

Chapter 29. Analgesic Drugs for Cancer Pain Management

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I. INTRODUCTORY REMARKS

Pain directly related to cancer or caused by treatments for cancer is a highly prevalent clinical problem. Between 30-85% of patients experience pain at some point during the illness trajectory, with estimates of 18-78% experiencing substantial pain in developed countries.

The current therapies for severe pain in cancer patients remain unsatisfactory. Opioids, the mainstay of cancer pain therapy, have a number of limitations. First, they are accompanied by a significant risk of dose limiting toxicity such as constipation, nausea and drowsiness. Second, some types of cancer pain, such as neuropathic pain and movement related bone pain, are difficult pain problems and carry a less good prognosis for control by opioids at doses that are tolerable. Third, opioids carry a significant perceived risk of abuse potential by society in general, which may at times represent barriers to the effective management of cancer pain. Fourth, cancer patients are at high risk for organ failure such as renal impairment or liver disease as their underlying disease progresses, and this comorbidity increases the risk of multifactorial, dose limiting symptoms associated with opioid administration such as delirium.

For cancer pain problems that have limited responsiveness to opioids, the World Health Organization (WHO) recommends the use of non-opioid (e.g. non-steroidal anti-inflammatory drugs) and adjuvant analgesics, in addition to opioids. Adjuvant analgesics include tricyclic antidepressants, anticonvulsants, *N*-methyl-D-aspartate antagonists, corticosteroids and others. The likelihood of effectiveness of many of the major classes of analgesics for *difficult cancer pain problems* remains disputed. There is an urgent need for controlled trials to evaluate the efficacy and adverse effect profiles of currently available non-opioid and adjuvant analgesics for cancer pain. There is also a need for newer analgesic drugs that have greater efficacy for severe cancer pain, better adverse effect profiles, and a reduced potential for toxicity, tolerance and addiction.

This chapter profiles a randomized, double-blind, placebo-controlled parallel-group trial design to evaluate the efficacy and safety of investigational drug XXX for patients with moderate to severe cancer pain. Based on the results from previous clinical studies, it is known that this drug has several important properties. Specifically, drug XXX has a rapid onset of action (5-30 minutes post injection), cumulative analgesic effect with twice-daily injections, long duration of action extending for days or weeks beyond the treatment period, and a favourable adverse effect profile at the studied doses. The trial described in this chapter is designed to better characterize these properties of drug XXX. For specific aspects of clinical trial design, the authors will also broaden the discussion to alternative approaches to help guide the development of Phase II clinical trials for analgesic drugs with different pharmacokinetic and pharmacodynamic properties. The examples in this chapter are most applicable to trials for evaluating analgesic drugs intended to be used in addition to patients' current analgesic therapy.

II. PHASE II STUDIES FOR REGISTRATION OF NEW ANALGESIC DRUGS

II.1. Outline of a typical development plan

Early Phase II analgesic studies are typically multiple-dose clinical trials designed to identify the optimal dose for later Phase II studies, and to characterize the drug's analgesic and adverse effect profiles. Once the optimal dose has been identified, later Phase II analgesic studies tend to be multicenter, randomized, double-blind, controlled trials involving larger sample sizes. When evaluating drugs that are intended to be used in addition to opioid therapy, the use of a placebo control is appropriate and ethical. There are two major types of randomized, double-blind, placebo-controlled trial designs in analgesic studies: parallel-group and crossover. However, if there is a significant chance that the drug will have a carryover effect or the duration of a drug's effect is difficult to predict or is variable, a parallel-group design should be used. One should also consider that a crossover design extends the length of a trial. For the cancer pain

population progression of the disease over the course of many weeks and a consequential worsening of pain over the duration of the trial could complicate the interpretation of the results.

II.2. Short term studies

The following example will be used to illustrate a pivotal, later Phase II analgesic study: a multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of subcutaneously administered drug XXX in patients with moderate to severe cancer pain. For this example, drug XXX or placebo is administered b.i.d. (twice each day) to patients over a four day period.

II.2.A. Study Objectives

Below is an example of a set of objectives for a clinical trial to evaluate investigational drug XXX as an adjuvant to opioid therapy for patients with moderate to severe cancer pain.

