation Test (LOT-R) and Expectation. Related to pain disease such as Brief Pain Inventory (BPI), Douleur Neuropathique en 4 questions (DN4), Neuropathic Pain Symptom Inventory (NPSI), and Pain Catastrophizing Scale (PCS). Related to quality-of-Life: Quality-of-Life Questionnaire in 30 questions (QLQ-C30).
CPAs:	The Most Painful Area (MPA), Static Allodynia (SA), Dynamic Mechanical Allodynia (DMA), Mechanical Pain Threshold (MPT), Thermal Pain Sensitivity (TPS).
Diary:	The following information will be collected daily in the diary: APS and Worst Pain Score (WPS) for the past 24-hours, intake of additional to prescribed analgesic treatment (rescue analgesic treatment).
Study Evaluation Criteria and methods:	
Patient general health status	Symptoms related to analgesic treatment will be listed, and if the frequency of symptoms allows, they will be summarized using descriptive statistics.
Pharmacokinetic	Not applicable
Pharmacodynamic	Analysis of subjective changes from baseline of pain severity as measured by the weekly means of the daily APS and WPS, by Brief Pain Inventory (BPI), Investigator Global Assessment of Change (IGAC) and Patient Global Assessment of Change (PGAC), QLQ-C30 will be performed. In addition, analysis of quantitative changes measured by MPA, SA, MDA, MPT and TPS will be performed and compared between enrolment Visit and Visit 2. These tests will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon data review
Statistical Analysis:	Both effects on subjective and quantitative measures will be analyzed using Statistical Learning approaches potentially including covariates to be described in the Statistical Analysis Plan (SAP).
Safety:	Not applicable
Exploratory measures:	For patients who give their consent, archived tumor tissue block, if any and/or aliquot of standard safety laboratory blood sample will be used for genotyping exploratory research.
Interim Analysis	A preliminary analysis will be scheduled after approximately 60 patients complete the study

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Rationale for Protocol Amendment

Protocol T2001-01 version 1.0, An Observational Study to Collect Data Characterizing Analgesia in Patients Suffering from Bone Metastasis induced Pain. The new protocol version is version 2.0 and will be used to conduct the study in place of the preceding version.

The overall changes and rationale for the changes made to this protocol are as follows:

- Study design, study schedule and related sections were modified to give patients more flexibility to perform study procedures. Visit 1 and previous Visit 2 procedures can be performed either on the same visit or 2 different ones, allowing enrolment to take place at the first patient visit. Previous Visit 3 is now made optional. The numbering of the visits was therefore reviewed throughout the entire protocol.
- The number of questionnaires to be completed by patients during the study was decreased: QLQ-BM22 is no longer used and QLQ-C30 will only be performed twice.
- The information to be collected in the diary was also significantly decreased. Patients will only be asked to daily report APS, WPS and intake of additional rescue medication.
- The number of patients required to have completed the study before interim analysis was decreased from 90 to approximately 60.
- It was clarified in inclusion criterium n°1 that patients with bone tumors could be enrolled into the study.
- It was also clarified in inclusion criterium n°2 that patients having been treated for their bone metastasis and/or their primary cancer could be included.
- Inclusion criterium n°3 was rephrased to patients who require analgesic treatment for unsatisfactory pain relief.
- Inclusion criterium n°4 was modified to include patients having a score of at least 4 at the Weekly Average Pain Score (WAPS) during the week preceeding enrolment.
- It was clarified in inclusion criterium n°5 that patients undergoing or not a radiotherapy program could be included into the study provided visit procedures are performed before radiotherapy sessions, if scheduled on the same visit days.
- Exclusion disease criteria n°2 was changed by decreasing life expectancy from < 6 to < 3 months.
- The World Health Organization (WHO) score corresponding to Karnofsky performance status < 70% in exclusion criterium n°5 was added.
- Clarifications were brought to section 8.2.1 on Clinical Pain Assessments.
- It was clarified that symptoms related to pain treatment should be recorded.
- The physical examination at screening was alleviated to an abbreviated one and patient's body weight will not be collected any more.

- It is not asked any more to try to refrain as much rescue medications within 24 hours before study visits
- It was specified that only cancer concomitant medications should be recorded.
- Finally, it was clarified if several safety laboratory analysis are performed during the study that only one per week should be recorded.

All other parts of the protocol remain unchanged.

All modifications are presented in Attachment 3 Section 16.3 Protocol Amendment Summary.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE

To define predictive factors of pain management/treatments efficacy in cancer patients with bone metastasis suffering from pain (or cancer-induced bone pain (CIBP), based on individual patient disease, therapy history, personality traits and expectation.

2.2. PRIMARY ENDPOINT

Individual analgesic treatment efficacy endpoint: patient's change from baseline of pain severity, as measured by the weekly means of the daily Average Pain Scores (APS).

2.3. SECONDARY ENDPOINTS

Individual analgesic treatment efficacy outcomes:

- Patient's change from baseline of pain severity, as measured by the weekly means of the daily Worst Pain Score (WPS),
- Patient's change from baseline of pain severity and interference as measured by the Brief Pain Inventory (BPI),
- Patient's change from baseline of Investigator and Patient Global Assessment of Changes (IGAC and PGAC),
- Patient's change from baseline of pain intensity measured after Clinical Pain Assessments (CPAs) at Visit 2.
- Patient's change from baseline of Quality-of-Life Questionnaire in 30 questions (QLQ-C30).

Endpoints used for the predictive factors (independent variables).

3. STUDY BACKGROUND INFORMATION

3.1. INVESTIGATIONAL MEDICINAL PRODUCT(S) NAME(S)

There is no Investigational Medicinal Product (IMP) administered in this study.

3.2. INTRODUCTION - LITERATURE AND/OR DATA BACKGROUND

Pain is a significant issue in patients with advanced cancer. Bone is one of the common site for tumor metastasis development and CIBP is the most frequent types of cancer pains, which affect Quality-of-Life (QoL), mood, and is associated with increased morbidity. More than 80% of patients with cancer develop pain before death.

The most common cause of pain in cancer is bone metastasis. More than 70% of patients with bone metastasis suffer from pain (moderate and severe) (Langford et al. 2011). Bone metastasis does not only result from primary bone cancer which is relatively rare (2/1000 cancer diagnosed) compared to the other cancers but also from other cancers such as lung, breast, prostate and kidney cancers that have a strong predilection to metastasize to multiple bones at the same time. Tumor growth in bones results in many severe issues including pain, which altogether compromise the patient's functional status, QoL and survival. The majority of patients suffering from CIBP require pain treatments, in particular analgesic medications on a daily basis.

Description and Etiology of CIBP

CIBP is characterized by an "ongoing" pain and a "breakthrough" pain. Once the tumor has metastasized at the level of the bones, "ongoing" pain is observed characterized by continuous dull pain and gradually increasing in intensity with time. When the tumor grows and induces bone remodeling severe incident pain appears, also known as "breakthrough pain" (the pain "breaks through" the analgesic regime that is controlling the "ongoing pain"). This incident pain is an intermittent episode of extreme pain that occurs spontaneously, without any obvious precipitating event and that may occur many times a day. Current pain therapies address ongoing pain but largely remain ineffective to treat breakthrough pain that contributes greatly to decrease the patient's functional status as well as its QoL (Middlemiss et al. 2011).

The etiology of cancer pain remains unclear, as it is a complex pathology where symptoms are related to cellular, tissue, and systemic changes that occur during cell proliferation, invasion, and metastasis. In addition, the cancer cell produces mediators that affect other cells leading to nociception or neuropathy (Schmidt et al. 2010).

In approximately two thirds of cancer pain, pain is directly related to the presence of primary or metastatic disease and one third is linked to the treatment itself i.e. radiation, chemotherapy induced peripheral neurotoxicity (Cavaletti et al., 2010), post-mastectomy (Nogueira-Fabro et al. 2012), or postoperative pain after lymph node biopsy (Høimyr et al. 2011), immobility.

Different components of CIBP

At least theoretically, to maximize the likelihood to select the right therapy for a patient suffering from CIBP, a correct assessment of the CIBP level and evolution should be performed. This assessment should take into account the specific features of CIBP at the level of the patient. These are briefly summarized below.

The main physiological components of CIBP are the neuropathic components associated with the inflammatory process of pain but linked to specificities of bone. In addition, the other physiological component is connected to disruption of bone homeostasis (nociceptive component). Drivers of nociceptor activation are the local release of algogenic substances related to bone osteolysis and inflammation, and the occurrence of micro fractures, increased pressure within bone, periosteal stretching, and damage to adjacent tissues (Mercadante 1997). Because these processes activate intact nociceptors, bone pain now may be viewed as a mixed nociceptive and neuropathic pain, which presumably is determined by a variable and dynamic set of events that activate some normally-functioning nerves while simultaneously causing aberrant somatosensory processing by others (Jimenez-Andrade et al. 2011, Middlemiss et al. 2011).

Short overview of CIBP treatments today – Application of WHO

Today many therapies are available to lessen CIBP although they remain largely unsatisfactory. These treatments include drug therapies, medical treatment and procedures (such as External beam Radiation Therapy (XRT), surgery (radiofrequency ablation, vertebroplasty…), non-drug therapies and supportive care. The treatments used mainly depend on the location and the severity of CIBP. Although palliative XRT (radiotherapy) remains the gold standard to treat CIBP, not all patients respond evenly to the treatment and not all of them can benefit from the needed infrastructure. Accordingly, drug therapies remain the most widely used either alone or in combination with additional non-drug therapies.

Drug used are mainly paracetamol, Non-Steroid Anti-Inflammatory Drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, opioids, bisphosphonates, Receptor Activator of Nuclear factor Kappa-β Ligand (RANKL) inhibitors such as denosumab. Adjuvant analgesics are also used such as antidepressants, corticoids, anesthesia drugs, anticonvulsants, muscle relaxants etc.

The medications selected by the doctor to treat his patient are often based on a best-guess approach based on its clinician experience as well as on guidelines and recommendations to alleviate pain in cancer populations (WHO 1996; European Society for Medical Oncology (ESMO): Ripamonti et al. 2012). The WHO recommendations are: “If pain occurs, there should be prompt oral administration of drugs in the following order: non-opioids (aspirin and paracetamol) (Step 1); then, as necessary, mild opioids (codeine) (Step 2); then strong opioids such as morphine (step 3), until the patient is free of pain. To calm fears and anxiety, additional drugs – “adjuvants” – should be used. To maintain freedom from pain, drugs should be given “by the clock”, that is every 3-6 hours, rather than “on demand”. This three-step approach of administering the right drug in the right dose at the right time has been claimed inexpensive and 80-90% effective”. Adjuvants may be bisphosphonates, corticosteroids, radiotherapy, and radionucleotides.

Major improvements in drug-based pain management are expected today to rely on necessary reassessment of pain, emergence of opioid rotation and on methadone (Bruera and Kim 2003). It is clear that the optimum treatment in the future is likely to be multimodal but should be guided:

- by reliable and improved pain assessment at the beginning and alongside the treatment,
- by combination of the best treatments depending also on the improvement of appropriate designs of analgesic compound clinical investigation in particular in relation to patient and pain assessment and outcomes measures (Delaney et al. 2008).

Recently, this message has been reinforced where it was advocate to use reliable and patient-specific pain assessments for improving analgesic treatment (Piano et al. 2012). According to these authors, the most reliable and primary source of information should be the individual's report of pain. A description, characteristics and diagnostics can help to determine treatment approaches, evaluates efficacy of treatments and identifies new pathology. Assessment of the person experiencing the pain is necessary prior to decisions about interventions (Cummings et al. 2011).

Weaknesses of the current treatments and Internal Association for the Study of Pain (IASP) recommendations

Thus, the population-based treatment strategies based on the optimization of pain management efficacy and pricing reimbursement duties, as recommended/imposed by health policy providers is too often unsatisfactory or, at least, show clear weaknesses. As a matter of fact, the choice of drugs and the protocols for using them (including the sequence of administration) is common for each patient and is based on population-based observations of the patient’s reactions to both pain (or pain stimuli) and to pain treatments as well as pain evolution.

Pain treatment protocols, especially in CIBP, do not take into account enough:

- The patient-specific nature of pain and response to pain treatment. Nowadays pain is viewed as a unique brain response to a complex interplay between physiological phenomena and emotional and cognitive responses and is, thus, patient-specific. As a result, the rating of pain intensity by a given patient is not solely a translation of the level of nociception produced e.g. by the painful tumor but should be considered as a multidimensional brain construct.
- The complexity of the CIBP by itself, its multiple components, in particular its neuropathic component and the associated neurobiological changes. Basic studies of CIBP have shown that there are major changes in the somatosensory system, both peripherally and centrally, which are indeed unique to this pain state. Changes in somatosensory processing may also occur in clinical settings. These changes on the time period of a treatment or a clinical trial (for testing new compounds) can give misleading data on the efficacy of a drug or treatment,
- The specific traits of patients, in particular their own disease and therapy history.

Accordingly, better patient-specific CIBP characterization is urgently needed to refine analgesic pain relief treatments. Such characterization should integrate the pain

assessment performed by the patient as well as somatosensory testing to follow the neurobiological changes alongside the disease evolution combined to relevant patient-specific data such as patient traits and disease/therapy history globally contributing the reaction to pain.

- As a first step into the direction of cancer pain assessment, the WHO recommendations include an attempt (the WHO's "pain ladder") to deal with non-uniform reactions vis-à-vis pain and pain treatment. Indeed, the analgesic ladder suggests an analgesic treatment that is mainly based on a pain intensity assessment performed by patients using visual analogue scales, Numerical Rating Scales (NRS) or verbal rated scales. This is applied with some relative success but there are still patients receiving inappropriate care pain. As example, 43% of cancer patients across 44 studies were inappropriately treated for pain (Deandrea et al. 2008). Indeed, the WHO's ladder achieves its goal to provide a simple and inexpensive way to deliver relief from cancer pain but mainly relies on recommended without considering alternative solutions compared to the ladder recommendations. Indeed, generally the (opioid) prescription using the WHO's ladder is effective and well tolerated by number of patients and it is also useful for controlling the costs of medical care. Many opioids and adjuvants medications are relatively inexpensive compared to more advances procedures for controlling pain. Because of cost optimizations, these other procedures come only as a Step 4 of the WHO's ladder, only to be activated after failure of the opioid therapy is recognized (no effect or/and to high unwanted side-effects). Therefore, a move away from strict adherence to the WHO's ladder and toward multimodal therapy is currently advocated (Picot and Hamid 2010) where early advanced procedures may be introduced in the pain management schedule, either alone or in combination with the opioids and adjuvant medications.
- The data revealed also that pain in cancer belonging to heterogeneous group is poorly characterized with no optimal therapeutic practices available yet (Portenoy 2011). This can be partly explained by the observation that some patients have scores of expressed pain that are high relative to the pathophysiological status. In these cases, physicians should try to identify the causes contributing to pain expression (such as fatigue, anxiety, depression etc. or modification of the somatosensory system) because any of these symptoms can affect the expression of pain and introduce a bias in the efficacy assessment of analgesic-based only treatment.
- As a first attempt to take into account the changes of the somatosensory system, Quantitative Sensory Testing (QST) first developed in the field of neuropathic pain has been used in CIBP for assessing the neuropathic component of pain (Scott et al. 2012). QST is a psychophysical testing for measuring sensory responses to defined thermal and mechanical pain stimuli and been recognized as a valuable assessment tool in the diagnosis of neuropathic pain with a yet relatively acceptable quality evidence for its usefulness in predicting treatment efficacy in neuropathic pain. In CIBP, a simplified QST approach (acceptable to patients) has been used to assess somatosensory changes and the effect of XRT treatment on the pain evolution (Scott et al. 2012). The results confirm the somatosensory changes after XRT but are unable to predict who will benefit most from XRT.

Accordingly QST appears to be a step towards the right direction but does not provide a complete solution to stratify CIBP patients and orient the caregiver in the direction of treatment that best fits the patient needs. QST addresses only the neuropathic component of pain.

Thus, so far, no unified approach exists neither for correctly/completely assess pain levels in CIBP patients nor for evaluating patient-specific pain response, nor to link these scores to pain mechanisms or other factors such as patient traits and disease/therapy history that may contribute to pain scoring. This explains some failure of CIBP management in particular the classical drug-based pain management approach based on pre-defined administration of medication classes of compounds, doses and schedule (treatment algorithm) as recommended by the WHO's ladder and translated in national guidance.

The failure to identify the neuropathic component of pain can lead to non-effective pain treatment in cancer patients (Mulvey et al. 2013). Additional prescribing strategies are required for taking into account that component. The fraction of cancer patient with neuropathic pain was estimated from 19% to 39 % amongst patients with mixed pain and around 20 % of cancer's pain had pain with a neuropathic mechanism (Bennett et al. 2012). This neuropathic component of pain may be diagnosed by clinical examination, screening neuropathic questionnaires including accurate sensory examination (Bouhassira and Attal 2011; Haanpää et al. 2011).

There is thus a need to individualize the CIBP treatments by, firstly, correctly characterize the patient (responsiveness to pain stimuli, particular traits and disease history) and, secondly, to adapt or change the treatment algorithm.

3.3. RATIONALE FOR THE STUDY

The aim of this observational study is to collect individual data from patients with CIBP to better characterize the source of pain and patient's specificities in terms of primary disease history and personality traits to improve analgesic treatment recommendation.

4. STUDY DESIGN

4.1. DESCRIPTION OF STUDY DESIGN

This multicentre study is an observational study collecting data in cancer patients with bone metastasis suffering from pain.

This study will include up to 180 patients with bone tumor or metastasis from any primary cancer origin that are supported by histological or radiological investigations corresponding to CIBP.

Patients will be treated by the Investigators for pain relief exactly as they would normally be based on their needs and clinician practice. The enrolled patients must be requiring analgesic treatment. They will be followed over a period from 4 to 10 weeks. The analgesic treatment will be reviewed based upon patient's needs and patient general health status collected throughout the entire study.

During the study, visits may be adapted according to Investigator-patients agreement, as presented in Section 8.5.4. Patients may also visit the Investigator as many times as required by their pain conditions.