Primary Objectives

- a. to compare the efficacy of subcutaneous (s.c.) XXX treatment versus placebo in reducing the intensity of pain
- b. to compare the safety of s.c. XXX treatment versus placebo

Secondary Objectives

- a. to estimate the onset of analgesic effect of s.c. XXX
- b. to estimate the time of peak analgesic effect of s.c. XXX
- c. to estimate the duration of analgesic effect of s.c. XXX treatment
- d. to determine whether s.c. XXX treatment reduces the need for breakthrough medication
- e. to determine whether s.c. XXX treatment improves patient function.

Exploratory Objective

- a. to generate preliminary information about the specificity of XXX's analgesic action for neuropathic, visceral, and somatic pain

II.2.B. Primary endpoints

A wide variety of assessment tools are used for study endpoints to evaluate the efficacy of analgesic drugs in clinical trials and, unfortunately, there is currently no one gold standard for this very important task. Choice of pain intensity measures varies considerable across published clinical trials. These measures include variations in numeric rating scales, visual analogue scales, and verbal rating scales. All three of these scale types have been shown to be sensitive to treatment- and time-related changes in pain intensity. Pain intensity measures are also diverse with respect to whether they measure worst pain, average pain, or least pain over a specified period of time, or current pain. The Brief Pain Inventory (BPI) and other instruments use several pain intensity measures, concurrently, to estimate the degree of this dimension of pain. Measures of pain relief or patient evaluation of analgesic efficacy should also be considered in addition to pain intensity measures, since they can be effective in detecting a clinically meaningful analgesic response to treatment. However, in the literature there is considerable variation in the types of scales used to assess these two constructs. Pain intensity and pain relief measures are often concurrently used to characterize the onset, peak, and duration of an investigational drug's analgesic effect. The post-treatment times for evaluating pain intensity and pain relief for study endpoints will vary across clinical trials and will be based on the known pharmacodynamic properties of the drug. Assessment of efficacy in the cancer pain population is often more challenging than in the non-malignant pain population. Patients with cancer often suffer with more than one pain syndrome, each syndrome presenting with one or more pain symptoms. Furthermore, cancer pain syndromes and pain symptoms can differ with respect to their underlying pathophysiological mechanisms. For trials involving the evaluation of drugs with a very specific mechanism of action, the use of one global pain

intensity measure for the primary efficacy endpoint may not be sufficiently sensitive to detect an analgesic response. A global pain intensity or pain relief measure may have limited sensitivity in situations where a particularly bothersome pain symptom responds to the drug in a clinically meaningful way, but the patient's other pain symptoms have not responded due to differences in their underlying pathophysiological mechanisms. Unfortunately, there is currently no assessment tool specifically designed to simultaneously evaluate changes in the intensity of patients' distinct pains to an intervention. The Neuropathic Pain Scale (NPS) comes closest to achieving this, but it is intended to be used for simultaneously evaluating multiple symptoms of neuropathic pain only (1). Thus, a patient diary can be developed for a clinical trial to include validated pain intensity and or pain relief scales that allow assessment of treatment-related changes in specific pain symptoms over time.

In further consideration of the multidimensional nature of cancer pain and to increase the sensitivity of a clinical trial in detecting clinically meaningful responses to treatment, additional measures of efficacy should be considered for study endpoints, including measures of physical functioning, emotional functioning, and opioid requirements. It is best, however, that the assessment tools chosen to measure these constructs have been validated in the cancer pain population and have been demonstrated to be sensitive to analgesic drug interventions.

See references 2 through 7 for discussions about efficacy measures for analgesic drug clinical trials. In the example below, multiple primary and secondary endpoints have been chosen to increase the sensitivity of the trial to detect a clinically meaningful response to the investigational drug and to better understand its pharmacodynamic properties. Both Day 5 and Day 8 were chosen for the endpoints in an attempt to maximize the difference in the proportion of responders in the active versus placebo groups. Based on previous studies, it is known that drug XXX produces analgesia that persists well beyond the treatment period.