Depending on patients/Investigator site availabilities, Visit 1 assessments may be performed in one visit (Visit 1) or 2 visits (Visit 1A and Visit 1B).

The design of the study for the 2 case scenarii is illustrated in Figure 1.

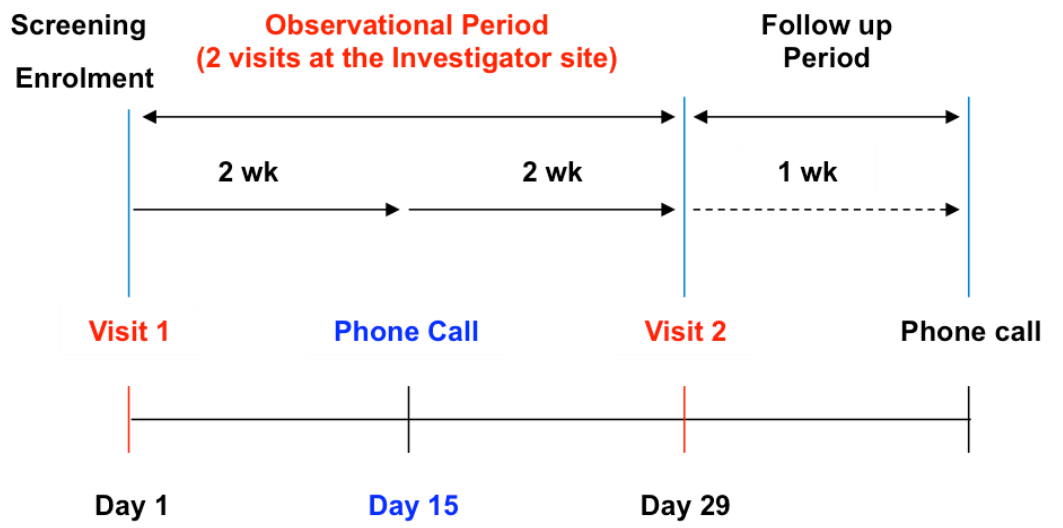


Figure 1'. Study Design when Visit 1 Assessments are Performed at the Same Visit/ Screening and Enrolment at Visit 1

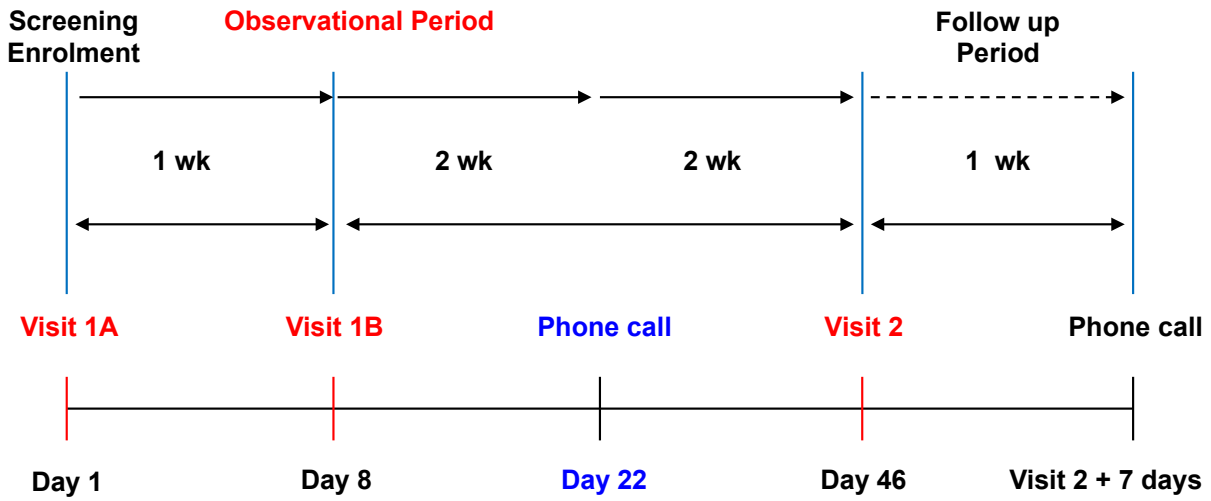


Figure 1". Study Design when Visit 1 Assessments are Performed in 2 Visits – Screening and Enrolment at Visit 1A

Figure 1. Study Diagram

4.1.1. SCREENING AND ENROLMENT VISIT

FIRST CASE SCENARIO: SCREENING AND ENROLMENT AT VISIT 1

In this case scenario, all Visit 1 assessments are performed during only one visit, this visit will take place as described below.

First, the study purpose – including the optional genotyping research study - will be explained to patients who will then sign and date the Informed Consent Document (ICD) before completing any study procedure. In addition, patients who consent to take part in the genotyping exploratory research will also sign a specific genotyping ICD to allow the use of their archived tumor tissue block, if any and/or of an aliquot of standard safety laboratory blood sample.

Patients' WAPS will be collected and a value of at least 4 will be required to take part in the study. Patients' standard demographic, relevant medical and primary disease history, primary disease treatment history, analgesic treatment history up to one month prior to entry into the study, symptoms related to analgesic treatment, if any as well as cancer concomitant therapies will then be recorded. Patients will also undergo an abbreviated physical examination.

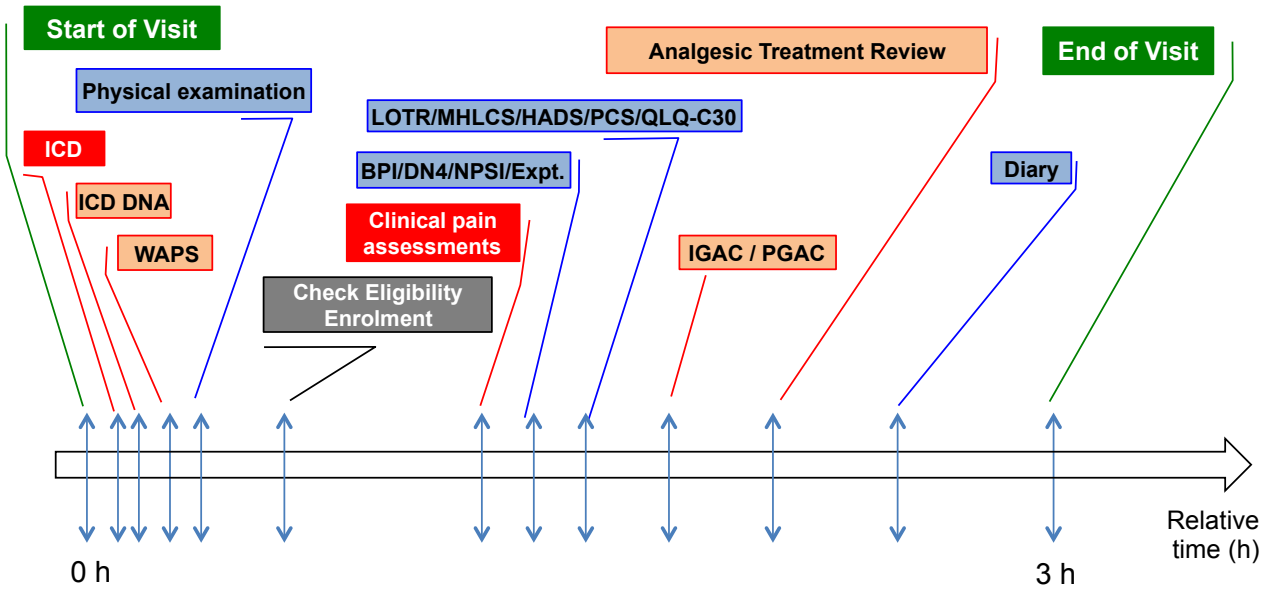
After checking completion of all inclusion/exclusion criteria, eligible patients will be enrolled in the study and perform the baseline Clinical Pain Assessments (CPAs). The following questionnaires will also be completed: pain disease questionnaires (DN4, NPSI and PCS), Brief Pain Inventory (BPI) questionnaire, expectation questionnaire, personality traits questionnaires (MHLCS, HADS and LOT-R) and quality of life questionnaire (Quality-of-Life Questionnaire in 30 questions (QLQ-C30)). The PGAC and IGAC will be completed by the patient and the Investigator, respectively.

At the end of the Visit and after patient evaluation, the Investigator will initiate or review as necessary the analgesic treatment and the patients will enter an observational period of approximately 4 weeks.

Before patients leave the site, Investigator site staff will dispense them a diary and educate them on proper completion of the 2 pain scales, the daily APS and WPS. The APS measures the average pain intensity over the last 24 hours; the WPS, the worst pain intensity over the last 24 hours, both on an 11-point Numeric Rating Scale (NRS) where 0 means no pain and 10, pain as bad as you can imagine. The APS and WPS of Visit 1 day will be completed by the patients at site with investigator site staff help. Between Visit 1 and Visit 2, the patients will also be asked to report in their diary intake of additional to prescribed analgesic treatment (rescue analgesic treatment), if any.

For a complete list of assessment procedures to be performed at Visit 1, see Study Schedule – Enrolment at Visit 1 - Section 16.1. Study Visit 1 is also depicted in Figure 2.

Patients will spend about 3 hours at the Investigator site during this visit.



Abbreviations: BPI = Brief Pain Inventory; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; ICD= Informed Consent Document; ICD DNA= Informed Consent Document for genotyping research; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; NPSI= Neuropathic Pain Symptom Inventory; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; WAPS: Weekly Average Pain Score

Figure 2. Sequence of Assessments at Visit 1

SECOND CASE SCENARIO: VISIT 1 ASSESSMENTS PERFORMED IN 2 VISITS – SCREENING AND ENROLMENT AT VISIT 1A

In this case scenario, Visit 1A and Visit 1B will be organized as follows. Eligible patients will be enrolled into the study at Visit 1A (screening and enrolment visit) but a few defined questionnaires will be completed at Visit 1B one to four weeks after Visit 1A. For a complete list of assessment procedures to be performed at Visit 1A and Visit 1B, see Study Schedule – Enrolment at Visit 1A - Section 16.2.

Visit 1A: Screening and Enrolment

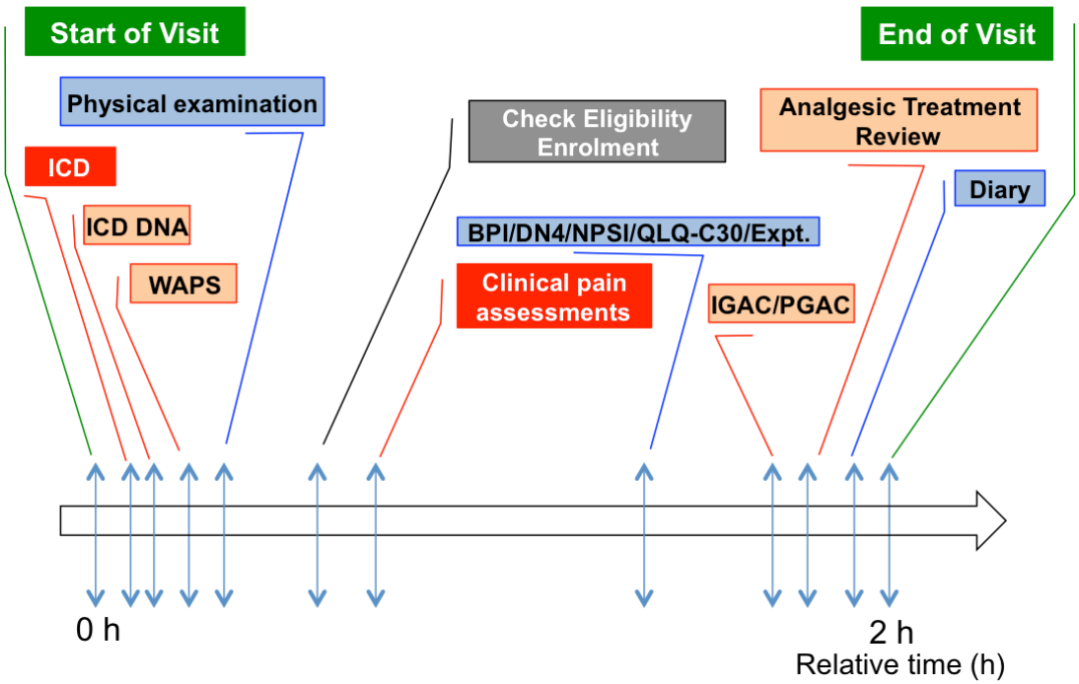
The assessments will be performed as described for Visit 1 in the first case scenario up to patient enrolment into the study. After checking WAPS and completion of all inclusion/exclusion criteria, eligible patients will be enrolled in the study and perform the CPAs. The following questionnaires will be completed during this visit: DN4, NPSI, BPI, Expectation and QLQ-C30. The PGAC and IGAC will be completed by the patient and the Investigator, respectively.

At the end of the Visit and after patient evaluation, the Investigator will initiate or review the analgesic treatment and the patients will enter an observational period of 5 to 10 weeks depending on when Visit 1B is scheduled.

Before patients leave the site, Investigator site staff will dispense them a diary and educate them on proper completion of the 2 pain scales, the daily APS and WPS. The APS and WPS of Visit 1A day will be completed by the patients at site with Investigator site staff help. Between Visit 1A and Visit 2, the patients will also be asked to report in their diary intake of supplemental analgesic treatment (rescue analgesic treatment), if any.

Study Visit 1A is depicted in Figure 3.

During this visit, patients will spend about 2 hours at Investigator site.



Abbreviations: BPI = Brief Pain Inventory; DN4= Douleur Neuropathique en 4 questions; ICD= Informed Consent Document; ICD DNA= Informed Consent Document for genotyping research; IGAC=Investigator Global Assessment of Changes; NPSI= Neuropathic Pain Symptom Inventory; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; WAPS: Weekly Average Pain Score

Figure 3. Sequence of Assessments at Visit 1A

Visit 1B

This visit will start with checking compliance to prescribed analgesic treatment and diary completion instructions. MHLCS, HADS, LOT-R questionnaires and PCS questionnaire will then be completed by the patients. The Investigator will review the analgesic treatment.

4.1.2. OBSERVATIONAL PERIOD – INTERMEDIATE PHONE CALL

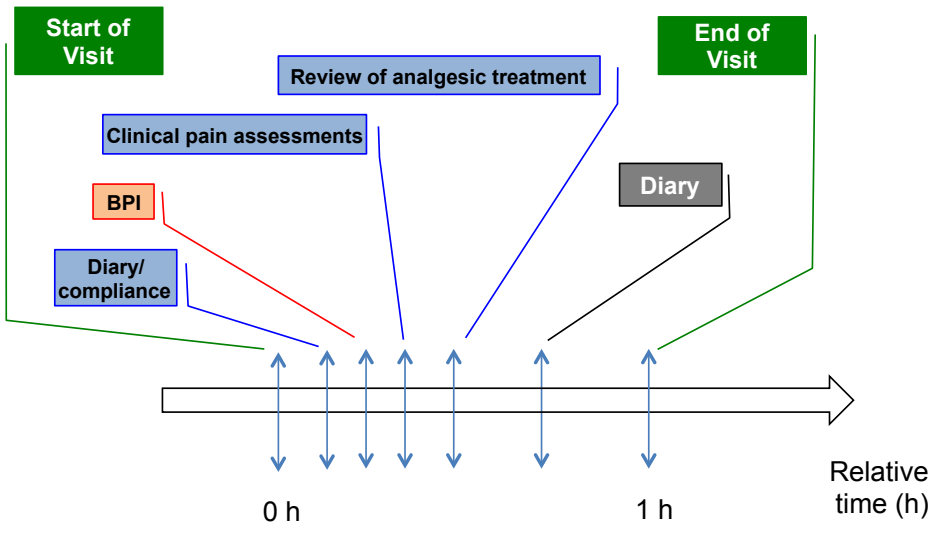
The observational period is a 4- to 10-week analgesic treatment therapy period including a phone call scheduled approximately 2 weeks after Visit 1 or Visit 1B (See figure 1. Study Diagram).

During this phone call, the Investigator site staff will inquire about patient general health status and pain relief. The patient will be reminded about Visit 2 scheduled date, diary and prescribed analgesic treatment compliance. At the end of the phone call, an intermediate visit to Investigator site may be organized within the next days at the discretion of Investigator.

If organized, this visit will start with collection of the diary, checking compliance to diary completion instructions and to prescribed analgesic treatment. Patient will complete BPI and go through all CPAs. At the end of this optional visit, the Investigator will review the analgesic treatment. Patients will continue to complete a diary up to Visit 2.

For a complete list of assessments to be performed at Intermediate Evaluation Visit , see Study Schedule Sections 16.1. and 16.2. This optional visit is also depicted in Figure 4.

At this visit, patients will remain at the Investigator site for approximately 1 hour.



Abbreviations: BPI = Brief Pain Inventory

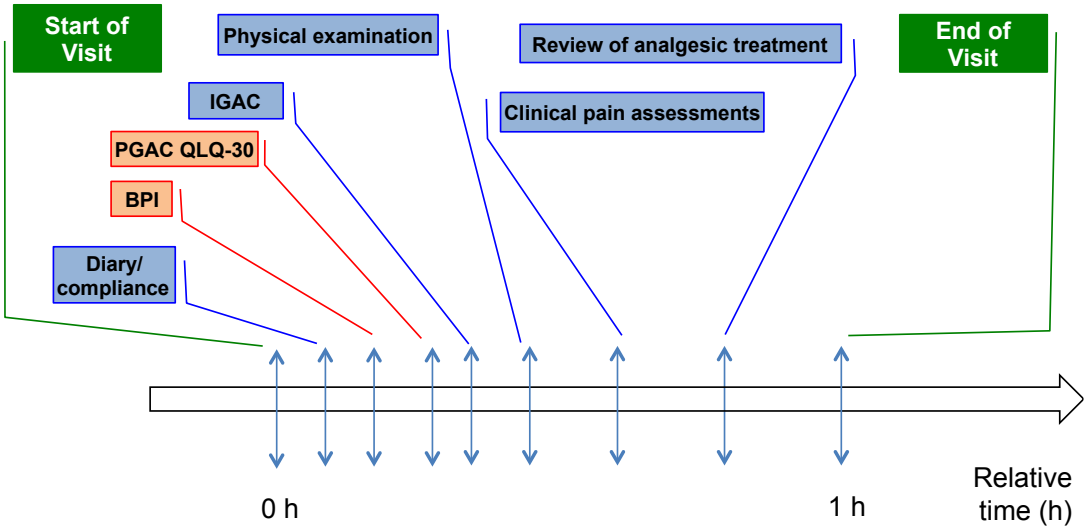
Figure 4. Sequence of Assessments at Intermediate Evaluation Visit

4.1.3. VISIT 2: END OF OBSERVATIONAL PERIOD AND FOLLOW-UP VISIT

Approximately 4 weeks after Visit 1 or Visit 1B (depending on the case scenario selected to complete Visit 1 assessments), Visit 2 will start with collecting the diary, checking compliance to diary completion instructions. All patients will complete BPI, PGAC and QLQ-30, while Investigator will complete IGAC as described in Figure 5. In addition, patients will undergo an abbreviated physical examination and the last CPAs. At the end of Visit 2, the Investigator will review patients analgesic treatment therapy.

For a complete list of assessments to be performed at Visit 2, see Study Schedule Sections 16.1. and 16.2.

Patients will remain at the Investigator site for approximately 1 hour at Visit 2.



Abbreviations: BPI = Brief pain Inventory; IGAC = Investigator Global Assessment of Changes ; PGAC= Patient Global Assessment of Changes; QLQ-C30 = Quality-of-Life Questionnaire in 30 questions.

Figure 5. Sequence of Assessments at Visit 2

Phone Call: End of Data Collection

A phone call will take place approximately 1 week after Visit 2. Patients will provide their last APS and WPS and give information on their current analgesic treatment. This phone call will last less than 10 minutes.

4.2. RATIONALE FOR THE STUDY DESIGN

4.2.1. POPULATION SELECTION AND SAMPLE SIZE

It is intended that up to 180 patients with CIBP will be enrolled to ensure that up to approximately 140 patients complete the study.

No a priori hypothesis tests or precision confidence intervals were used to determine the sample size. This sample size is rather justified by similar studies described in literature.

In the field of CIBP, several works have been reported. For example, Langford studied 97 cancer patients with CIBP, and managed to model the pain evolution for a particular subgroup of patients (Langford et al. 2011). Scott showed a link between QST and analgesia response on 23 patients suffering from CIBP. In other domains that are close, other works have been reported as well (Scott et al. 2012). First, Attal managed to show the relation between a pain-related marker (thermal hyperalgesia) and oxalyplatin neurotoxicity in cancer patients, based on a cohort of 48 patients (Attal et al. 2009). Second, Geber showed the ability of some psychological traits to discriminate between patient subgroups with different pain evolution scenarios based on a cohort of 146 patients suffering from chemotherapy-induced neuropathy (Geber et al. 2013).

The considered sample size for this trial seems therefore reasonable: higher than the sizes of the samples cited above. This larger number is motivated by the more complete set of features studied in the current study (patient history, psychological traits, pain assessments). Moreover as presented in Section 4.2.3, an interim analysis will be performed to confirm the final sample size of the study.

4.2.2. JUSTIFICATION FOR STUDY DESIGN

This study is an observational study. This design has been selected to collect data of analgesic treatment that would reduce pain severity after 4 to 10 weeks of analgesic treatment administration to patients.

4.2.3. INTERIM ANALYSIS

An interim analysis is planned after study completion of approximately 60 patients. Its main objective is to confirm the considered sample size of approximately 140 patients completing this study. Its secondary objectives will be to confirm questionnaires and historical data to be collected.

At this stage, each input feature (e.g. questionnaire items, historical data) will be evaluated with respect to its ability to discriminate on its own (i.e. not yet in conjunction within a set of features) between several levels of pain evolution. In case a non-significant correlation is found for a feature, the estimated sample size required will be computed. This analysis will allow getting a view on which features might show satisfactory results with a number of patients below 140.

The outcome of the interim analysis can therefore be either a confirmation of the initial sample size or a decrease of the number of required patients if striking relations are observed between a sufficiently high number of patients' features and pain-related outcomes (as defined by primary and/or secondary endpoints).

If following the interim analysis, substantial changes were to be brought to study, protocol and ICD would be amended and submitted for approval.

5. POPULATION RECRUITMENT, ENROLMENT AND WITHDRAWAL

5.1. DEFINITIONS

Screening Failure:

A patient is considered as a screening failure when he/she is screened but not enrolled in the study as not meeting eligibility criteria.

Patient Enrolment:

A patient is considered as enrolled in the study when he/she meets all eligibility criteria and he/she performs CPAs at Visit 1 or Visit 1A.

Patient Dropout:

A patient will be considered as dropout when, for any reason, he/she withdraws from the study or is discontinued from the study prior to study completion.

5.2. POPULATION RECRUITMENT

Patients will be recruited on a free voluntary basis. The criteria for enrolment must be followed explicitly. The Investigator(s) should demonstrate due diligence in recruitment and screening of potential study patients.

As illustrated in Sections 16.1 and 16.2 Study Schedule, eligibility of patients in the study will be based on the results of a screening visit.

5.3. INCLUSION DISEASE CRITERIA

Patients are eligible to be included into the study if they meet all of the following CIBP disease diagnosis criteria:

[1] Patients with bone tumors or bone metastasis from any primary cancer origin that is supported by histological or radiological investigations.

[2] Patients having been or being treated for their bone metastasis and/or their primary cancer.

[3] Patients who require analgesic treatment for unsatisfactory pain relief.

[4] Patients will be required to score at least 4 on the WAPS 11-point NRS during the week preceeding enrolment.

[5] Patients undergoing or not a radiotherapy program provided visit procedures are performed before any radiotherapy sessions if scheduled on the same visit days.

5.4. INCLUSION CRITERIA

Patients may be included in the study only if they meet all of the following criteria:

[6] Are men or women of at least 18 years of age.

[7] Being affiliated to country welfare.

[8] Are reliable and willing to make themselves available for the entire duration of the study and are willing to follow study procedures.

[9] Have given written informed consent approved by the relevant Ethics Committee (EC) governing the study site.

5.5. EXCLUSION DISEASE CRITERIA

Patients will be excluded from the study if they meet any of the following criteria related to CIBP:

[1] Patients having had a major surgery within 28 days prior to signing ICD or planning to have a major surgery during the study.

[2] Patients having a life expectancy < 3 months according to Investigator judgment.

5.6. EXCLUSION CRITERIA

Potential study patients may not be entered into the study if they meet any of the following criteria:

[3] Patients having poor nutritional status or whose condition is unstable or who could be rapidly deteriorating in such a way that they would not be able to complete the study.

[4] Patients with a current or recent history unrelated to their cancer condition, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease which would interfere with the patient's participation in the study.

[5] Patients having a Karnofsky performance status below 70% or WHO score (Eastern Cooperative Oncology Group (ECOG)/Zubrod score) above 1.

[6] Are Investigator site staffs directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[7] Any other relevant medical disorder likely to interfere with the trial or represent a risk for the patient.

[8] Patients under legal protection, according to the country law.

[9] Patients currently enrolled in a clinical trial involving use of an investigational drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or in an exclusion period according to the national law.

5.7. RANDOMIZATION

Not applicable.

5.8. PATIENT WITHDRAWAL, DISCONTINUATION AND REPLACEMENT

5.8.1. WITHDRAWAL /DISCONTINUATION CRITERIA

All patients are free to withdraw their consent to participate in the study at any time, for any reason, specified or non-specified, and without penalty.

The Sponsor and/or the Investigator for some possible reasons listed below may discontinue a patient from the study:

- If, in the opinion of the Investigator and/or the Sponsor, patient's general health status contra-indicates patient continuation in the study,
- The Investigator or delegate decides that the study participant should be withdrawn from the study,
- Non-compliance of the patient with study instructions, such as the patient fails to return to the study site for a scheduled visit and/or does not respond to the attempts of the study site staff to contact him/her (considered as lost to follow-up).

All cases of discontinuation will be discussed between the Investigator and the Sponsor.

5.8.2. FOLLOW-UP PROCEDURES FOR DROP-OUT PATIENTS

In case a patient enrolled in the study drops out or is discontinued from the study earlier than study end, he/she will answer a few questions by phone as indicated in the early discontinuation phone call described in Sections 16.1 and 16.2 Study Schedule. The reason and date for dropout should be documented.

5.8.3. REPLACEMENT STRATEGY

No replacement of patient is foreseen.

5.9. DISCONTINUATION OF STUDY SITE

Study site participation may be discontinued if the Sponsor, the Investigator, or the EC of the study site judges it necessary for any reason.

5.10. DISCONTINUATION OF PATIENT'S PARTICIPATION

The criteria for enrolment should be followed explicitly. If a patient who does not meet enrolment criteria is inadvertently enrolled in the study, that patient should be discontinued from the study, and the Sponsor must be informed.

5.11. DISCONTINUATION OF STUDY

The study can be discontinued prematurely at any time if the Sponsor judges it necessary for any reason. In that case, all scheduled procedures and/or procedures of early discontinuation phone call will be performed.

6. STUDY TREATMENT

6.1. STUDY DRUG AND TREATMENT OF PATIENTS

No IMP will be administered in this observational study.

Patients will be treated by the Investigator for pain relief exactly as they would normally be based on their needs and clinician practice.

6.1.1. INVESTIGATIONAL DRUG FORMULATION(S)

Not applicable.

6.1.2. SUPPLIES, PACKAGING, LABELING, ACCOUNTABILITY AND STORAGE

Not applicable.

6.1.3. STUDY DRUG ADMINISTRATION

Not applicable.

6.2. BLINDING MAINTENANCE / UNBLINDING

Not applicable.

6.3. CONCOMITANT THERAPY

Patients will take their analgesic treatment as prescribed by the Investigator. Drug therapy for cancer will be continued following patient needs.

See section 7.2.2 for supplemental rescue analgesic medication information.

All analgesic medication taken over the last month preceding enrolment and primary disease medication will be recorded on the Case Report Form (CRF). Any investigational drug taken over the previous year will also be recorded.

6.4. PRODUCT COMPLAINT

Not applicable.

7. PATIENT MANAGEMENT AND INSTRUCTIONS

7.1. STUDY PATIENT MANAGEMENT AND REQUIREMENTS

The patients will be required to attend the Investigator site at the following occasions: at screening/enrolment, Visit 2, optional Visit 1B and intermediate evaluation Visit. The patients will be discharged from the study at Visit 2.

Throughout the study, patients may undergo medical assessments and review of compliance with restrictions before continuing in the study.

7.2. STUDY RESTRICTIONS

7.2.1. STUDY DRUG ADMINISTRATION

No investigational drug will be administered to patients during this study. The Investigator will prescribe analgesic treatment to patients based upon their regular practice.

7.2.2. OTHER RESTRICTIONS

Medications

During the study and in addition to their current analgesic treatment, patients will be permitted to supplement their analgesic treatment with rescue analgesic drugs (named rescue medication). Type and dose regimen of these rescue medications will be left at the discretion of Investigator.

7.2.2.1. Diary

Once a day from enrolment till Visit 2, approximately at the same time of the day in the evening, patients will complete their diary.

The following data will be recorded:

- pain intensity assessment by recording APS and WPS for the last 24 hours (from enrolment till Visit 2 or early discontinuation). See Sections 8.2.4.4 and 8.2.4.5 for further description of APS and WPS,
- any potential event that may help to understand unexpected study outcomes,
- intake of rescue analgesic treatment if any (from enrolment to Visit 2 or early discontinuation).

8. STUDY ASSESSMENTS

Timing of assessments is specified in Sections 16.1 and 16.2 Study Schedule.

8.1. PHARMACOKINETICS ASSESSMENT

Not applicable.

8.2. PHARMACODYNAMIC ASSESSMENTS

8.2.1. CLINICAL PAIN ASSESSMENTS (CPAS)

The following CPAs will be performed at enrolment, at Visit 2 and at optional intermediate evaluation Visit as specified in Sections 16.1 and 16.2 Study Schedule.

First, the painful areas (PA) will be defined by patients, using a standardized blank body map. CPAs will then be carried out by the Investigator or his/her designee on the skin overlying the most painful area (MPA) reported by the patient. The control area to compare to would be the equivalent dermatome region on the contralateral side of the body, or for central spinal sites an alternative non-painful area at the spinal level. This control area site will be defined as “normal”.

If the MPA is different at the next visit from the previous one, all assessments will be performed on the current MPA first and then again on the previous visit MPA. However, in the case scenario of the MPA at Visit 2 is different from both the one identified at intermediate evaluation Visit and the other at enrolment, only MPA defined as such at previous visit (intermediate evaluation) and at this current Visit 2 will be assessed.

Regarding MPA, clinical signs are identified as follows:

- Hypoesthesia is defined as the presence of an area where light touch of the blunt end of a paintbrush is felt less precisely than in referent control areas.
- Sensory loss is defined as the presence of an area where the same light touch as referred above is not felt at all.
- Hyperalgesia is defined as the presence of an area where the pain induced by stimulus applied perpendicularly to the skin is felt abnormally intensely.
- Allodynia is defined as the presence of an area of pain after the application of non-painful stimulus.

The centre of an area with allodynia or hyperalgesia is considered for further evaluation. However, in the absence of allodynia and hyperalgesia the centre of the area of hypoesthesia or sensory loss is then considered.

All CPAs will be carried out in a quiet environment, with a relaxed patient, previously instructed on the procedure. If a test provoked pain, the Investigator will wait for pain disappearance before proceeding with the next test. All CPAs will be completed within approximately 20 minutes.

The CPAs will include the following parameters:

The Most Painful Area (MPA)

The MPA will be mapped on a standardized body map. The area with abnormal sensation will be delimited with a dermographic pencil and a picture of it will be taken in such a way the MPA surface can be calculated. Patient identity must always be concealed when taking the photography. Further instructions will be given in a dedicated manual.

Static Allodynia (SA)

SA will be assessed using a standardized calibrated von Frey hair number 13 (5,1g) (or equivalent device) at the centre of both painful and control areas. The patient will be asked to describe this sensation compared with the control area (hyperesthesia, hypoesthesia or unchanged) and, if painful, to rate the pain on an 11-point NRS.

Dynamic Mechanical Allodynia (DMA)

DMA will be assessed using a standardized calibrated brush (SENSELab Brush-05, Somedic or equivalent device). 3 successive gentle strokes will be performed over a 40mm length of skin bilaterally at interval of 1 second interval. The patient will be asked to describe this sensation compared with the control area (hyperesthesia, hypoesthesia or unchanged) and, if painful, to rate the pain on an 11-point NRS.

Mechanical Pain Threshold (MPT)

MPT will be assessed with a series of 7 von Frey monofilaments (SENSELab von Frey Aesthesiometer II, Somedic or equivalent device) of varying thickness, calibrated according to the force required to make them bend. The force of the stimulus becoming painful is recorded. This assessment is conducted one time on the control area but repeated 3 times on the affected area. Suprathreshold level may be measured in both the control area and affected area using the strongest von Frey hair number 16 and will be rated with an 11-point NRS.

Thermal Pain Sensitivity (TPS)

Responses to heat at 40 °C (H-TPS) and cool at 25°C (C-TPS) will be examined using thermal rollers (Rolltemp, Somedic or equivalent device) in both the affected and control areas. The presence of hyperesthesia or hypoesthesia or thermal allodynia will be recorded and rated on an 11-point NRS if painful. Responses will be recorded as increased, reduced or equivalent sensation compared to the control area.

8.2.2. PERSONALITY EVALUATIONS

The following personality questionnaires will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.2.1. Multidimensional Health Locus of Control Scale (MHLCS)

Pain perception may be related to patient perceptions of control of life event. The MHLCS classify patients within 2 categories: patients with internal locus of control, who believe that their life events are controlled by themselves, patients with external locus of control who believe that their life events are controlled by factors such as luck or fate and

patients with external locus of control who believe that their life events are controlled by powerful others (such as health professionals, relatives and some other people). The MHLCS consists of 18 self-report items with a rating ranging from 1 (strongly disagree) to 4 (strongly agree) (Wallston et al. 1978).

8.2.2.2. Hospital Anxiety and Depression Scale (HADS)

The depression and the anxiety scale of the HADS consist of 14 items, which are rated on a 4-point scale (Zigmond and Snaith 1983).

8.2.2.3. Revised Life Orientation Test (LOT-R)

The LOT-R is an improved version of the original Life Orientation Test (LOT) and it defines optimism-pessimism as generalized positive and negative outcome expectancies. The LOT-R consists of 6 self-report items and 4 filler items. Each item is rated on a 5-point scale ranging from 0 (strongly disagree) to 4 (strongly agree). To calculate optimism-pessimism scores, the three pessimism items (e.g. I hardly ever expect things to go my way) are reverse coded and added to the three optimism items (e.g., In uncertain times, I usually expect the best) to create a summary optimism-pessimism score (Scheier et al. 1994).

8.2.2.4. Expectation Questionnaire

Directed expectancy is measured by asking the patients: “How much do you expect this analgesic treatment will change your current pain?”

Similarly, the desire for pain relief is measured by asking the patients “How strong is your desire to find an analgesic treatment relieving you from pain?”

The ratings will be reported using an 11-point NRS ranging from 0 (not at all) to 10 (as best as possible).

8.2.3. PAIN DISEASE EVALUATION

The following evaluations will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.3.1. DN4 Questionnaire (DN4)

“Douleur Neuropathique en 4 questions’’ (DN4) questionnaire is a clinician-administered questionnaire including both items related to the interview (i.e. symptoms) and items related to the sensory examination (i.e. signs) (Bouhassira et al. 2005).

It consists of 7 dichotomous questions (yes/no) related to the painful area from interview of the patient (burning, painful cold, electric shocks, tingling, pins and needles, numbness and itching) and of 3 items (yes/no) related to the physical examination in the PA (hypoesthesia to touch, hypoesthesia to prick and pain caused or increased by brushing).