The Primary endpoints include:

- a. the proportion of responders in the drug XXX versus placebo groups, where a response is defined as:
 - a $\geq 30\%$ reduction in pain intensity from baseline, on Day 5 and Day 8 post treatment, as measured by the Brief Pain Inventory – Short Form Question #3 (BPI-SF Q#3; numeric rating scale the worst pain in the last 24 h). The reduction in pain intensity must be accompanied by either a decrease or stabilization ($<15\%$ increase) in mean opioid analgesic consumption compared with baseline.
- b. the proportion of *clinical responders* in the drug XXX versus placebo groups, where a clinical response is defined as:
 - a $\geq 30\%$ reduction in pain intensity from baseline, on Day 5 and Day 8 post treatment, as measured by the BPI-SF Q#5 (numeric rating scale for average pain in the last 24 hours) if average baseline pain intensity score is ≥ 4 , **or**
 - a $\geq 30\%$ reduction in pain intensity from baseline, on Day 5 and Day 8 post treatment, as measured by any component-specific pain scale from Patient Diary that has an average baseline pain intensity score of ≥ 4 , **or**
 - a $\geq 30\%$ reduction in pain intensity from baseline, on Day 5 and Day 8 post treatment, as measured by any component-specific pain measured by the subscales of the Neuropathic Pain Scale (NPS) that has an average baseline pain intensity score of ≥ 4 , **and**
 - the patient confirms that the global pain (BPI-SF Q#5) or component-specific pain (Patient Diary or NPS) has “very much improved” or “much improved” since the start of the study (Note: these are two categories from a 7-point verbal evaluation scale asking the patient to assess how much their pain has changed since the start of the study, with response categories ranging from 1=very much improved – 7=very much worse).

Safety is assessed through the number of adverse events, the number and nature of abnormal laboratory results, and changes in 12-lead electrocardiogram, blood pressure, heart rate, respiratory rate, and SaO₂.

II.2.C. Secondary endpoints

- a. the time of onset of a consistent decrease in pain intensity on the visual analogue scale (VAS) compared to baseline following the first dosing of the treatment phase
- b. the post treatment day during which the greatest reduction in pain intensity (BPI-SF Q#3, BPI-SF Q#5, and/or any component-specific pain intensity rating scale) is reported by Responders, or Clinical Responders compared to baseline
- c. the interval in days from the first of two consecutive days a patient reports a $\geq 30\%$ reduction in pain intensity (BPI-SF Q#3, BPI-SF Q#5, and/or any component-specific pain intensity rating scale) until the reduction in pain intensity score is $\leq 15\%$ compared to baseline
- d. the number of treated breakthrough pain episodes post-treatment
- e. the proportion of patients achieving a $\geq 30\%$ of improvement in their general activity (BPI-SF Q#9A) or walking ability (BPI-SF Q#9C)

II.2.D. Exploratory endpoints

- a. the proportion of patients with a neuropathic pain component or without a neuropathic pain component who are categorized as *responders* and *non-responders*

II.2.E. Study Design

Drug XXX is being evaluated by a multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of subcutaneously administered drug XXX in patients with inadequately controlled moderate to severe cancer pain. Drug XXX or placebo will be administered b.i.d. to patients over a four day period. The study duration will extend from three to 10 weeks, beginning the first day of screening until the end of patients' analgesic response.

All concomitant medications taken by the subject from the start of the first treatment period to the completion of the Follow-Up Visit will be documented. The reported medications will be reviewed and evaluated by the Qualified Investigator or designate to determine if they affect the subject's eligibility to continue to participate in the study.

Screening for Eligibility (Day -28 to -7)

- a. Each subject will undergo screening procedures within 7-28 days prior to the baseline period. The following will be required during the screening period to determine eligibility:
- b. Informed consent
- c. Medical history
- d. Review of concomitant medication (including analgesics)
- e. Physical and neurological examinations
- f. Vital signs (pulse rate, blood pressure, respiratory rate) and body weight
- g. 12-lead ECG
- h. Laboratory tests (haematology, clinical chemistry; urinalysis)
- i. Pregnancy test for women of childbearing potential
- j. Review of inclusion and exclusion criteria
- k. Characterization of pain and disease:
 - primary cancer site and type
 - identification and characterization of patients' three most bothersome pains (e.g. location, etiology, pathophysiology, quality, intensity)
- l. Patient categorization in part based on the Neuropathic Pain Questionnaire (NPQ) responses (presence versus absence of a neuropathic pain component)
- m. BPI-SF

Baseline Period (Day -7 to Day -1):

The duration of the baseline period will be between 5 to 7 days. The following assessments will be completed once during the baseline period, unless otherwise specified:

- a. Review of medical history from last visit to present date
- b. Review of inclusion and exclusion criteria
- c. Vital signs (pulse rate, blood pressure, respiratory rate) and body weight
- d. Review of concomitant medications
- e. Review of information related to the patients' three most bothersome pains
- f. BPI-SF (completed daily between 18:00h-21:00h)
- g. Patient Diary (completed daily between 18:00h-21:00h):
 - intensity of three most bothersome pains
 - recording of concurrent medications, including analgesics
- h. Neuropathic Pain Scale (NPS), if applicable

Note: Calculation of average baseline pain intensity will determine final eligibility (the mean “worst” pain intensity score, calculated from the last five BPI-SF Q #3 scores recorded by the patient during the baseline period; “moderate” pain will be defined as an average score of 4-5, and “severe” defined as an average score of 6 or higher).

Treatment Phase (Days 1-4)

Patients will be admitted to the hospital (in-patient) or at the site's care facility on a daily basis and will be allowed to leave the facility upon completion of each daily treatment session if judged appropriate by the investigator. All patients will be randomized on Day 1 to receive a s.c. injection of drug XXX or placebo twice daily for 4 consecutive days. The first dosing will be given between 8:00-10:00h, and the second dosing between 14:00-16:00h.

The following will be required prior to each dosing unless otherwise specified:

- a. Review of concomitant medication
- b. Vital signs
- c. VAS for pain intensity (VAS-PI) to help determine acute analgesic response to XXX treatment (completed prior to first dosing of Day 1 and Day 4)
- d. 12-lead ECG

Following the first dosing of Day 1 and 4, acute analgesic response will be assessed (VAS-PI) every 15 minutes for the first hour, and then every 30 minutes until the second dosing of the day. A 12-lead ECG will be completed 1-2 hours after the morning (Days 1-4) and afternoon (Days 2 and 3) dosing. The following will be required prior to discharge unless otherwise specified:

- a. Vital signs
- b. Brief neurological examination
- c. Review of adverse events/ Adverse event recording
- d. Review of around-the-clock (ATC) analgesics and breakthrough pain medications
- e. BPI-SF (completed daily between 18:00h-21:00h)
- f. Patient Diary (completed daily between 18:00h-21:00h):
 - intensity of three most bothersome pains
 - recording of concurrent medications, including analgesics

Follow-up Visits

All patients will be assessed at the clinic on follow-up Days 5, 8, and 15 and then when pain intensity returns to baseline levels. Each evening between 18:00h-21:00h during the follow-up period, patients will complete the BPI-SF, and record in their Patient Diary the intensity of the three most bothersome pains and concomitant medications. In addition, patients will record their impression of change for each

bothersome pain (from 1 = very much improved to 7 = very much worse) in their Diary on Days 5, 8 and 15. All patients will have the option to enroll in an open label extension protocol on Day 15 or later. The following will be required at each follow-up clinic visit:

- a. Physical examination
- b. Vital signs
- c. Completed BPI-SFs
- d. Completed NPSs, if applicable
- e. Review of the Patient Diary, including patient's assessment of change
- f. Review of concomitant medication

Whenever Day 15 is the last visit, laboratory evaluations (clinical chemistry, haematology, and urinalysis), 12-lead ECG, and pregnancy test for women of childbearing potential will be completed. Patients who have experienced Severe Adverse Effects (SAEs) or Adverse Effects (AEs) that are at least possibly related to the study medication will be followed-up by telephone on Day 35 to assess their outcome.

If patient's pain is adequately controlled in the opinion of the investigator and the subject, the following assessments will be completed by telephone or at clinic visits (required at least every two weeks) for up to 6 weeks (Day 43):

- a. Patient Diary (weekly post Day 15 until last day of study)
- b. BPI-SF (weekly post Day 15 until last day of study)
- c. Vital signs (every 2 weeks at a minimum, for a maximum of 4 weeks)
- d. NPS, if applicable (at last visit)
- e. Laboratory evaluations (clinical chemistry, haematology, and urinalysis at last visit)

II.2.E. Planned sample

Sample size calculation will be based on the primary efficacy endpoint, i.e. comparison of the proportion of responders, based on the worst pain in the last 24 hours from baseline to Day 5 between the XXX and placebo study drug groups. A total of 116 evaluable subjects will be required to detect a difference in proportion of responders between study drug groups of 20% (placebo) versus 50% (XXX) under the following assumptions: Equal numbers of subjects in the two treatment conditions; and 2-sided test, using a significance level of 0.049; and minimum power of 0.90 (90%). A 30% decrease in pain intensity is considered to be a clinically meaningful response (2). The choice of a within-patient 30% reduction in pain intensity is also based on discussion of clinical importance of changes in chronic pain intensity using an 11-point scale (3).