Pain is considered as neuropathic if the DN4 score is ≥ 4.

8.2.3.2. Neuropathic Pain Symptom Inventory (NPSI)

The NPSI is a self-administered questionnaire that includes 10 pain descriptors of intensity and 2 temporal items (Bouhassira et al. 2004). The intensity of pain is rated on an 11-point NRS. The 10 pain descriptors of the NPSI pertain to 5 distinct clinically relevant dimensions: spontaneous burning pain, spontaneous deep pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. The scoring of the NPSI includes both a total score of neuropathic symptoms intensity and 5 sub-scores. Temporal items are designed to assess spontaneous ongoing pain duration and the number of pain paroxysms over 24 hours.

8.2.3.3. Pain Catastrophizing Scales (PCS)

Catastrophizing thoughts concerning pain are measured with the PCS (Sullivan et al. 1995). It consists of 13 items that are answered on a 5-point scale ranging from 0 (not at all) to 4 (all the time). The subscale ‘‘Rumination’’ describes the inability to stop thoughts concerning pain. The subscale ‘‘Magnification’’ reflects the tendency to exaggerate the threat value of pain stimuli. The subscale ‘‘Helplessness’’ describes the feeling of inability to deal with the pain. The PCS total score is calculated by summing up all the items.

8.2.4. PAIN EVALUATIONS

The following pain evaluations will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.4.1. Brief Pain Inventory (BPI) Short Form

BPI is a self-reported scale that measures the severity of pain and the interference of pain on function (Charles S. Cleeland © 2009). In the short form of BPI, there are 4 questions assessing worst pain, least pain, actual pain and average pain in the past 24 hours. The severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are 7 questions assessing the interference of pain in the past 24 hours for general activity, mood, walking ability, normal work, relation to other people, sleep and enjoyment of life. The interference scores range from 0 (does not interfere) to 10 (completely interferes).

8.2.4.2. Investigator Global Assessment of Changes (IGAC)

The IGAC is a subjective evaluation using a NRS to answer the following question: “If you take into consideration all the various ways the pain influence the patient and his/her life, how do you then evaluate the patient’s condition today?” with 0 meaning “best” and 10 “worst”.

8.2.4.3. Patient Global Assessment of Changes (PGAC)

PGAC is a subjective evaluation using a NRS to answer the following question: “If you take into consideration all the various ways the pain influence you and your life how do you then evaluate your condition over the last week?” with 0 meaning “very good” and 10 meaning “very bad”.

8.2.4.4. Average Pain Score (APS)

The APS will measure the average pain intensity over the last 24 hours by asking the patient "Could you please indicate us how was your average pain during the last 24 hours? For this, circle the most descriptive number on this scale." The patient will be asked to rate it on an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as you can imagine). However, before being enrolled into the study, the patient will be asked an APS over the past week (WAPS).

8.2.4.5. Worst Pain Score (WPS):

The WPS will measure the worst pain intensity over the last 24 hours by asking the patient "Could you please indicate us how was your worst pain during the last 24 hours? For this, circle the most descriptive number on this scale." The patient will be asked to rate it on an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as you can imagine).

8.2.5. QUALITY-OF-LIFE QUESTIONNAIRE IN 30 QUESTIONS (QLQ-C30)

The health related quality-of-life in cancer patient will be measured with the Quality-of-Life Questionnaire-C30 (QLQ-C30; Copyright © 2002 EORTC Quality-of-Life Group). This core questionnaire contains 30 items divided into functional scales, symptom scales, single items and global quality-of-life. It will be completed at enrolment and at Visit 2 as specified in Sections 16.1 and 16.2 Study Schedule.

8.3. INFORMATION ON GENERAL HEALTH STATUS

This is an observational study and it does not therefore interfere with the way the Investigator is managing patients.

The Investigator remains responsible for adequate patient management and for a clinical assessment of the study participants before discharge from the study as well as for the set up of a discharge plan, if needed.

In addition to records of observations made at specific times, symptoms related to analgesic treatment will be recorded in the clinical study records throughout the study.

The following parameters will be collected during this study at specific timepoints as described in the Study Schedule (Sections 16.1 and 16.2):

- Symptoms related to pain treatment (e.g. nausea).
- Potential historical laboratory analysis data (biochemistry and hematology data) defined as the most recent safety laboratory analysis obtained within one month before the screening and/or ongoing laboratory safety analysis and urine analysis, if available, performed as part of patient management by the Investigator. In case several safety laboratory analysis are performed during the study, only one per week will be recorded.
- Abbreviate physical examination at screening and Visit 2..

Further routine medical assessments may be performed during the study, if warranted or when clinically indicated.

8.3.1. SYMPTOMS MONITORING

Definition of Adverse Event (AE)

Typically, a clinical study AE is any untoward medical occurrence in a patient or clinical study patient administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

This does not apply to this observational study. Nevertheless the symptoms related to analgesic treatment(s) will be collected.

Symptoms Collection and Reporting

At enrolment, study site personnel will record the occurrence, time of onset, nature and severity of symptoms related to analgesic treatment. Up to Visit 2, site personnel will record any change in the occurrence and nature of symptoms related to analgesic treatment or having an impact on pain evaluation. The nature, time of onset, duration, severity will be documented and each symptom will be classified by the most suitable term from a version of a Medical Dictionary for Regulatory Activities (MedDRA) agreed by the Sponsor and other parties involved in the study.

The condition of each patient will be monitored throughout the study. In addition, any sign or symptom related to pain treatment will be observed and elicited at least at each visit by open questioning, such as “How have you been feeling since you were last asked?”

Patients will also be encouraged to report spontaneously any symptom occurring at any other time during the study.

8.3.1.1. Symptom Intensity

The clinical intensity of symptom will be classified as:

- Mild: the event results in a mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (*e.g.* mild headache, insomnia),
- Moderate: the event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (*e.g.* fever requiring antipyretic medication),
- Severe: the event results in significant symptoms that prevent normal daily activities; may require prolonged interventional treatment, hospitalization or invasive intervention (*e.g.* anemia resulting in blood transfusion).

8.3.2. SERIOUS ADVERSE EVENT AND REPORTING

Not applicable (observational study). Nevertheless, if a patient is withdrawn from the study because of an SAE, this information will be collected.

8.4. STUDY PROCEDURE PRIORITY ORDER

Figures 2 to 5 in Section 4.1 are describing the sequence of procedures at each visit.

8.5. COMPLIANCE TO STUDY PROCEDURES

Compliance is the adherence to trial-related requirements, to GCP, to protocol and to regulatory rules and regulations.

8.5.1. COMPLIANCE TO PROTOCOL

Every attempt will be made to select patients who have the ability to understand and comply with instructions. Non-compliant patients may be discontinued from the study.

8.5.2. COMPLIANCE TO TIMING OF PROCEDURES

The Investigator should make a reasonable attempt to complete the scheduled study procedures on the appropriate scheduled visit and in the appropriate sequence.

The specifications in this protocol for the sequence of procedures are given as targets, to be achieved if possible.

It is recognized that deviations may occur for logistic or other reasons and will not be considered as protocol violations. The scheduled timepoints may be subject to alterations; however, the actual time must always be correctly recorded in the CRF, diary or other documents.

8.5.3. COMPLIANCE TO ANALGESIC PATIENT 'S THERAPY

Patient's compliance to prescribed analgesic medication will be assessed at each visit by direct questioning and checking diary. The investigator will evaluate if patient fails to take more than 50% of the prescribed analgesic medication for the visit interval.

8.5.4. COMPLIANCE TO STUDY VISITS

Depending on patient general health status, visits to the Investigator site may occur after enrolment at interval of 2 or 4 weeks. Visits schedule can be adapted according to Investigator-patients agreement, as presented in Tables 1 and 2.

Table 1. Study Visits with Allowed and Suggested Time Intervals – First Case Scenario – Enrolment at Visit 1

Visit Number	Time Interval (Days)	
	Suggested	Allowed
Visit 1 (Screening and Enrolment)	Day 1	
Intermediate Phone Call	Day 15	Day 13 to 17
Optional intermediate evaluation Visit	Day 15	Day 13 to 19
Visit 2	Day 29	Day 29 to 43
Phone Call	Visit 2 Day + 7 days	Visit 2 Day + 14 days

Table 2. Study Visits if with Allowed and Suggested Time Intervals – Second Case Scenario – Enrolment at Visit 1A

Visit Number	Time Interval (Days)	
	Suggested	Allowed
Visit 1A (Screening and Enrolment)	Day 1	
Visit 1B	Day 8	Day 8 to 29
Intermediate Phone Call	Visit 1B Day + 14 days	Visit 1B Day + 12 to 16 days
Optional intermediate evaluation Visit	Visit 1B Day + 14 days	Visit 1B Day + 12 to 18 days
Visit 2	Visit 1B Day + 28 days	Visit 1B day + 28 to 42 days
Phone Call	Visit 2 Day + 7 days	Visit 2 Day + 14 days

8.5.5. COMPLIANCE TO DIARY COMPLETION

Compliance to diary completion (APS, WPS, rescue analgesic treatment recording) will be checked by Investigator at each visit at Investigator site.

9. EXPLORATORY ASSESSMENTS

Use of potentially available archived tumor tissue block and/or aliquot of standard safety laboratory blood sample for genotyping purposes are optional in this study.

Since genetic variation may influence a patient's response to therapy and may impact the mechanism of action and fate of drugs (absorption, distribution, metabolism, and excretion), metabolism enzyme, transporter polymorphisms, expression of proteins, disease etiology and/or molecular subtype of the disease being treated, pharmacogenetic may be explored in this study.

If the patient agrees to and signs the specific genotyping ICD, an aliquot of standard safety laboratory blood sample will be collected for potential pharmacogenetic analysis and archived tumor tissue block available at the Investigator site may be re-analyzed for genetic purposes.

Genetic material derived from those samples may be tested in any circumstances of an unexpected observation of unusual response. These analyses of genetic variants may evaluate a genetic association with response. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed. Samples will only be used for investigations related to the pain disease and drug or class of drugs under study in the context of this clinical study. They will not be used for broad exploratory genetic analysis.

Procedures for management of blood sample aliquot and retrieved tissue will be specified in a separate document.

The samples will be identified by the patient number (coded) and may be stored for up to 15 years after study last patient visit at a facility selected by the Sponsor. Any remaining sample stored for this study at that time will be destroyed. The blood and tissue sample and any data generated from it can only be linked back to the patient by Investigator site personnel. Pharmacogenetic data will not be provided to the Investigator unless required.

Patients will not be notified with regard to genotyping results unless required by local regulations.

10. STATISTICAL ANALYSES

10.1. DATA ANALYSIS PLANS

10.1.1. GENERAL CONSIDERATIONS

For all enrolled patients, pharmacodynamic analyses will be conducted on the full analysis set.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, unless otherwise stated.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

Detailed plan for the statistical methods for the safety and other variables will be provided in a Statistical Analysis Plan (SAP). This plan will be finalized prior to database lock.

10.1.1.1. Analysis Populations

Statistical analysis and data tabulation will be performed using the full patient population unless specified otherwise.

The patients constitute data vectors of potentially all data sources:

- CRF entries,
- Item-level entries from personality questionnaires
- Facet-level summaries from personality questionnaires
- Meta-level summaries from personality questionnaires
- Diary entries
- Meta-level summaries from diary
- Pain evaluations

At any time during the statistical analyses, a subset of those vector entries (thus reducing the population to some of these input features only) might be considered.

In some exploratory analyses, new populations might also be defined, for example based on sub-groups of patients showing similar pain evolution throughout the study.

A special set of features – the target features – characterize the analgesic efficacy and are defined as follows:

- APS difference with respect to baseline (primary endpoint)
- WPS difference with respect to baseline (secondary endpoints)
- BPI difference with respect to baseline (secondary endpoints)
- IGAC difference with respect to baseline (secondary endpoints)
- PGAC difference with respect to baseline (secondary endpoints)
- QLQ-C30 with respect to baseline (secondary endpoints)
- CPAs difference with respect to baseline (secondary endpoints)

10.1.1.2. General Statistical Procedures

The statistical analyses will be divided into four main parts (P1 to P4): descriptive, univariate, multivariate and exploratory. The descriptive part intends to describe the data by generating a set of statistical summaries of each patient-vector entry. The univariate analysis will investigate the link between each patient-vector entry and the treatment response (as described by the pain evolution). All the statistical procedures will further be described in a dedicated SAP.

P1 - Data Description

P11: Data pre-processing and summary.

Classical statistical information will be computed for each input feature (mean, median, standard deviation). A log-transform will be applied to some features, when appropriate.

P12: Missing values management.

The number of missing values will be reported for each feature. In subsequent analyses, value imputation might be performed if needed. Such cases will be documented.

P13: Outlier detection.

Population outliers will be detected through a Principal Component Analysis (PCA) visualization. Outliers might be removed for at least parts of the further analyses. Such cases will be documented.

P2 - Univariate Analysis

P21: Features Impact Assessment.

The correlation between each feature and the treatment response in terms of target feature will be assessed.

For each test performed in P2, if a non-conclusive p-value is obtained and when possible, an estimation of the required sample size will be performed based on the study data.

P3 - Multivariate Analysis

The aims of the multivariate analysis are i) to explore links between features (including all input and target features), ii) to predict target features based on input features, iii) to identify most important input features for this predictive task.

P4 - Exploratory Analysis

P41 - New populations identification.

We identify subgroups of patients with intra-group similar pain evolution curves, and inter-group different pain evolution curves. We define new “class labels” accordingly. If coherent profiles are found, we might consider applying a modeling procedure similar to P3.

P42 – Genetic data exploitation.

In case the genetic material from patients is used, similar experiments as those described above might be performed to discover links between genetic traits (snips for example) and pain evolution or pain treatments efficacy.

10.1.2. DETERMINATION OF SAMPLE SIZE

The determination of the sample size is presented in Section 4.2.1.

10.1.3. STUDY PARTICIPANT DISPOSITION

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.1.4. STUDY PARTICIPANT CHARACTERISTICS

The patient's age, sex or other demographic characteristics will be recorded and may be used in the pharmacodynamic analyses as quantitative or classification variables.

10.1.5. STATISTICAL EVALUATION OF SYMPTOMS

All prescribed analgesic treatment, analgesic recue medication and symptoms related to pain treatment will be listed, and if the frequency of symptoms allows, they will be summarized using descriptive procedure.

The incidence of symptoms will be presented by severity and by association with class of analgesic treatment.

Where changes in severity are recorded in the CRF, the most severe incidence of the symptom will be reported in the tables and listings. A baseline sign and symptom is defined as a symptom that starts after the enrolment of patient.

The frequency (the number of symptoms, the number of patients experiencing a symptom and the percentage of patients experiencing a symptom) of symptoms will be summarized by class of treatment, MedDRA system organ class and preferred term. Any severe and/or serious symptom will be tabulated.

10.2. DATA CAPTURE

The following source data may be generated and handled for further data basing process:

- Data captured in electronic CRFs (e-CRFs),
- Paper-based data captured systems (i.e. diary, questionnaires).
- Electronic Data Capture systems (analysis,…)

To ensure accurate, complete, and reliable data, the Sponsor will provide instructional material to the study sites, as appropriate. Training session will be given during a start-up/initiation meeting for instructions on completion/data entry of any source data.

The Investigator or his/her designee must verify that all data entries in the e-CRFs are accurate and correct.

10.3. DATA HANDLING

All or part of the data will be monitored at periodic visit at the study sites, according to a monitoring plan. All entries in the e-CRFs, corrections and alterations are to be made by the responsible Investigator or his/her designee.

Since e-CRFs are used, data will be directly entered in the database.

Details of all data management procedures, from the initial planning to the archiving of final datasets/documents following database freeze/lock will be documented in appropriate data management and validation plan(s). Among others, these procedures will also describe quality control checks, data handling process for any missing, unused or spurious data, as well as coding procedures for symptoms, medical history, physical examination and medications.

10.4. RECORD KEEPING

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, patient diaries and clinical notes.

Depending on the data collected and the type(s) of data, records will be kept following storage and archiving procedures agreed by the Sponsor and Investigator sites involved in this study and in accordance to any regulations that are applicable in the countries where the study is conducted.

11. INFORMED CONSENT AND ETHICAL CONSIDERATIONS

11.1. PATIENT INFORMATION SHEET AND CONSENT

The Investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his/her participation in the study in a timely manner.

The patient information sheet and consent document will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his/her understanding of the study and is willing to participate.

The Investigator is ultimately responsible for ensuring that the EC-approved informed consent is appropriately signed and dated by each patient prior to any study procedures being performed. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legally acceptable representatives.

Patients will be given a copy of their informed consent forms.

Genotyping ICD will be used to collect consent from informed patients specifically on potential genetic research on their samples.

11.2. ETHICAL REVIEW CONSIDERATIONS

The relevant EC(s) will approve the study conduct after review of the following documents (this list may not be exhaustive):

- Protocol approved by the Sponsor,
- ICDs,
- Insurance certificate.

The EC decision on the conduct of the study will be made in writing. This approval document must be dated and clearly identify the version number(s) and date(s) of the documents submitted and approved by EC.

The study may begin at the Investigator sites only after receiving the dated and signed documentation of the EC(s) approval of the protocol and the ICDs.

During the study the following documents will be sent to the EC(s) for their information, or for review and approval: (1) all protocol amendments, (2) revised ICDs, if any.

At the end of the study, the EC(s) will be notified about the study completion.

11.3. REGULATORY CONSIDERATIONS

This study will be conducted in accordance with applicable laws and regulations, GCPs, and the ethical principles that have their origin in the Declaration of Helsinki.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting medical information and/or other trial-related data.

12. INSURANCE

The Sponsor declares that they have taken out an insurance policy covering the patients in respect to risks involved in the study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor will provide instructional material to the study sites, as appropriate. A site initiation training session will be held prior to screening start to instruct the Investigator sites staffs. This session will give instructions on the protocol, CRFs completion and study procedures.

13.1. MONITORING

Before the initiation visit, a monitoring plan will be issued describing how and when monitoring will be performed.

Periodic visits should be made to the study sites throughout the study at mutually agreed times. Any appropriate communication tools will be set up to ensure the Sponsor is available for consultation and timely communication.

Quality of the data will be reviewed to detect errors in data collection.

13.2. INVESTIGATOR'S REGULATORY OBLIGATIONS

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a Quality Assurance personnel designated by the Sponsor, or by regulatory bodies. The Investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

13.3. FINAL REPORT SIGNATURE

The Investigator or designee will sign the clinical study report for this study, indicating agreement with the analyzes, results and conclusion.

14. PUBLICATION POLICY

The rights of the Investigators and the Sponsor with regard to publication of the results of this study are described in the contracts with Investigator sites.

15. LITERATURE AND DATA REFERENCES

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16. ATTACHMENTS

16.1. ATTACHMENT 1 – STUDY SCHEDULE – ENROLMENT AT VISIT 1

	Screening Enrolment	Observational Period		Follow Up / Early Discontinuation Phone Call
Visit	**1**	**Optional Intermediate Evaluation** [f]	**2**	
Days	**Day 1**	**Day 15 (- 2/+ 4 days)**	**Day 29 (+ 14 days)**	**7 days after Visit 2 (+ 7 days)**
Informed Consent (general and genotyping)[a]	X			
Demographics	X			
Abbreviated Physical examination	X		X	
Primary disease and Relevant Medical History	X			
Primary disease treatment history	X			
Analgesic history (within 1 month before enrolment)	X			
Pre-existing Conditions/Symptoms related to pain treatment	X	X	X	X
Cancer Concomitant Medications	X	X	X	X
Personality trait questionnaires: MHLCS, HADS, LOT-R and Expectation questionnaire	X			
DN4, NPSI and PCS (Pain disease evaluation)	X			
QLQ-C30	X		X	
Inclusion/Exclusion Criteria	X			
Enrolment into study	X			
Safety Laboratory Analysis[b]				
Aliquot of blood sample for genotyping purpose[a]	←	———	→	
Diary completion	←	———	→	
Compliance to diary completion		X	X	
Analgesic treatment review	←	———	———	→
Compliance to prescribed analgesic treatment[c]		X	X	
Clinical Pain Assessments[d]	X	X	X	
APS and WPS[e]	X		X	X
BPI (short form)	X	X	X	

IGAC and PGAC	X		X	

Abbreviations:
APS = Average pain score; BPI = Brief Pain Inventory; DMA = dynamic mechanical allodynia; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; MPT= mechanical pain threshold; NPSI= Neuropathic Pain Symptom Inventory; MPA = Most Painful Area; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; SA= static allodynia; TPS= thermal pain sensitivity; WPS = Worst pain score.

[a] Aliquot of standard safety laboratory blood sample for genotyping is optional in this study (will be performed if patient gives his consent by signing the genotyping informed consent document). The aliquot can be taken at any time during the study.

[b] Potential historical safety laboratory data (biochemistry, hematology) defined as the most recent safety laboratory data obtained within one month before screening visit and/or standard safety laboratory analysis and urinalysis performed during the study as part of regular patient management by Investigator will be collected (one per week if several during the study).

[c] Compliance to prescribed analgesic treatment will be followed through diary completion and direct questioning.

[d] The Clinical pain assessments will include the following measurements: MPA, SA, DMA, MPT and TPS.

[e] APS and WPS will be collected in the diary. APS and WPS at visit 1 will be completed at site by patient with Investigator site staff help, if needed. The last APS and WPS will be completed by patients during the phone call with the Investigator. At Visit 1, the Weekly APS during the preceeding week will be assessed for enrolment.

[f] Optional Intermediate Evaluation Visit will be organized within the next days after the intermediate phone call at the discretion of the Investigator.

16.2. ATTACHMENT 2 – STUDY SCHEDULE – ENROLMENT AND SCREENING AT VISIT 1A

	Screening Enrolment		Observational Period		Follow UP / Early Discontinuation Phone Call
Visit	**1A**	**1B**	**Optional Intermediate Evaluation [f]**	**2**	
Days	**Day 1**	**Day 8 (+ 21 days)**	**Visit 1B Day + 14 days (+ 12 to + 18 days)**	**Visit 1B Day + 28 days (+ 14 days)**	**7 days after Visit 2 (+ 7 days)**
Informed Consent (general and genotyping)[a]	X				
Demographics	X				
Abbreviated physical examination	X			X	
Primary disease and Relevant Medical History	X				
Primary disease treatment history	X				
Analgesic history (within 1 month before enrolement)	X				
Pre-existing Conditions/Symptoms related to pain treatment	X	X	X	X	X
Cancer Concomitant Medications	X	X	X	X	X
Inclusion/Exclusion Criteria	X				
Enrolment into study	X				
Clinical Pain Assessments[d]	X		X	X	
DN4, NPSI	X				
Expectation questionnaire	X				
QLQ-C30	X			X	
BPI (short form)	X		X	X	
IGAC and PGAC	X			X	
APS and WPS[e]	X			X	X
Laboratory analysis[b]					
Aliquot of blood sample for genotyping purpose[a]	⟷				
Diary completion	⟷				
Compliance to diary completion		X	X	X	

Compliance to prescribed analgesic treatment[c]		X	X	X	
Analgesic treatment review	←	—	—	—	→
Questionnaires MHLCS, HADS, LOT-R, PCS		X			

Abbreviations:
APS = Average pain score; BPI = Brief Pain Inventory; DMA = dynamic mechanical allodynia; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; MPT= mechanical pain threshold; NPSI= Neuropathic Pain Symptom Inventory; MPA = Most Painful Area; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; SA= static allodynia; TPS= thermal pain sensitivity; WPS = Worst pain score.

[a] Aliquot of standard safety laboratory blood sample for genotyping is optional in this study (will be performed if patient gives his consent by signing the genotyping informed consent document). The aliquot can be taken at any time during the study.

[b] Potential historical safety laboratory data (biochemistry, hematology) defined as the most recent safety laboratory data obtained within one month before screening visit and/or standard safety laboratory analysis and urinalysis performed during the study as part of regular patient management by Investigator will be collected (one per week if several during the study).

[c] Compliance to prescribed analgesic treatment will be followed through diary completion and direct questioning.

[d] The Clinical pain assessments will include the following measurements: MPA, SA, DMA, MPT and TPS.

[e] APS and WPS will be collected in the diary. APS and WPS at visit 1A will be completed at site by patient with Investigator site staff help, if needed. The last APS and WPS will be completed by patients during the phone call with the Investigator. At Visit 1A, the Weekly APS during the preceeding week will be assessed for enrolment.

[f] Optional Intermediate Evaluation Visit will be organized within the next days after the intermediate phone call at the discretion of the Investigator.

16.3. ATTACHMENT 3 – LIST OF DEFINITIONS AND ABBREVIATIONS

Definitions

Assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some EC's).
Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, Sponsor's standard operating procedures, good clinical practices, and the applicable regulatory requirement(s).
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practices (GCP) requirements and the applicable regulatory requirements.
End of Study	End of study (study) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
EnrolL	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
Enter/Consent	The act of obtaining informed consent for participation in a clinical study from patients deemed- or potentially eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.
Ethics Committee	A board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ICD	Informed consent document: A Sponsor term used to describe (1) information regarding the trial for the patient, and (2) the document that the patient signs to indicate consent to participate in the clinical trial
Investigator	A physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Investigator is the responsible leader of the team and may be called the principal Investigator.
Legal representative	An individual or judicial or other body authoriZed under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
Patient	A study participant who has the disease or condition
Preliminary (interim) analysis	Any analysis intended at any time prior to the formal completion of a study.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves [invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws)]. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.

Abbreviations

AE	Adverse event
APS	Average Pain Score
BPI	Brief Pain Inventory
CIBP	Cancer-induced bone pain
CPAs	Clinical pain assessments
CRF	Case report form: a printed or electronic form for recording study subject/patients' data during a clinical study, as required by the protocol.
C-TPS	Cold-thermal pain sensitivity
DMA	Dynamic mechanical allodynia
DN4	Douleur Neuropathique en 4 questions
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic CRF
ESMO	European Society for Medical Oncology
GCP	Good clinical practice
HADS	Hospital Anxiety and Depression scale
H-TPS	Heat-thermal pain sensitivity
IASP	Internal Association for the Study of Pain
ICD	Informed consent document
IGAC	Investigator Global Assessment of Change
IMP	Investigational Medicinal Product
LOT	Life Orientation Test
LOT-R	Revised Life Orientation Test
MedDRA	Medical dictionary for regulatory activities
MHLCS	Multidimensional Health Locus of Control Scale
MPA	Most painful area
MPT	Mechanical pain threshold
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numeric Rating Scale
NSAID	Non-steroid anti-inflammatory drugs
PA	Painful area
PCA	Principal component analysis
PCS	Pain Catastrophizing Scale
PGAC	Patient Global Assessment of Change
QLQ	Quality-of-life questionnaire
QLQ-C30	Quality-of-life questionnaire in 30 questions
QoL	Quality-of-life
QST	Quantitative sensory testing
RANKL	Receptor activator of nuclear factor kappa β ligand
SA	Static allodynia
SAP	Statistical Analysis Plan
TPS	Thermal pain sensitivity
WAPS	Weekly Average Pain Score
WHO	World health organization
WPS	Worst pain score
XRT	External beam radiation therapy

16.4. ATTACHMENT 4 – PROTOCOL AMENDMENT SUMMARY

All modifications have been included in this attachment. All additions have been identified by the use of underline and all deletions by ~~strikethroughs~~.

1. SYNOPSIS

Study Duration	From screening to end of study, the study duration for each patient will be ~~up to approximately 9 weeks~~of a minimum of 5 weeks and a maximum of 12 weeks.
Objective	To define predictive factors of pain management/treatments efficacy in cancer patients with bone metastasis suffering from pain (or Cancer-Induced Bone Pain (CIBP)), based on individual patient disease, therapy history and personality traits.
Study Design	The study is an observational, multicentre clinical study that will be conducted in patients with CIBP requiring ~~either the initiation of~~ an analgesic treatment ~~or an adaptation of current analgesic treatment~~. Up to 180 patients will be enrolled and followed during ~~up to approximately 4 weeks~~ a period from 4 to 10 weeks of observation. All patients will continue to receive their cancer therapeutic treatments and will be treated for pain relief exactly as they would normally be by the Investigator based on patient needs and clinician practice. During their regular visits to the Investigator, patients will complete questionnaires and Clinical Pain Assessments (CPAs).
Main Diagnosis and Inclusion Criteria	• Are men or women of at least 18 years of age. • Patients with bone tumors or bone metastasis from any primary cancer origin that ~~is~~ are supported by histological or radiological investigations. • Patients having been or being treated for their bone metastasis and/or their primary cancer. • Patients who require ~~either the initiation or an adaptation of~~ analgesic treatment for unsatisfactory pain relief. • Patients will be required to have a score ~~>3 on the mean of daily Average Pain Scores (APS) during the baseline period preceeding Visit 2 and to have completed at least 4 days of pain assessments~~ of at least 4 on the weekly average pain score (WAPS) over the week preceeding enrolment.
Main Exclusion Criteria	• Patients having poor nutritional status or with unstable condition or who could be rapidly deteriorating in such a way that they would not be able to complete the study. • Patients having had a major surgery within 28 days prior to signing ICD or planning to have a major surgery during the study. • Life expectancy < 3 ~~6~~ months according to Investigator judgment. • Patients with a current or recent history unrelated to their cancer condition, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, h~~a~~ematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease which would interfere with the patient's participation in the study • Patients having at screening a Karnofsky performance status below 70% /or World Health Organization (WHO) score (Eastern Cooperative Oncology Group (ECOG)/Zubrod score) above 1.
Planned duration of observation	From ~~Up to approximately~~ 4 to 10 weeks
Studied procedures	
Safety data collection:	There will be no safety data collection per se as it is not an interventional study, nevertheless the following information will be collected to describe pre-existing patient condition: ~~a~~ relevant medical and primary disease history; primary disease treatment history; analgesic treatment history, if available, up

	to one month prior to study entry; abbreviated physical examination; ~~pain associated~~ symptoms related to analgesic treatment; most recent safety laboratory data if available, up to one month preceding screening visit and/or ongoing laboratory safety analysis and urine analysis, if available, performed as part of patient management by the Investigator.
Questionnaires:	Related to patient's personality such as Multidimensional Health Locus of Control Scale (MHLCS), Hospital Anxiety and Depression Scale (HADS), Revised Life Orientation Test (LOT-R) and Expectation. Related to pain disease such as Brief Pain Inventory (BPI), Douleur Neuropathique en 4 questions (DN4), Neuropathic Pain Symptom Inventory (NPSI), and Pain Catastrophizing Scale (PCS). Related to quality-of-Life: Quality-of-Life Questionnaire in 30 questions (QLQ-C30) ~~and Quality-of-Life Questionnaire for bone metastasis in 22 questions (QLQ-BM22)~~.
CPAs:	The Most Painful Area (MPA), Static Allodynia (SA), Dynamic Mechanical Allodynia (DMA), Mechanical Pain Threshold (MPT), Thermal Pain Sensitivity (TPS).
Diary:	The following information will be collected daily in the diary: APS and Worst Pain Score (WPS) for the past 24-hours, intake of ~~current and~~ additional to prescribed analgesic treatment (rescue analgesic treatment).
Study Evaluation Criteria and methods:	
Patient general health status	Symptoms related to ~~pain~~ analgesic treatment will be listed, and if the frequency of symptoms allows, they will be summarized using descriptive statistics.
Pharmacokinetic	Not applicable
Pharmacodynamic	Analysis of subjective changes from baseline of pain severity as measured by the weekly means of the daily APS and WPS, by Brief Pain Inventory (BPI), Investigator Global Assessment of Change (IGAC) and Patient Global Assessment of Change (PGAC), QLQ-C30 ~~and QLQ-BM22~~ will be performed. In addition, analysis of quantitative changes measured by MPA, SA, MDA, MPT and TPS will be performed and compared between enrolment Visit ~~2~~ and Visit 2 4. These tests will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon data review
Interim Analysis	A preliminary analysis will be scheduled after approximately ~~90~~ 60 patients complete the study

2.3 SECONDARY ENDPOINTS

Individual analgesic treatment efficacy outcomes:

- Patient's change from baseline of pain severity, as measured by the weekly means of the daily Worst Pain Score (WPS),
- Patient's change from baseline of pain severity and interference as measured by the Brief Pain Inventory (BPI),
- Patient's change from baseline of Investigator and Patient Global Assessment of Changes (IGAC and PGAC),
- Patient's change from baseline of pain intensity measured after Clinical Pain Assessments (CPAs) at Visit 4 2.
- Patient's change from baseline of Quality-of-Life Questionnaire in 30 questions (QLQ-C30) ~~and Quality of Life Questionnaire for bone metastasis in 22 questions (QLQ-BM22)~~.

3.2 INTRODUCTION - LITERATURE AND/OR DATA BACKGROUND

Short overview of CIBP treatments today – Application of ~~the World Health Organization~~ WHO

Today many therapies are available to lessen CIBP although they remain largely unsatisfactory.

4.1. DESCRIPTION OF STUDY DESIGN

This study will include up to 180 patients with bone tumor or metastasis from any primary cancer origin that are supported by histological or radiological investigations corresponding to CIBP.

~~At the screening visit, the Investigator will inquire individual patient's information to initiate or adjust their analgesic therapy.~~ Patients will be treated by the Investigators for pain relief exactly as they would normally be based on their needs and clinician practice. The enrolled patients must be requiring ~~either a new analgesic treatment or an adaptation of their current~~ analgesic treatment. ~~At each visit, the analgesic treatment may be adapted based upon patient's needs. Enrolled patients~~ They will be followed over a period ~~of up to approximately 4 weeks~~ from 4 to 10 weeks. ~~The analgesic treatment information will be collected throughout the entire study duration as well as patient general health status.~~ The analgesic treatment will be reviewed based upon patient's needs and patient general health status collected throughout the entire study.

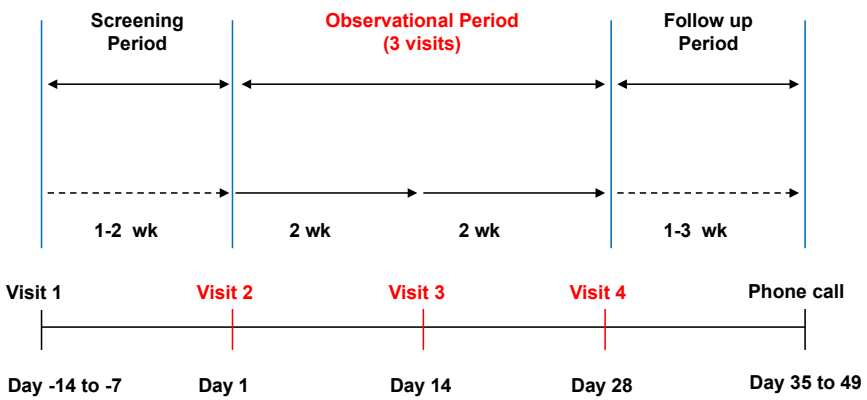
During the study, visits may be adapted according to Investigator-patients agreement, as presented in Section 8.5.4. Patients may also visit the Investigator as many times as required by their pain conditions.

Depending on patients/Investigator site availabilities, Visit 1 assessments may be performed in one visit (Visit 1) or 2 visits (Visit 1A and Visit 1B).

The design of the study for the 2 case scenarii is illustrated in Figure 1 ~~and the list of procedures to be administered at each visit in Section 16.1 Study Schedule~~.