In a population of subjects with painful diabetic neuropathy (8), investigators observed placebo response rates ranged from 10% to 40%, with an average of 26%; it is expected that a placebo response rate for subjects with cancer pain as in the current study will be similar. It has also been shown that the effect of placebo in the treatment of refractory pain in patients with cancer was 18.1% (9). Thus, a response rate of 20 % was selected as a reasonable estimate for a placebo effect for this study. If the placebo effect is larger than anticipated (e.g. 30 % responder rate in the placebo group), then power is still high enough (87%) to detect the 30% difference in responder rates between the two study groups.

Assuming that 20% of the enrolled patients will discontinue the study or be withdrawn from the study, a total of 146 patients will be required for this parallel-group trial. It is planned to recruit this sample in approximately 25-30 centres across the country with a mean enrolment of 4 patients per centre. Enrolment into the screening phase of the study will be stopped when the anticipated or actual number of subjects has been achieved across all study sites.

II.2.F. Study population

Male or female subjects over 18 years of age with stable but inadequately controlled moderate to severe cancer pain of at least two weeks duration. Patients may experience visceral, somatic and/or neuropathic pain, requiring opioid administration.

II.2.G. Specific inclusion criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

- a. Male or female 18 years of age and over;
- b. In-patient or out-patient with a diagnosis of cancer;
- c. Stable but inadequately controlled pain with current therapy for at least two weeks;
- d. Experiencing somatic, visceral and/or neuropathic pain related to cancer;
- e. Pain intensity, as assessed by BPI-SF Q#3 meets the definition of “moderate” (score of 4-5) or “severe” (score of 6-10) pain;
- f. Life expectancy of > 3 months;

II.2.H. Specific exclusion criteria

For this example, the exclusion criteria have to be adapted to characteristics of the drug, e.g. the pharmacokinetics, pharmacodynamics, potential drug-drug interactions, and adverse effects. A patient will **not** be eligible for inclusion in this study if any of the following criteria apply:

- a. Planned initiation of chemotherapy, radiotherapy, or bisphosphonates within 30 days prior to randomization;
- b. Taking lidocaine, mexiletine, or other anaesthetics;
- c. History of CO₂ retention, or oxygen saturation (SaO₂) <90% despite O₂ via nasal prongs
- d. Use of scopolamine, acetylcholinesterase-inhibiting drugs, beta-blockers and antiarrhythmic drugs;
- e. Second or third degree heart block or prolonged QT_c interval (corrected for rate) on screening ECG (confirmed > 470 msec on repeated occasion);
- f. Known hypersensitivity to XXX and/or its derivatives;
- g. Received an investigational agent within 30 days prior to screening or who is scheduled to receive an investigational drug other than XXX during the course of the study;
- h. Females who are lactating or at risk of pregnancy (i.e., sexually active with fertile males and not using an adequate form of birth control);
- i. Females with a positive serum pregnancy test at screening or positive urine pregnancy test on admission to study site; or
- j. Any other condition that, in the opinion of the investigators, is likely to interfere with the successful collection of the measures required for the study or poses a risk to the patient.

II.2.I. Tools for assessing the endpoints

II.2.I.i. Tools to assess efficacy

The following table 1 summarizes the assessment tools chosen for this example to measure efficacy variables.

II.2.I.ii. Tools to assess safety

Safety will be evaluated through the assessment of spontaneously reported adverse events, vital signs, physical exam findings and laboratory tests. Other safety data will include 12-lead ECG measurements and brief neurological examinations.

- a. Adverse events (AEs)
Adverse events will be recorded daily beginning on Day 1 up to Day 15 for non-serious AEs, and from screening up to 30 days after the last dose of the investigational product

Table 1. Tools to assess efficacy variables

Variable	Assessment Tool Used to Measure Variable	Time of Assessment
Global Pain Intensity in Last 24 Hours ('worst' & 'average' pain) and current pain	BPI-SF (Q#3, Q#5, Q#6)	Daily through all phases of the trial until Day 15 and then weekly until the end
Pain Relief in Last 24 Hours	BPI-SF (Q#8)	Daily through all phases of the trial until Day 15 and then weekly until the end
Component-Specific Pain Intensity	Patient Diary (NRSs; 0=no pain, 10=pain as bad as you can imagine)	Daily through all phases of the trial until Day 15 and then weekly until the end
Component-Specific Pain Intensity	NPS (subscales)	Baseline (once), Days 5, 8, 15 and last day of trial
Acute Analgesic Response	VAS-PI	On Day 1 and Day 4, prior and after first dosing (every 15 minutes for the first hour, and then every 30 minutes until the second dosing)
ATC and Breakthrough Analgesic Use	Patient Diary	Continually through all stages of the trial until the end (morphine equivalents will be calculated)
Patient's Impression of Change in Pain	Patient Diary (7-point categorical scale; 'very much improved' to 'very much worse')	Days 5, 8, 15
Time to Analgesic Response	BPI-SF (Q#3, Q#5) Patient Diary (component-specific pain intensity NRSs)	Daily through all phases of the trial until Day 15 and then weekly until the end
Duration of Analgesic Response	BPI-SF (Q#3, Q#5) Patient Diary (component-specific pain intensity NRSs)	Daily through all phases of the trial until Day 15 and then weekly until the end
Time to Peak Analgesic Response	BPI-SF (Q#3, Q#5) Patient Diary (component-specific pain intensity NRSs)	Daily through all phases of the trial until Day 15 and then weekly until the end
Walking Ability	BPI-SF (Q#9C)	Daily through all phases of the trial until Day 15 and then weekly until the end
General Activity	BPI-SF (Q#9A)	Daily through all phases of the trial until Day 15 and then weekly until the end

for severe AEs (SAEs). The frequency of adverse events will be tabulated and summarized according to:

- Type: clinical laboratory abnormalities detected in biological samples, abnormalities detected on physical and neurological examinations, adverse reactions described by the patient.
- Severity: mild, moderate, severe, life threatening
- Association with treatment (causality): probably related, possibly related, not related, unknown.

- b. Clinical laboratory evaluations
Clinical laboratory tests will be performed by a central laboratory. The following evaluations will be conducted: clinical chemistry, haematology and coagulation, urinalysis, and pregnancy test.
- c. Physical examination, vital signs, body weight, height, brief neurological examination
- d. 12-lead ECG
A 12-lead ECG will be recorded after 10 minutes rest in the supine position at: Screening, Pre-dose on Day 1 (randomization; triplicate), 1 hour post dose on Day 1 (triplicate), Pre-dose on Day 2 (triplicate), 1 hour post dose on Day 2 (triplicate), 1 hour post PM dose on Day 2 (triplicate), Pre-AM dose on Day 3 (triplicate), 1 hour post-PM dose on Day 3 (triplicate), Pre-AM dose on Day 4 (triplicate), 1 hour post-AM dose on Day 4 (triplicate), and Day 15.

The central reader will measure the electrocardiographic intervals manually on a computer screen using digital callipers. Each interval will be derived as a mean of three measurements taken from three consecutive QRST complexes. Mean QT and PR intervals will be used to derive the Bazett (QTcB) and Fridericia (QTcF) corrected QT intervals. A computer interpretation will be faxed to the site within 30 minutes of transmission. A cardiologist-reviewed ECG report including a full diagnostic interpretation will be faxed to the site next business day.

II.2.J. Specific criteria for early withdrawal and discontinuation

Subjects will be permitted to leave the study at any time. Subjects can be withdrawn from the study for any of the following reasons:

- a. Occurrence of a SAE
- b. Administrative reasons (e.g. sponsor decision)
- c. Withdrawal of consent
- d. Major violation of the protocol
- e. Pregnancy
- f. Non-compliance
- g. If it is of the opinion of the Qualified Investigator that it is in the best interest of the patient to discontinue

Patients discontinuing because of a SAE or because it is in the Qualified Investigator's opinion that it is in the best interest of the patient, will be considered to have completed the study. Patients discontinuing because of withdrawn consent, a major violation of the protocol, pregnancy, or non-compliance will be non-completers and replaced if they leave prior to drug administration. If a patient is prematurely discontinued from participation in the study for any reason after drug administration, the investigator must make every effort to perform the following evaluations: physical examination, 12-lead ECG, vital signs, clinical laboratory tests including haematology, clinical chemistry, and urinalysis, adverse event assessment, and pregnancy test (females of childbearing potential). These data should be recorded in the source documentation and CRF, as they comprise an essential evaluation that should be done prior to discharging any patient from the study. These subjects will be considered to have completed the study.