Figure 1. Study Diagram herebelow was removed:

Overall Study :



Study Sequence:

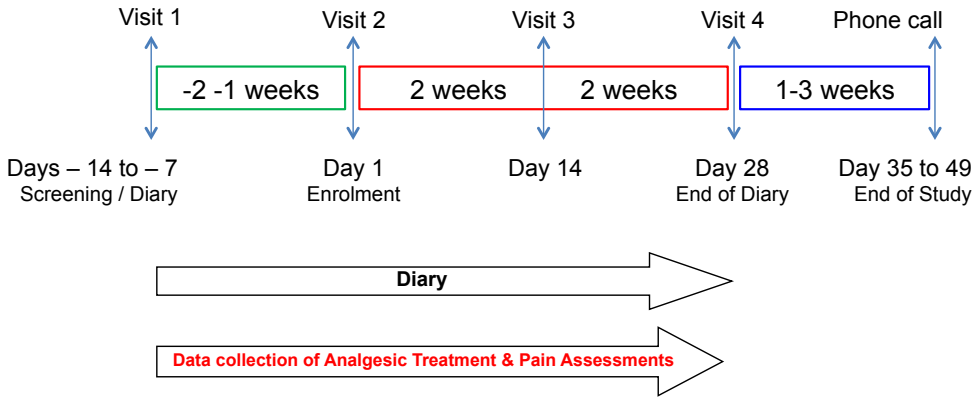


Figure 1. Study Diagram

And replaced by:

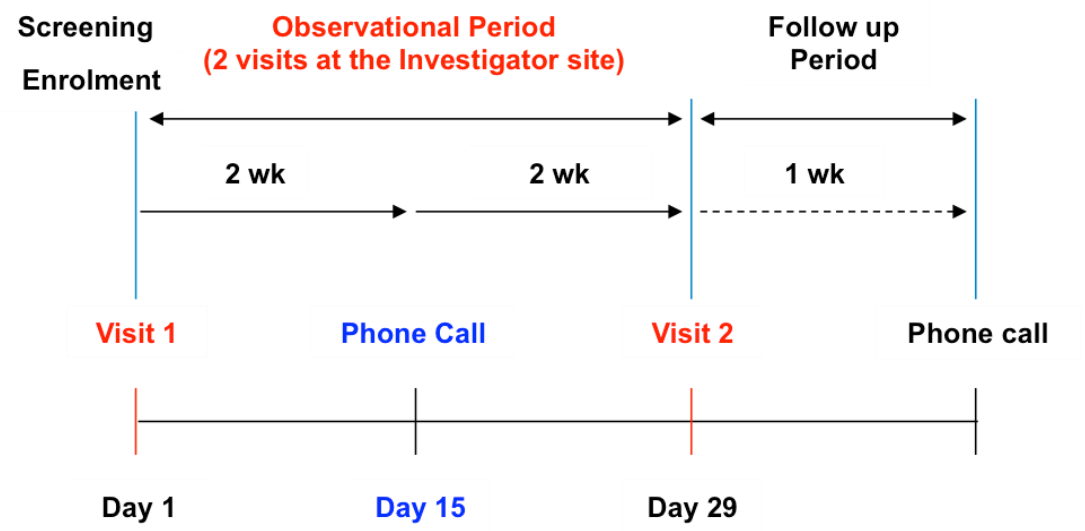


Figure 1'. Study Design when Visit 1 Assessments are Performed at the Same Visit/ Screening and Enrolment at Visit 1

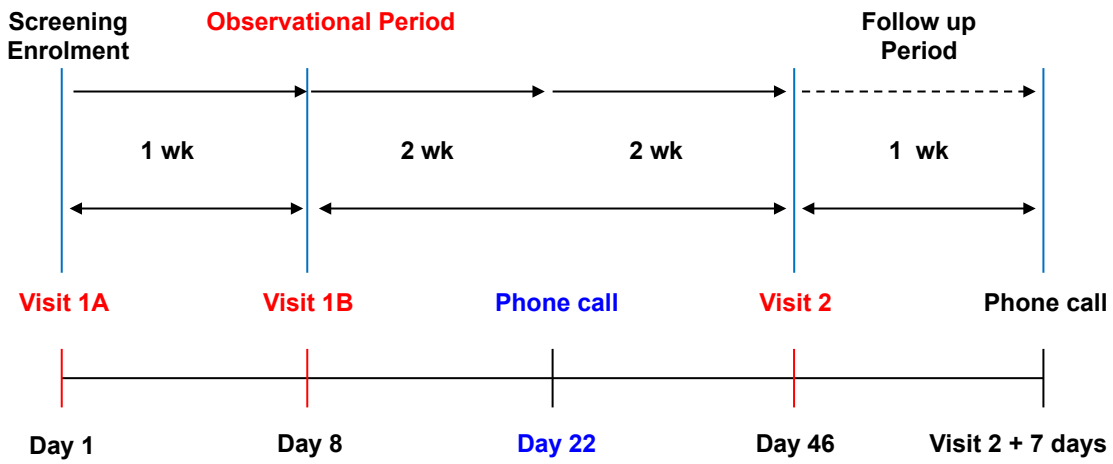


Figure 1". Study Design when Visit 1 Assessments are Performed in 2 Visits – Screening and Enrolment at Visit 1A

Figure 1. Study Diagram

Visit 1: Screening Visit

Screening period can last up to 2 weeks before enrolment into the study. At Visit 1, the study purpose will be explained to patients who will then sign and date the Informed Consent Document (ICD) before completing any study procedure. In addition, patients who consent to the use of their archived tumor tissue block, if any and/or to the use of an aliquot of standard safety laboratory blood sample for genotyping exploratory research will also sign a specific genotyping informed consent.

During this visit, patients' standard demographic (including body weight), medical and primary disease history, primary disease treatment history, analgesic treatment history up to one month prior to entry into the study, pain associated symptoms as well as concomitant therapies will be recorded. The Investigator will prescribe an initial analgesic therapy or adjust patient current analgesic therapy based upon his practice.

Patients will undergo a physical examination and complete personality traits and pain disease questionnaires. For a complete list of assessment procedures to be performed at Visit 1, see Study Schedule Section 16.1. Study Visit 1 is also depicted in Figure 2.

Patients will remain at the Investigator site for approximately 90 minutes at Visit 1.

At the end of this visit, the Investigator site staff will dispense a diary to patients and educate them on proper completion of the 2 pain scales, the APS and WPS on an 11-point NRS where 0 means no pain and 10, pain as bad as you can imagine. The APS will measure the average pain intensity over the last 24 hours; the WPS, the worst pain intensity over the last 24 hours. The APS and WPS of Visit 1 will be completed by the patients at site with investigator site staff help. The patients will also report in their diary intake of current and rescue analgesic treatment. As far as possible, patients should be compliant in completing their diaries until Visit 2 to be enrolled into the study.

The result of all assessments must be obtained and reviewed by the Investigator or his delegates at Visit 2. Patients who do not meet all entry criteria at Visit 2 will not be enrolled in the study.

Visit 2: Enrolment and Observation Visit

The observational period is a 4-week analgesic treatment therapy observation period including 3 visits. Ideally, visits at the Investigator site will occur every 2 weeks. However, visits may be adapted according to Investigator-patients agreement, as presented in Section 8.5.4 and patients may visit the Investigator as many times as required by their pain conditions.

Visit 2 will occur up to 1 or 2 weeks after the screening visit and will last approximately 90 minutes. After checking completion of the diary and all inclusion/exclusion criteria, patients will be enrolled in the study. Each patient will complete the BPI, QLQ-C30 and QLQ-BM22.

The Investigator will perform baseline assessments of CPAs. After patient evaluation, the Investigator will continue to prescribe the same analgesic treatment or will adapt the current analgesic treatment to be taken by the patient ideally for 2 weeks up to Visit 3. The patient and the Investigator will complete the PGAC and IGAC, respectively.

~~For a complete list of assessments to be performed at Visit 2, see Study Schedule Section 16.1. Visit 2 is also depicted in Figure 3.~~

~~Patients will continue to complete their diary between Visit 2 and Visit 3.~~

4.1.1. SCREENING AND ENROLMENT VISIT

FIRST CASE SCENARIO: SCREENING AND ENROLMENT AT VISIT 1

In this case scenario, all Visit 1 assessments are performed during only one visit, this visit will take place as described below.

First, the study purpose – including the optional genotyping research study - will be explained to patients who will then sign and date the Informed Consent Document (ICD) before completing any study procedure. In addition, patients who consent to take part in the genotyping exploratory research will also sign a specific genotyping ICD to allow the use of their archived tumor tissue block, if any and/or of an aliquot of standard safety laboratory blood sample.

Patients' WAPS will be collected and a value of at least 4 will be required to take part in the study. Patients' standard demographic, relevant medical and primary disease history, primary disease treatment history, analgesic treatment history up to one month prior to entry into the study, symptoms related to analgesic treatment, if any as well as cancer concomitant therapies will then be recorded. Patients will also undergo an abbreviated physical examination.

After checking completion of all inclusion/exclusion criteria, eligible patients will be enrolled in the study and perform the baseline Clinical Pain Assessments (CPAs). The following questionnaires will also be completed: pain disease questionnaires (DN4, NPSI and PCS), Brief Pain Inventory (BPI) questionnaire, expectation questionnaire, personality traits questionnaires (MHLCS, HADS and LOT-R) and quality of life questionnaire (Quality-of-Life Questionnaire in 30 questions (QLQ-C30)). The PGAC and IGAC will be completed by the patient and the Investigator, respectively.

At the end of the Visit and after patient evaluation, the Investigator will initiate or review as necessary the analgesic treatment and the patients will enter an observational period of approximately 4 weeks.

Before patients leave the site, Investigator site staff will dispense them a diary and educate them on proper completion of the 2 pain scales, the daily APS and WPS. The APS measures the average pain intensity over the last 24 hours; the WPS, the worst pain intensity over the last 24 hours, both on an 11-point Numeric Rating Scale (NRS) where 0 means no pain and 10, pain as bad as you can imagine. The APS and WPS of Visit 1 day will be completed by the patients at site with investigator site staff help. Between Visit 1 and Visit 2, the patients will also be asked to report in their diary intake of additional to prescribed analgesic treatment (rescue analgesic treatment), if any.

For a complete list of assessment procedures to be performed at Visit 1, see Study Schedule – Enrolment at Visit 1 - Section 16.1. Study Visit 1 is also depicted in Figure 2.

Patients will spend about 3 hours at the Investigator site during this visit.

SECOND CASE SCENARIO: VISIT 1 ASSESSMENTS PERFORMED IN 2 VISITS – SCREENING AND ENROLMENT AT VISIT 1A

In this case scenario, Visit 1A and Visit 1B will be organized as follows. Eligible patients will be enrolled into the study at Visit 1A (screening and enrolment visit) but a few defined questionnaires will be completed at Visit 1B one to four weeks after Visit 1A. For a complete list of assessment procedures to be performed at Visit 1A and Visit 1B, see Study Schedule – Enrolment at Visit 1A - Section 16.2.

Visit 1A: Screening and Enrolment

The assessments will be performed as described for Visit 1 in the first case scenario up to patient enrolment into the study. After checking WAPS and completion of all inclusion/exclusion criteria, eligible patients will be enrolled in the study and perform the CPAs. The following questionnaires will be completed during this visit: DN4, NPSI, BPI, Expectation and QLQ-C30. The PGAC and IGAC will be completed by the patient and the Investigator, respectively.

At the end of the Visit and after patient evaluation, the Investigator will initiate or review the analgesic treatment and the patients will enter an observational period of 5 to 10 weeks depending on when Visit 1B is scheduled.

Before patients leave the site, Investigator site staff will dispense them a diary and educate them on proper completion of the 2 pain scales, the daily APS and WPS. The APS and WPS of Visit 1A day will be completed by the patients at site with Investigator site staff help. Between Visit 1A and Visit 2, the patients will also be asked to report in their diary intake of supplemental analgesic treatment (rescue analgesic treatment), if any.

Study Visit 1A is depicted in Figure 3.

During this visit, patients will spend about 2 hours at Investigator site.

Visit 1B

This visit will start with checking compliance to prescribed analgesic treatment and diary completion instructions. MHLCS, HADS, LOT-R questionnaires and PCS questionnaire will then be completed by the patients. The Investigator will review the analgesic treatment.

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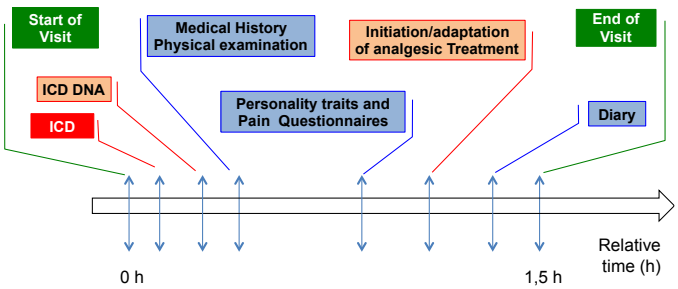
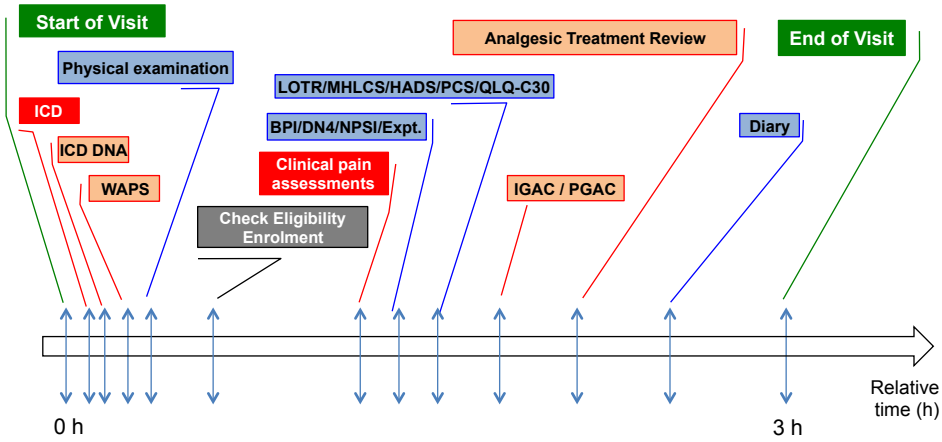


Abbreviations: ICD= Informed Consent Document; ICD DNA= Informed Consent Document for genotyping research

Figure 2. Scheme of Visit 1

And replaced by:



Abbreviations: BPI = Brief Pain Inventory; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; ICD= Informed Consent Document; ICD DNA= Informed Consent Document for genotyping research; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; NPSI= Neuropathic Pain Symptom Inventory; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; WAPS: Weekly Average Pain Score

Figure 2. Sequence of Assessments at Visit 1

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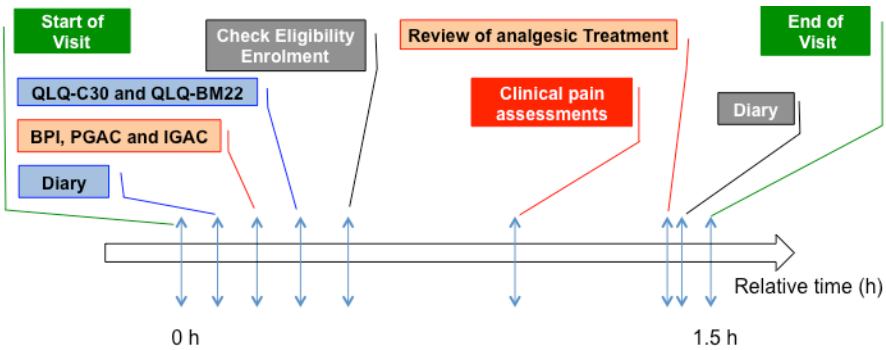

Abbreviations: BPI = Brief Pain Inventory; IGAC = Investigator Global Assessment of Changes ; PGAC= Patient Global Assessment of Changes; QLQ-C30 = Quality-of-Life Questionnaire in 30 questions; QLQ-BM22 = Quality-of-Life Questionnaire in 22 questions in bone metastasis

Figure 3. Scheme of Visit 2

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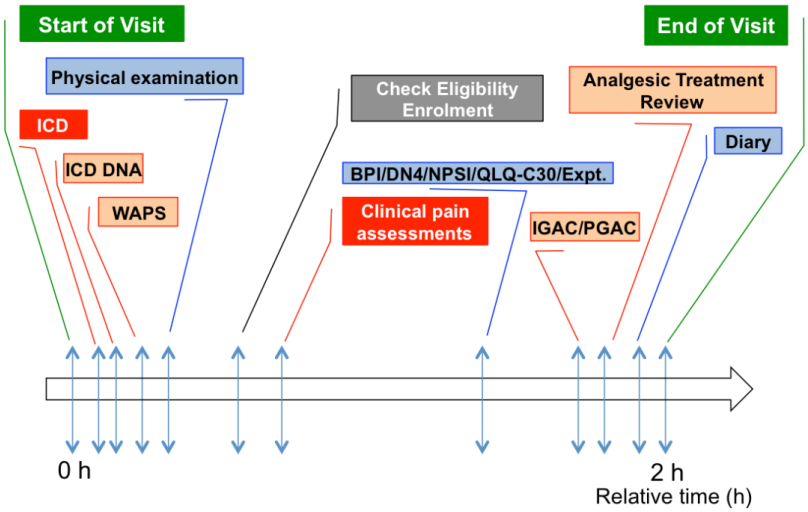

Abbreviations: BPI = Brief Pain Inventory; DN4= Douleur Neuropathique en 4 questions; ICD= Informed Consent Document; ICD DNA= Informed Consent Document for genotyping research; IGAC=Investigator Global Assessment of Changes; NPSI= Neuropathic Pain Symptom Inventory; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; WAPS: Weekly Average Pain Score

Figure 3. Sequence of Assessments at Visit 1A

~~Visit 3 and Visit 4: Observational Visits and Follow-up Visit~~

~~Approximately 2 weeks after Visit 2, Visit 3 will start with collection of the diary and checking compliance to analgesic treatment and diary completion. All patients will complete BPI and QLQ-30 and go through all CPAs as at Visit 2 as described in Figure 4. At the end of Visit 3, the patient will be prescribed the same analgesic treatment therapy or an adapted therapy for 2 weeks up to Visit 4. Between Visits 3 and 4, patients will continue to complete their diary.~~

~~The last observational visit, Visit 4, will take place approximately 2 weeks after Visit 3. Compliance to analgesic treatment and diary completion will be checked. Thereafter BPI, IGAC, PGAC as well as the 2 QoL questionnaires will be completed. In addition, patients will undergo an abbreviated physical examination and the last CPAs. At the end of Visit 4, the Investigator may adapt the analgesic treatment therapy based on patient needs.~~

~~Patients will remain at the Investigator site for approximately 1 hour at Visits 3 and 4.~~

4.1.2. Observational Period – Intermediate Phone Call

The observational period is a 4- to 10-week analgesic treatment therapy period including a phone call scheduled approximately 2 weeks after Visit 1 or Visit 1B (See figure 1. Study Diagram).