In the event that a patient is prematurely discontinued from the study at any time due to an AE or SAE, the procedures stated in Section XII must be followed. The "End of Study Record" page of the CRF will be completed for any patient withdrawn from the study.

Patients who drop out of the study due to changing medical status not related to pain, clinically important changes in non-pain-related medications, or whose status meets one or more exclusion criteria will be replaced. These patients will not be considered treatment failures.

II.2.K. Data analysis

a. Analysis populations

All efficacy analyses will be performed using the intent-to-treat principle, i.e. subjects will be analyzed based on the study drug group to which they were randomized. All safety analyses will be performed for subjects as dosed. In addition to the intent-to-treat analysis approach for efficacy (primary), if a substantial proportion of subjects (>10%) fail to complete four days of study treatment or there are a substantial number of subjects (>10%) with critical protocol violations (e.g. baseline worst pain < 4 for the BPI-SF Q#3), per-protocol analyses will be performed using subjects who complete all four days of study treatment with no critical protocol violations.

b. Significance/confidence level

Differences will be considered statistically significant if the significance level is ≤ 0.049 , 2-tailed. Confidence intervals for the absolute difference between the treatment groups in the outcomes will be calculated using 95.1% confidence, 2-tailed.

c. Efficacy analysis

The overall objective is to determine the efficacy of s.c. XXX in reducing the intensity of cancer-related inadequately controlled pain compared to placebo.

Primary efficacy analysis

The primary efficacy analysis will be performed to compare the proportion of patients who are responders to XXX with the proportion of patients who are responders to placebo, based on the BPI-SF Q#3. Comparison of the proportion who responds in each treatment group will be made using the Mantel-Haenszel procedure, stratifying for: baseline pain pathophysiology (includes neuropathic component/does not include neuropathic component) and baseline pain intensity as determined by the average of BPI-SF Q#3 score (moderate/severe). For the primary efficacy analysis, missing data for Day 5 or Day 8 will constitute a non-responder. As a co-primary analysis, a responder analysis will be performed using the clinical responder definition of response. The same statistical analysis method will be used for the co-primary efficacy analysis as for the primary efficacy analysis. See responder and clinical responder definitions on page 4. Exploratory analyses will be performed to compare the mean change from baseline in component BPI-SF pain intensity scores and NPS scores using an analysis of covariance (ANCOVA) model, with change from baseline in pain as the dependent variable, the study drug group and baseline pain pathophysiology as independent variables, and mean baseline pain intensity score as a covariate. Least squares means for the study drug groups will be reported.

Secondary efficacy analysis

(i) Determination of whether s.c. XXX treatment improves daily mobility in patients with refractory cancer pain.

The mean change from baseline in BPI-SF Q #9A (general mobility) and BPI-SF Q #9C (walking ability) scores will be combined and compared between treatment groups using an analysis of covariance (ANCOVA) model, with change from baseline in daily mobility as the dependent variable, the study group and pain pathophysiology stratum as independent variables, and baseline score as a covariate.

(ii) Determination of whether s.c. XXX treatment reduces the need for breakthrough medication.

The overall number of treated breakthrough episodes per patient will be summarized. The number of treated breakthrough episodes per patient will be compared between treatment groups using a Poisson regression model with the study drug group and pain pathophysiology stratum as independent variables.

(iii) Determination of the onset, duration, and peak of XXX analgesic effect

The onset of analgesia is defined as the first time point showing a consistent decrease in pain intensity, as measured by the VAS-PI, compared with baseline following the first XXX dosing on Day 1 and Day 4.

The duration of analgesic response is defined as the interval in days from the first of two consecutive days a patient reports a $\geq 30\%$ reduction in pain intensity (BPI-SF Q#3, BPI-SF Q#5, and/or any component-specific pain intensity rating scale) until the reduction in pain intensity score is $\leq 15\%$ compared to baseline or the patient confirms that the decrease in pain intensity from baseline is no longer meaningful to him or her. The duration of analgesic response may differ depending on the pain component.

Peak analgesic effect is defined as the day during which the greatest reduction in worst pain intensity occurs (BPI-SF Q#3) for responders. Time of peak analgesic effect and duration of analgesic effect will be summarized across treatment groups.

Exploratory efficacy analysis

The proportion of responders, using the definition of responder for the primary efficacy analysis will be summarized separately for each pain pathophysiology category (neuropathic, visceral, somatic, and mixed).

d. Safety analysis

Adverse events

Adverse event rates will be summarized and compared between the study drug groups for: overall incidence, incidence of related adverse events (according to the causality assessment), incidence of grade 3/4 toxicity per NCI-CTC toxicity criteria, incidence of serious adverse events (including death), and incidence of adverse events leading to discontinuation. Incidence will be counted as treatment-emergent if adverse event onset or worsening occurs after first dose of study drug. For purposes of adverse event analysis, adverse events related to pain will not be summarized.

Vital signs assessments

Vital sign data will be summarized at each time point and change from baseline using descriptive statistics (mean, median standard deviation, minimum, and maximum), for systolic blood pressure, diastolic blood pressure, and heart rate. Changes from baseline that exceed the limits indicated in table 2 will be tabulated for each study group.

Table 2. Vital sign limits

Parameters:	Change Criteria:
Systolic Blood Pressure:	Change from baseline $\geq \pm 15$ mmHg
Diastolic Blood Pressure:	Change from baseline $\geq \pm 10$ mmHg
Heart Rate:	Change from baseline $\geq \pm 20$ bpm

ECG assessments

ECG data will be summarized at each time point (using the mean of 3 observations observed at baseline and 3 observations observed following dosing each day) and reported as change from baseline using descriptive statistics (mean, median standard deviation, minimum, and maximum) for each day for: R-R interval, PR, QRS, QT, and QTc. Regarding QTc, the Bazett and Fredericia corrections for R-R interval will be used. Tolerance limits (Confidence Interval) for the difference between study groups for mean change in QTc at each time point will be estimated. Shift tables will be used to assess baseline versus post-baseline relation of ECG value to reference range for each study drug group, and changes in ECGs from baseline that exceed limits defined in table 3 will be tabulated for each study drug group.

Table 3. ECG reference ranges and change limits

Parameters:	Change Limit:	Reference Range:
Heart Rate:	Change from baseline $\geq \pm 10$ bpm	
PR Interval:	Change from baseline $\geq \pm 32$ msec	115 msec - 200 msec
QRS Interval:	Change from baseline $\geq \pm 16$ msec	80 msec - 100 msec
QT/ QTc Interval:	Change from baseline $> \pm 30 - 60$ msec/ Change from baseline $> \pm 60$ msec	320 msec - 470 msec

In addition, abnormalities in T wave/U-wave morphology will be summarized for each study drug group.

Laboratory assessments

Laboratory data will be assessed using descriptive statistics (mean, median standard deviation, minimum, and maximum) for each of the time points for haematology, blood chemistry, and urinalysis parameters. Shift tables will be used to assess baseline versus post-baseline relation of laboratory value to reference range for each study drug group, and changes to laboratory values that are grade 3 or 4 using the NCI-CTC criteria will be tabulated for each study drug group.

II.2.L. Adverse events (AEs) and severe adverse events (SAEs)

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study site personnel will be responsible for XXX AEs and SAEs.

An adverse event (AE) is defined as an unusual and most often undesirable symptom or sign that occurs in human subjects participating in a study. Adverse Events include clinically significant abnormal laboratory values and test results, concomitant illness, accident, medical occurrence or worsening of existing medical condition that emerge during study participation.

All AEs will be recorded on the Adverse Event CRF at each assessment time or when otherwise volunteered by the subject. The investigator will actively solicit this information and assess the AEs from the subject in terms of severity and relationship to study drug. The investigator will treat the subject as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The investigator will record treatment and medications required for treatment on the appropriate CRF(s) and will provide reports of AEs to the sponsor's clinical monitor on a regular basis during the study conduct.

The investigator will also report to the sponsor all AEs that come to his/her attention after the study termination within 30 days of the last dose of study drug(s).

III. EXAMPLES OF LANDMARK WELL DESIGNED ANALGESIC TRIALS

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2. Farrar JT, Young Jr. JP, Lamoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-158.
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