During this phone call, the Investigator site staff will inquire about patient general health status and pain relief. The patient will be reminded about Visit 2 scheduled date, diary and prescribed analgesic treatment compliance. At the end of the phone call, an

intermediate visit to Investigator site may be organized within the next days at the discretion of Investigator.

If organized, this visit will start with collection of the diary, checking compliance to diary completion instructions and to prescribed analgesic treatment. Patient will complete BPI and go through all CPAs. At the end of this optional visit, the Investigator will review the analgesic treatment. Patients will continue to complete a diary up to Visit 2.

For a complete list of assessments to be performed at Intermediate Evaluation Visit , see Study Schedule Sections 16.1. and 16.2. This optional visit is also depicted in Figure 4.

At this visit, patients will remain at the Investigator site for approximately 1 hour.

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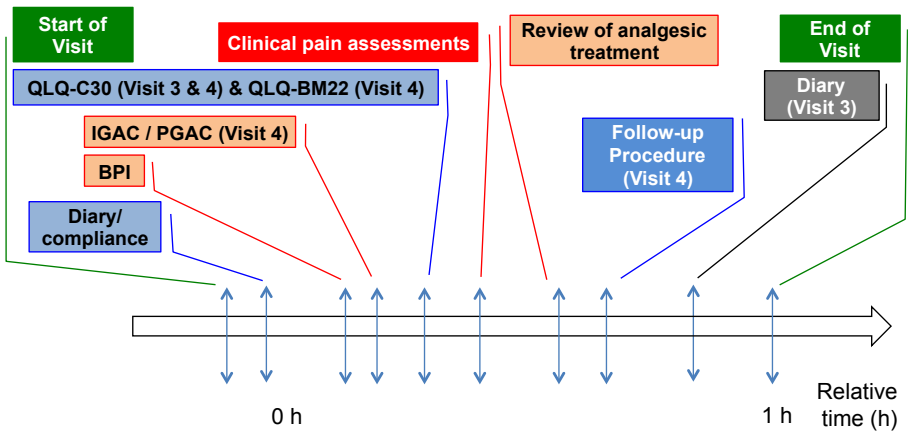

Abbreviations: BPI = Brief pain Inventory; IGAC = Investigator Global Assessment of Changes ; PGAC= Patient Global Assessment of Changes; QLQ-C30 = Quality-of-Life Questionnaire in 30 questions; QLQ-BM22 = Quality-of-Life Questionnaire in 22 questions in bone metastasis

Figure 4. Scheme of Visit 3 and Visit 4

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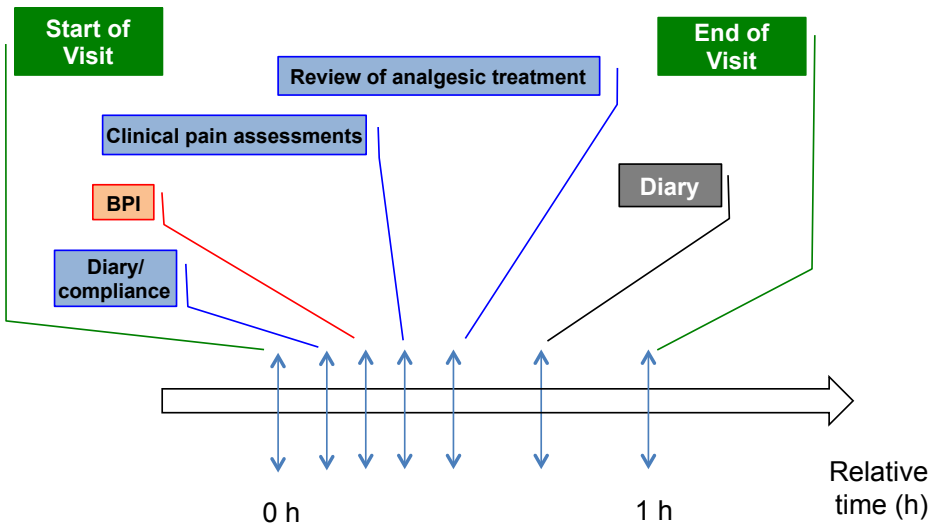


Abbreviations: BPI = Brief Pain Inventory

Figure 4. Sequence of Assessments at Intermediate Evaluation Visit

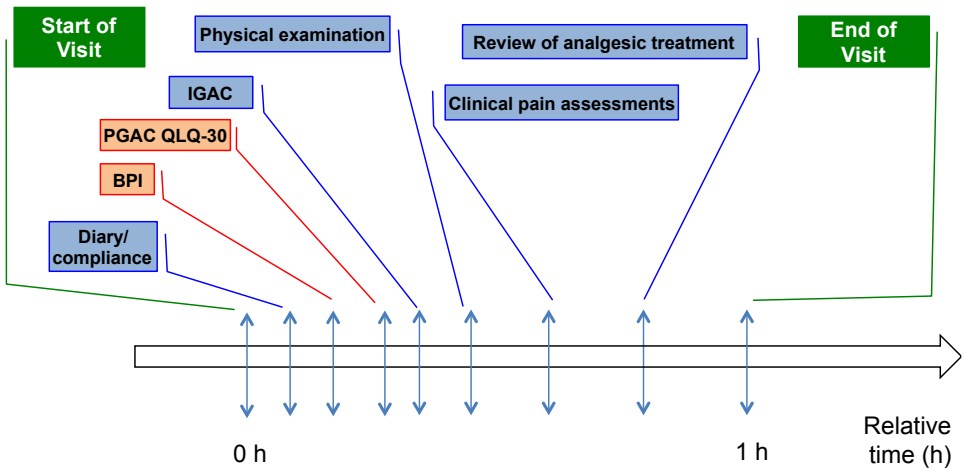
4.1.3. VISIT 2: END OF OBSERVATIONAL PERIOD AND FOLLOW-UP VISIT

Approximately 4 weeks after Visit 1 or Visit 1B (depending on the case scenario selected to complete Visit 1 assessments), Visit 2 will start with collecting the diary, checking compliance to diary completion instructions. All patients will complete BPI, PGAC and QLQ-30, while Investigator will complete IGAC as described in Figure 5. In addition, patients will undergo an abbreviated physical examination and the last CPAs. At the end of Visit 2, the Investigator will review patients analgesic treatment therapy.

For a complete list of assessments to be performed at Visit 2, see Study Schedule Sections 16.1. and 16.2.

Patients will remain at the Investigator site for approximately 1 hour at Visit 2.

Figure 5 herebelow was added:



Abbreviations: BPI = Brief pain Inventory; IGAC = Investigator Global Assessment of Changes ; PGAC= Patient Global Assessment of Changes; QLQ-C30 = Quality-of-Life Questionnaire in 30 questions.

Figure 5. Sequence of Assessments at Visit 2

Phone Call: End of Data Collection

A phone call will take place approximately 1 week after Visit 2 ~~between 1 and 3 weeks after Visit~~ 4. Patients will ~~complete~~ provide their last APS and WPS and give information on their current analgesic treatment. This phone call will last less than 10 minutes.

4.2.2. JUSTIFICATION FOR STUDY DESIGN

This study is an observational study. This design has been selected to collect data of analgesic treatment that would reduce pain severity after 4 to 10 weeks of analgesic treatment administration to patients.

~~The initial screening period of 1 to 2 weeks is designed to ensure that the patients meet the eligibility criteria, including diagnosis and ability to complete daily a diary. In addition, it allows the collection of patient's disease history including individual pain characteristics and patients' personality traits. The chosen trial design and interval of two weeks between observational visits is chosen to reflect the interval between regular visits of~~

~~patient to their physician. Two weeks of treatment is a reasonable period of time to assess the effect of an analgesic treatment.~~

4.2.3. INTERIM ANALYSIS

An interim analysis is planned after study completion of approximately ~~90~~ 60 patients. Its main objective is to confirm the considered sample size of approximately 140 patients completing this study. Its secondary objectives will be to confirm questionnaires and historical data to be collected.

5.1. DEFINITIONS

Patient Enrolment:

A patient is considered as enrolled in the study when he/she meets all eligibility criteria and he/she performs CPAs at Visit ~~2~~1 or Visit 1A.

5.2. POPULATION RECRUITMENT

As illustrated in Sections 16.1 and 16.2 Study Schedule, eligibility of patients in the study will be based on the results of a screening visit.

5.3. INCLUSION DISEASE CRITERIA

Patients are eligible to be included into the study if they meet all of the following CIBP disease diagnosis criteria:

[1] Patients with bone tumors or bone metastasis from any primary cancer origin that is supported by histological or radiological investigations.

[2] Patients having been or being treated for their bone metastasis and/or their primary cancer.

[3] Patients who require ~~either initiation or adaptation of~~ analgesic treatment for unsatisfactory pain relief.

[4] Patients will be required to score ~~>3 on the mean of daily APS~~ at least 4 on the WAPS 11-point NRS during the ~~baseline period preceding Visit 2 and to have completed at least 4 days of pain assessments~~ week preceeding enrolment.

[5] Patients undergoing or not a radiotherapy program provided visit procedures ~~being~~ are performed before any radiotherapy sessions if scheduled on the same visit days.

5.5. EXCLUSION DISEASE CRITERIA

Patients will be excluded from the study if they meet any of the following criteria related to CIBP:

[1] Patients having had a major surgery within 28 days prior to signing ICD or planning to have a major surgery during the study.

[2] ~~Life~~ Patients having a life expectancy < 3 ~~6~~ months according to Investigator judgment.

5.6. EXCLUSION CRITERIA

Potential study patients may not be entered into the study if they meet any of the following criteria:

[3] Patients having poor nutritional status or whose condition is unstable or who could be rapidly deteriorating in such a way that they would not be able to complete the study.

[4] Patients with a current or recent history unrelated to their cancer condition, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease which would interfere with the patient's participation in the study.

[5] Patients having a Karnofsky performance status below 70% or WHO score (Eastern Cooperative Oncology Group (ECOG)/Zubrod score) above 1.

[6] Are Investigator site staffs directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[7] Any other relevant medical disorder likely to interfere with the trial or represent a risk for the patient.

[8] Patients under legal protection, according to the country law.

[9] Patients currently enrolled in a clinical trial involving use of an investigational drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or in an exclusion period according to the national law.

5.8.2. FOLLOW-UP PROCEDURES FOR DROP-OUT PATIENTS

In case a patient enrolled in the study drops out or is discontinued from the study earlier than study end, he/she ~~should follow an~~ will answer a few questions by phone as indicated in the early discontinuation ~~visit~~ phone call ~~as~~ described in Sections 16.1 and 16.2 Study Schedule. The reason and date for dropout should be documented.

5.11. DISCONTINUATION OF STUDY

The study can be discontinued prematurely at any time if the Sponsor judges it necessary for any reason. In that case, all scheduled procedures and/or procedures of early discontinuation ~~visit~~ phone call will be performed.

6.3. CONCOMITTANT THERAPY

All analgesic medication taken over the last month preceding enrolment ~~Visit 1, concomitant~~ and primary disease medication will be recorded on the Case Report Form (CRF). Any investigational drug taken over the previous year will also be recorded.

7.1. STUDY PATIENT MANAGEMENT AND REQUIREMENTS

The patients will be required to attend the Investigator site at the following ~~on several~~ occasions: at screening ~~(Visit1), during observational period at Visits 2, 3 and~~

4/enrolment, Visit 2, optional Visit 1B and intermediate evaluation Visit. The patients will be discharged from the study at Visit 42.

Throughout the study, patients may undergo medical assessments and review of compliance with restrictions before continuing in the study. ~~Patients should continue to meet the eligibility criteria including restrictions described in Section 7.2.~~

7.2. STUDY RESTRICTIONS

Medications

During the study and in addition to their current analgesic treatment, patients will be permitted to supplement their analgesic treatment with rescue analgesic drugs (named rescue medication). Type and dose regimen of these rescue medications will be left at the discretion of Investigator. ~~Ideally, the rescue medication should be as much as possible refrained within 24 hours before Visits 2, 3 and 4.~~

7.2.2.1. Diary

Once a day from enrolment ~~Visit 1~~ till Visit 4 2, approximately at the same time of the day in the evening, patients will complete their diary.

The following data will be recorded:

- pain intensity assessment by recording APS and WPS for the last 24 hours (from ~~Visit 1~~enrolment till Visit 42 or early discontinuation). See Sections 8.2.4.4 and 8.2.4.5 for further description of APS and WPS,
- any potential event that may help to understand unexpected study outcomes,
- intake of ~~current and~~ rescue analgesic treatment if any (from ~~Visit 1~~enrolment to Visit 42 or early discontinuation).

8. STUDY ASSESSMENTS

Timing of assessments is specified in Sections 16.1 and 16.2 Study Schedule.

8.2.1. CLINICAL PAIN ASSESSMENTS (CPAS)

The following CPAs will be performed at ~~Visits 2, 3 and 4 or at early discontinuation if possible~~ enrolment, at Visit 2 and at optional intermediate evaluation Visit as specified in Sections 16.1 and 16.2 Study Schedule.

First, the painful areas (PA) will be defined by patients, using a standardized blank ~~pain drawing~~ body map. CPAs will then be carried out by the Investigator or his/her designee on the skin overlying the most painful area ~~of CIBP~~ (MPA) reported by the patient. The control area to compare to would be the equivalent dermatome region on the contralateral side of the body, or for central spinal sites an alternative non-painful area at the spinal level. This control area site will be defined as “normal”.

If the MPA is different at the next visit from the previous one, all assessments will be performed on the current MPA first and then again on the previous visit MPA. However, in the case scenario of the MPA at Visit 2 is different from both the one identified at

intermediate evaluation Visit and the other at enrolment, only MPA defined as such at previous visit (intermediate evaluation) and at this current Visit 2 will be assessed.

Regarding ~~painful area~~ MPA, clinical signs are identified as follows:

- Hypoesthesia is defined as the presence of an area where light touch of the blunt end of a paintbrush is felt less precisely than in referent control areas.
- Sensory loss is defined as the presence of an area where the same light touch as referred above is not felt at all.
- Hyperalgesia is defined as the presence of an area where the pain induced by stimulus applied perpendicularly to the skin is felt abnormally intensely.
- Allodynia is defined as the presence of an area of pain after the application of non-painful stimulus.

~~The control area would be the equivalent dermatome region on the contralateral side of the body, or for central spinal sites an alternative non-painful spinal level. This control area site will be defined as "normal".~~

The centre of an area with allodynia or hyperalgesia is considered for further evaluation. However, in the absence of allodynia and hyperalgesia the centre of the area of hypoesthesia or sensory loss is then considered.

All CPAs will be carried out in a quiet environment, with a relaxed patient, previously instructed on the procedure. If a test provoked pain, the Investigator will wait for pain disappearance before proceeding with the next test. All CPAs will be completed within approximately 20 minutes.

The CPAs will include the following parameters:

The Most Painful Area (MPA)

The MPA will be mapped ~~in~~ on a standardized ~~pain drawing~~ body map. ~~It will be marked out on the skin if there is abnormal sensation. The area of abnormal sensation is measured using tracing paper (recorder in mm^2) or alternative methods. If photography is performed, it should be done in such a way patient identity is always concealed.~~The area with abnormal sensation will be delimited with a dermographic pencil and a picture of it will be taken in such a way the MPA surface can be calculated. Patient identity must always be concealed when taking the photography. Further instructions will be given in a dedicated manual.

Static Allodynia (SA)

SA will be assessed using a standardized calibrated ~~vVon~~ Frey hair number 13 (5,1~~8~~g) (or equivalent device) at the centre of both painful and control areas. The patient will be asked to describe this sensation compared with the control area (hyperesthesia, hypoesthesia or unchanged) and, if painful, to rate the pain on an 11-point NRS.

Dynamic Mechanical Allodynia (DMA)

DMA will be assessed using a standardized calibrated brush (~~Senselab 0,5 mN~~SENSELab Brush-05, Somedic ~~Sweden~~or equivalent device) ~~where~~. 3 successive gentle strokes will be performed over a 40mm length of skin bilaterally at interval of 1 second interval. The patient will be asked to describe this sensation compared with the

control area (hyperesthesia, hypoesthesia or unchanged) and, if painful, to rate the pain on an 11-point NRS.

Mechanical Pain Threshold (MPT)

MPT will be assessed with a series of ~~17~~ 7 von Frey monofilaments (SENSELab von Frey Aesthesiometer II, Somedic or equivalent device) of varying thickness, calibrated according to the force required to make them bend. The force of the stimulus becoming painful is recorded. This assessment is conducted one time on the control area but repeated 3 times on the affected area. Suprathreshold level may be measured in both the control area and MPA using the strongest von Frey hair number 16 ~~with a force of 137 g/mm^2~~ and will be rated with an 11-point NRS.

8.2.2. PERSONALITY EVALUATIONS

~~The following personality tests will be performed at screening: Multidimensional Health Locus of Control Scale (MHLCS), Hospital Anxiety and Depression Scale (HADS), Revised Life Orientation Test (LOT-R)) and Expectation.~~

The following personality questionnaires will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.3. PAIN DISEASE EVALUATION

~~The following evaluation will be performed at screening.~~

The following evaluations will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.4. PAIN EVALUATIONS

The following pain evaluations will be collected at the times specified in Sections 16.1 and 16.2 Study Schedule.

8.2.4.4. Average Pain Score (APS)

The APS will measure the average pain intensity over the last 24 hours by asking the patient "Could you please indicate us how was your average pain during the last 24 hours? For this, circle the most descriptive number on this scale." The patient will be asked to rate it on an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as you can imagine). However, before being enrolled into the study, the patient will be asked an APS over the past week (WAPS).

8.2.5. ~~QUALITY-OF-LIFE QUESTIONNAIRES (QLQ)~~ QUALITY-OF-LIFE QUESTIONNAIRE IN 30 QUESTIONS (QLQ-C30)

~~The following QLQ will be completed at Visit 2, Visit 3 (only QLQ-30) and at Visit 4 or at early discontinuation as specified in Section 16.1 Study Schedule.~~

~~8.2.5.1 Quality-of-Life Questionnaire in 30 questions (QLQ-C30)~~

The health related quality-of-life in cancer patient will be measured with the Quality-of-Life Questionnaire-C30 (QLQ-C30; Copyright © 2002 EORTC Quality-of-Life Group). This core questionnaire contains 30 items divided into functional scales, symptom scales, single items and global quality-of-life. It will be completed at enrolment and at Visit 2 as specified in Sections 16.1 and 16.2 Study Schedule

~~**8.2.5.2 Quality-of-Life Questionnaire for Bone Metastasis (QLQ-BM22)**~~

~~To assess specific disease sites, symptoms and/or treatment-related quality-of-life issues related to bone metastasis; the QLQ-C30 will be supplemented with QLQ-BM22 (Chow et al. 2009). QLQ-BM22 contains 22 items, conceptualized into both symptom scales (five painful sites and three pain characteristics) and functional scales (eight functional interference and six psychosocial aspects).~~

8.3. INFORMATION ON GENERAL HEALTH STATUS

In addition to records of observations made at specific times, ~~unexpected signs and pain associated~~ symptoms related to analgesic treatment will be recorded in the clinical study records throughout the study.

The following parameters will be collected during this study at specific timepoints as described in the Study Schedule (Sections 16.1 and 16.2):

- ~~Pain associated~~ ~~S~~symptoms related to pain treatment (e.g. nausea).
- Potential historical laboratory analysis data (biochemistry and hematology data) defined as the most recent safety laboratory analysis obtained within one month before the screening and/or ongoing laboratory safety analysis and urine analysis, if available, performed as part of patient management by the Investigator. In case several safety laboratory analysis are performed during the study, only one per week will be recorded.
- ~~Physical examination (at screening visit) and a~~Abbreviate physical examination ~~(~~at ~~Visit 4 or early discontinuation visit)~~ screening Visit and Visit 2.
- ~~Body weight (at screening)~~

8.3.1 SYMPTOMS MONITORING

Symptoms Collection and Reporting

At ~~visit~~enrolment, study site personnel will record the occurrence, time of onset, nature and severity of ~~each patient pre-existing conditions and~~ symptoms related to ~~pain~~analgesic treatment. ~~After the ICD is signed,~~ Up to Visit 2~~4~~, site personnel will record any change in the occurrence and nature of symptoms related to ~~pain condition~~ analgesic treatment or having an impact on pain evaluation. The nature, time of onset, duration, severity will be documented and each symptom will be classified by the most suitable term from a version of a Medical Dictionary for Regulatory Activities (MedDRA) agreed by the Sponsor and other parties involved in the study.

The condition of each patient will be monitored throughout the study. In addition, any sign or symptom related to pain treatment will be observed and elicited at least at each visit by open questioning, such as “How have you been feeling since you were last asked?”

8.3.2. SERIOUS ADVERSE EVENT AND REPORTING

Not applicable~~. As this is an~~ (observational study)~~ all serious symptoms that will occur during the observational period will only be reported in the final study report~~. Nevertheless, if a patient is withdrawn from the study because of an SAE, this information will be collected.

8.4. STUDY PROCEDURE PRIORITY ORDER

Figures 2~~, 3 and 4~~ to 5 in Section 4.1 are describing the sequence of procedures at each visit.

8.5.2. COMPLIANCE TO TIMING OF PROCEDURES

The Investigator should make a reasonable attempt to complete the scheduled study procedures on the appropriate scheduled visit and in the appropriate sequence.

The specifications in this protocol for the sequence of procedures are given as targets~~,~~ to be achieved ~~within reasonable limites~~ if possible.

It is recognized ~~,however,~~ that deviations may occur for logistic or other reasons and will not be considered as protocol violations. The scheduled timepoints may be subject to ~~minor~~ alterations; however, the actual time must always be correctly recorded in the CRF, diary or other documents.

8.5.3. COMPLIANCE TO ANALGESIC PATIENT 'S THERAPY

Patient's compliance ~~with~~ to prescribed analgesic medication will be assessed at each visit by direct questioning and checking diary. The investigator will evaluate if patient fails to take more than 50% of the prescribed analgesic medication for the visit interval.

~~A patient will be considered as non-compliant if he/she fails to take the prescribed analgesic medication for more than 50% of the prescribed dose in a visit interval. A patient will be considered significantly non-compliant if he/she is judged by the Investigator to have repeatedly (for 2 visit intervals) taken less than 50 % of the prescribed amount of medication. As a result, significantly non-compliant patients may be discontinued from the study.~~

8.5.4. COMPLIANCE TO STUDY VISITS

Depending on patient general health status, visits to the Investigator site ~~will~~ may occur ~~approximately every 2~~ after enrolment at interval of 2 or 4 weeks. ~~However, visits may~~Visits schedule can be adapted according to Investigator-patients agreement, as presented in Tables 1 and 2.

Table 1 herebelow was removed:

Table 1. Study Visits with Allowed and Suggested Time Intervals

Visit Number	Time Interval (Days)	
	Suggested	Allowed
Visit 1	-7 to -14 days	-5 to -16 days
Visit 2	Day 1	Day 1
Visit 3	14 days	10 to 18 days
Visit 4	28 days	24 to 32 days
Phone Call	35 to 49 days	33 to 51days

And replaced by:

Table 1. Study Visits with Allowed and Suggested Time Intervals – First Case Scenario – Enrolment at Visit 1

Visit Number	Time Interval (Days)	
	Suggested	Allowed
Visit 1 (Screening and Enrolment)	Day 1	
Intermediate Phone Call	Day 15	Day 13 to 17
Optional intermediate evaluation Visit	Day 15	Day 13 to 19
Visit 2	Day 29	Day 29 to 43
Phone Call	Visit 2 Day + 7 days	Visit 2 Day + 14 days

Table 2 herebelow was added:

Table 2. Study Visits if with Allowed and Suggested Time Intervals – Second Case Scenario – Enrolment at Visit 1A

Visit Number	Time Interval (Days)	
	Suggested	Allowed
Visit 1A (Screening and Enrolment)	Day 1	
Visit 1B	Day 8	8 to 29 days
Intermediate Phone Call	Visit 1B Day + 14 days	Visit 1B Day + 12 to 16 days
Optional intermediate evaluation Visit	Visit 1B Day + 14 days	Visit 1B Day + 12 to 18 days
Visit 2	Visit 1B Day + 28 days	Visit 1B day + 28 to 42 days
Phone Call	Visit 2 Day + 7 days	Visit 2 Day + 14 days

8.5.5. COMPLIANCE TO DIARY COMPLETION

Compliance to diary completion (APS, WPS, ~~current and~~ rescue analgesic treatment recording) will be checked by Investigator at each visit ~~Visits 2, 3, 4 and early discontinuation~~ at Investigator site.

10.1.1.1. Analysis Populations

A special set of features – the target features – characterize the analgesic efficacy and are defined as follows:

- APS difference with respect to baseline (primary endpoint)
- WPS difference with respect to baseline (secondary endpoints)
- BPI difference with respect to baseline (secondary endpoints)

- IGAC difference with respect to baseline (secondary endpoints)
- PGAC difference with respect to baseline (secondary endpoints)
- QLQ-C30 ~~and QLQ-BM22~~ with respect to baseline (secondary endpoints)
- CPAs difference with respect to baseline (secondary endpoints)

10.1.4. STUDY PARTICIPANT CHARACTERISTICS

The patient's age, sex~~, weight~~ or other demographic characteristics will be recorded and may be used in the pharmacodynamic analyses as quantitative or classification variables.

10.1.5. STATISTICAL EVALUATION OF SYMPTOMS

All prescribed analgesic treatment, analgesic recue medication and symptoms related to pain treatment will be listed, and if the frequency of symptoms allows, they will be summarized using descriptive procedure.

Section 16.1. Attachment 1 – Study Schedule on next page was removed :

16.1 ATTACHMENT 1 – STUDY SCHEDULE

	Screening Period	Observation Period			Phone Call	Early Discontinuation
Visit	**1**	**2**	**3**	**4**		
Days	**-14 to -7 (+/-2 days)**	**Day 1**	**Day 14 (+/- 4 days)**	**Day 28 (+/- 4 days)**	**Day 35 to 49 (+/-2 days)**	
Informed Consent (general and genotyping)[a]	X					
Demographics (including body weight)	X					
Physical examination	X			X[b]		X[b]
Primary disease (anamnesis) and Medical History	X					
Primary disease treatment history	X					
Analgesic treatment history (within one month prior to study entry)	X					
Pre-existing Conditions/Pain associated symptoms	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Personality trait questionnaires[d]	X					
DN4, NPSI and PCS (Pain disease evaluation)	X					
QLQ-C30 and QLQ-BM22		X	X[e]	X		X
Inclusion/Exclusion Criteria		X				
Enrolment into study		X				
Laboratory analysis[c]						
Aliquot of standard safety laboratory blood sample for genotyping purpose[a]		←	—	→		
Diary completion	←	—	—	→		
Compliance to diary completion		X	X	X		X
Analgesic treatment review	←	—	—	—	—	→
Compliance to prescribed analgesic treatment[f]		X	X	X		X
Clinical Pain Assessments[g]		X	X	X		X
Pain evaluation questionnaires:						
APS and WPS[h]	X				X	X
BPI (short form)		X	X	X		X
IGAC and PGAC		X		X		X

Abbreviations:
APS = Average pain score; BPI = Brief Pain Inventory; DMA = dynamic mechanical allodynia; DN4= Douleur Neuropathique en 4 questions; IGAC=Investigator Global Assessment of Changes; MPT= mechanical pain threshold; NPSI= Neuropathic Pain Symptom Inventory; PA = painful area; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; QLQ-BM22 = quality-of-life questionnaire in 22 questions in bone metastasis; SA= static allodynia; TPS= thermal pain sensitivity; WPS = Worst pain score.

[a] Aliquot of standard safety laboratory blood sample for genotyping is optional in this study (will be performed if patient gives his consent by signing the genotyping informed consent document). The aliquot can be taken at any time between Visit 2 and 4

[b] Abbreviated physical examination

[c] Potential historical safety laboratory data (biochemistry, hematology) defined as the most recent safety laboratory data obtained within one month before screening visit and/or standard safety laboratory analysis and urinalysis performed during the study as part of regular patient management by Investigator will be collected

[d] Multidimensional Health Locus of Control Scale (MHLCS), Hospital Anxiety and Depression Scale (HADS), Revised Life Orientation Test (LOT-R) and Expectation questionnaire.

[e] Only QLQ-C30.

[f] Compliance to prescribed analgesic treatment will be followed through diary completion and direct questioning.

[g] The Clinical pain assessments will include the following measurements: PA, SA, DMA, MPT and TPS.

[h] APS and WPS will be collected in the diary. APS and WPS at visit 1 will be completed at site by patient with Investigator site staff help, if needed. The last APS and WPS will be completed by patients during the phone call with the Investigator.

And replaced by Section 16.1. Attachment 1 – Study Schedule – Enrolment at Visit 1 on next page

16.1 ATTACHEMENT 1 - STUDY SCHEDULE – ENROLMENT AT VISIT 1

	Screening Enrolment	Observational Period		Follow Up / Early Discontinuation Phone Call
Visit	**1**	**Optional Intermediate Evaluation** [f]	**2**	
Days	**Day 1**	**Day 15 (- 2/+ 4 days)**	**Day 29 (+ 14 days)**	**7 days after Visit 2 (+ 7 days)**
Informed Consent (general and genotyping)[a]	X			
Demographics	X			
Abbreviated Physical examination	X		X	
Primary disease and Relevant Medical History	X			
Primary disease treatment history	X			
Analgesic history (within 1 month before enrolment)	X			
Pre-existing Conditions/Symptoms related to pain treatment	X	X	X	X
Cancer Concomitant Medications	X	X	X	X
Personality trait questionnaires: MHLCS, HADS, LOT-R and Expectation questionnaire	X			
DN4, NPSI and PCS (Pain disease evaluation)	X			
QLQ-C30	X		X	
Inclusion/Exclusion Criteria	X			
Enrolment into study	X			
Safety Laboratory Analysis[b]				
Aliquot of blood sample for genotyping purpose[a]	←	→		
Diary completion	←	→		
Compliance to diary completion		X	X	
Analgesic treatment review	←	→		
Compliance to prescribed analgesic treatment[c]		X	X	
Clinical Pain Assessments[d]	X	X	X	
APS and WPS[e]	X		X	X
BPI (short form)	X	X	X	
IGAC and PGAC	X		X	

Abbreviations:
APS = Average pain score; BPI = Brief Pain Inventory; DMA = dynamic mechanical allodynia; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; MPT= mechanical pain threshold; NPSI= Neuropathic Pain Symptom Inventory; MPA = Most Painful Area; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; SA= static allodynia; TPS= thermal pain sensitivity; WPS = Worst pain score.

[a] Aliquot of standard safety laboratory blood sample for genotyping is optional in this study (will be performed if patient gives his consent by signing the genotyping informed consent document). The aliquot can be taken at any time during the study.
[b] Potential historical safety laboratory data (biochemistry, hematology) defined as the most recent safety laboratory data obtained within one month before screening visit and/or standard safety laboratory analysis and urinalysis performed during the study as part of regular patient management by Investigator will be collected (one per week if several during the study).
[c] Compliance to prescribed analgesic treatment will be followed through diary completion and direct questioning.
[d] The Clinical pain assessments will include the following measurements: MPA, SA, DMA, MPT and TPS.
[e] APS and WPS will be collected in the diary. APS and WPS at visit 1 will be completed at site by patient with Investigator site staff help, if needed. The last APS and WPS will be completed by patients during the phone call with the Investigator. At Visit 1, the Weekly APS during the preceeding week will be assessed for enrolment.
[f] Optional Intermediate Evaluation Visit will be organized within the next days after the intermediate phone call at the discretion of the Investigator.

SECTION 16.2. ATTACHMENT 2 – STUDY SCHEDULE – ENROLMENT AT VISIT 1A WAS ADDED

	Screening Enrolment		Observational Period		Follow UP / Early Discontinuation Phone Call
Visit	**1A**	**1B**	**Optional Intermediate Evaluation [f]**	**2**	
Days	**Day 1**	**Day 8 (+21 days)**	**Visit 1B Day+ 14 days (+12 to +18 days)**	**Visit 1B Day + 28 days (+ 14 days)**	**7 days after Visit 2 (+ 7 days)**
Informed Consent (general and genotyping)[a]	X				
Demographics	X				
Abbreviated physical examination	X			X	
Primary disease and Relevant Medical History	X				
Primary disease treatment history	X				
Analgesic history (within 1 month before enrolement)	X				
Pre-existing Conditions/Symptoms related to pain treatment	X	X	X	X	X
Cancer Concomitant Medications	X	X	X	X	X
Inclusion/Exclusion Criteria	X				
Enrolment into study	X				
Clinical Pain Assessments[d]	X		X	X	
DN4, NPSI	X				
Expectation questionnaire	X				
QLQ-C30	X			X	
BPI (short form)	X		X	X	
IGAC and PGAC	X			X	
APS and WPS[e]	X			X	X
Laboratory analysis[b]					
Aliquot of blood sample for genotyping purpose[a]					
Diary completion					
Compliance to diary completion		X	X	X	
Compliance to prescribed analgesic treatment[c]		X	X	X	

Analgesic treatment review	⟷				
Questionnaires MHLCS, HADS, LOT-R, PCS		X			

Abbreviations:
APS = Average pain score; BPI = Brief Pain Inventory; DMA = dynamic mechanical allodynia; DN4= Douleur Neuropathique en 4 questions; HADS = Hospital Anxiety and Depression Scale; IGAC=Investigator Global Assessment of Changes; LOT-R = Revised Life Orientation Test; MHLCS = Multidimensional Health Locus of Control Scale; MPT= mechanical pain threshold; NPSI= Neuropathic Pain Symptom Inventory; MPA = Most Painful Area; PCS= Pain Catastrophizing Scale; PGAC= Patient Global Assessment of Changes; QLQ-C30=quality-of-life questionnaire in 30 questions; SA= static allodynia; TPS= thermal pain sensitivity; WPS = Worst pain score.

[a] Aliquot of standard safety laboratory blood sample for genotyping is optional in this study (will be performed if patient gives his consent by signing the genotyping informed consent document). The aliquot can be taken at any time during the study.

[b] Potential historical safety laboratory data (biochemistry, hematology) defined as the most recent safety laboratory data obtained within one month before screening visit and/or standard safety laboratory analysis and urinalysis performed during the study as part of regular patient management by Investigator will be collected (one per week if several during the study).

[c] Compliance to prescribed analgesic treatment will be followed through diary completion and direct questioning.

[d] The Clinical pain assessments will include the following measurements: MPA, SA, DMA, MPT and TPS.

[e] APS and WPS will be collected in the diary. APS and WPS at visit 1A will be completed at site by patient with Investigator site staff help, if needed. The last APS and WPS will be completed by patients during the phone call with the Investigator. At Visit 1A, the Weekly APS during the preceeding week will be assessed for enrolment.

[f] Optional Intermediate Evaluation Visit will be organized within the next days after the intermediate phone call at the discretion of the Investigator.

Abbreviations

ECOG	Eastern Cooperative Oncology Group
MPA	Most painful area
~~QLQ-BM22~~	~~Quality-of-life questionnaire for bone metastasis in 22 questions~~
WAPS	Weekly Average Pain Score