# SIGNATURE PAGE FOR PROTOCOL OXN10-CN-303

**Protocol Number:** OXN10-CN-303

**Title:** A Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain

**Test Drug:** Oxycodone/naloxone prolonged release tablets (OXN)

| | |
|---|---|
| **Clinical Lead**<br><br>Mei Wang<br>Associate R&D Director<br>Mundipharma(China) Co., Ltd<br>Beijing, China | Signature<br>Date 14 Mar. 2013 |
| **Statistician**<br><br>**Bjoern Bosse**<br>Director of European Data management Statistics, Medical Science.<br>Mundipharma Research GmbH & Co. KG<br>Limburg, Germany | Signature:<br>Date 14 Mar 2013 |
| **Drug Safety:**<br><br>Grace Wang<br>Drug Safety Manager<br>Mundipharma(China) Co., Ltd<br>Beijing, China | Signature<br>Date 14 Mar, 2013 |
| **Medical Director**<br><br>Jingdong Ma<br>Medical Director<br>Mundipharma(China) Co., Ltd<br>Beijing, China | Signature<br>Date Mar 14, 2013 |

## SIGNATURE PAGE FOR INVESTIGATORS

**Protocol Number:** OXN10-CN-303

**Title:** A Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain

**Test Drug:** Oxycodone/naloxone prolonged release tablets (OXN)

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH and China Good Clinical Practice guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

| Investigator | Signature | Date |
|---|---|---|

# 1 TITLE PAGE

**Protocol Number:** OXN10-CN-303

**Title:** A Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain

**Sponsor:** Mundipharma (China) Pharmaceutical Co.LTD
18F, Tower D Central International Trade Center
6A Jianguomenwai Avenue
Chaoyang District
Beijing, China 100022

**Test Drug:** Oxycodone/naloxone prolonged release tablets

**Indication:** Chronic Cancer Pain

**Phase:** Phase 3

**Release Date:** 13 Mar. 2013

**GCP Statement:** This study is to be performed in full compliance with ICH and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by competent authorities.

**Confidentiality:** This document is confidential. It contains proprietary information of Mundipharma (China) Pharmaceutical Co.LTD. Any viewing or disclosure of such information that is not authorised in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

# 2 CLINICAL PROTOCOL SUMMARY

| | |
|---|---|
| **Name of company**：Mundipharma(China) Pharmaceutical Co., Ltd. | |
| **Name of Finished Product:**：Oxycodone/naloxone prolonged release tablets (OXN 5/2.5mg, 10/5mg, 20/10mg and 40/20mg) | **Name of Active Ingredient:** Oxycodone/naloxone combination |
| **Short Title of the Study:** OXN in Moderate to Severe, Chronic Cancer Pain | |
| **Full Title of the Study:** A Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain | |
| **Protocol No.**：OXN10-CN-303 | |
| **Investigators/study sites**：About 25 study sites in China | |
| **Study Initiation Plan**: May 2013 | **Phase of Development:** Phase III |

**Main Objectives:**

- To determine the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets(OXY) based on the Bowel Function Index (BFI).
- To demonstrate the non-inferiority (comparability) of oxycodone / naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets (OXY PR) for the management of chronic cancer pain as assessed by the average pain of the Brief Pain Inventory (BPI) recorded by subjects.

**Other objectives:**

- To compare the improvement in symptoms of constipation in subjects receiving treatment with OXN compared to OXY PR based on laxative use.
- To demonstrate the comparability of OXN compared to OXY PR for the management of chronic cancer pain as assessed by rescue medication use recorded by subjects.
- To assess safety of treatment with OXN compared with OXYPR based on the Modified Subjective Opiate Withdrawal Scale (SOWS), Adverse Events (AEs), Electrocardiograms (ECG) and laboratory tests.
- To assess quality of life based on EQ-5D

**Study Design (Methodology):**

This is a randomised, double-blind, double-dummy, parallel group study using OXN and OXY PR to treat moderate to severe, chronic cancer pain. Subjects with documented history of cancer pain that requires around-the-clock opioid therapy will be included. Subjects must have a medical history of constipation that was induced by, or worsened by their opioid therapy.

**Screening:** Subjects who sign informed consent will be screened for entry in to the study. The Inclusion/exclusion criteria will be assessed based on medical history, physical examination and lab test results. Subjects will be registered into the IRT system. After subjects have been qualified for the study during the initial screening visit (V1), they will return to visit the Investigator to be randomised and to enter the double-blind treatment phase of the study (V2).

**Double-blind Treatment Phase:** Subjects will receive either OXN or OXY at V2. At V2 subjects will stop their pre study opioid and laxative medication. Subjects will receive the double-blind medication for a period of 4 weeks. Investigators will change the subject's dose of pre study opioid to a dose of oxycodone prolonged release (PR). The starting dose of oxycodone PR will be based on the subject's prior dose of opioid and whether subjects need an increase in opioid dose to control their pain. During the double-blind treatment phase study medication will be titrated up to a maximum of 120 mg/day of oxycodone PR.

Open label Morphine Sulfate Tablets will be available to subjects as rescue medication throughout the double-blind treatment phase. Morphine Sulfate Tablets will be taken at a dose according to the table 5 and will be taken as required by subjects to treat breakthrough pain. A maximum of 6 doses of Morphine Sulfate Tablets can be taken in 24 hours. If a subject regularlyrequires more than 2 uses of rescue medication per day, the investigator should increase the subject's dose of double-blind medication by 10 mg/day or 20mg/day of OXN/OXY PR in a double-blind, double-dummy manner. If a subject requires greater than 120 mg OXY/OXN PR or 120 mg OXY/OXN PR and more than the maximum Morphine Sulfate Tablets allowed by the protocol e.g. regularly requires more than six rescue doses of Morphine Sulfate Tablets, then the subject must be withdrawn from the study (see section on Concomitant Medication Including Rescue - Analgesics).

Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication. On the day of randomisation pre study laxatives should be discontinued. If no bowel movement occurs within 3 days after the start of the double-blind phase, bisacodyl laxative intake will be commenced, which means that a laxative should be taken at that time. However investigators can instruct their subjects that if they exhibit discomfort during this period they can take oral bisacodyl as a laxative earlier than after 3 days as required to treat constipation. After that first 3 day period, bisacodyl tablets may be used no sooner than 72 h after the subjects' most recent bowel movement. However investigators can instruct their subjects that if they exhibit discomfort during the 72 hour period they can take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation. The maximum allowed number of bisacodyl intakes is 5 dosages within 7 consecutive days.

The double-blind phase is 4 weeks in duration. Following screening and randomisation subjects will attend 4 clinic visits (V5, V6, V7, V8) and 3 additional telephone visits (V3, V4, and V9) during the treatment period. Visits 3, 4, are scheduled as a telephone visits however at the discretion of the investigator these may be completed as clinic visits and the same assessments as scheduled will be completed. At each clinic visit, assessments will be carried out to assess the subjects pain control (Brief Pain Inventory), use of rescue medication, bowel function (Bowel Function Index), and use of laxative medication (last 7 days). Subjects will also be asked for the number of bowel movements they have had in the last 7 days before the study visit and the number of days that they had a bowel movement in the last 7 days before the study visit. At Visits 3 and 4 , subject will be checked about the pain control to determine whether need to be titrated to a higher/lower dose study medication., use of rescue medication and SOWS(on V3). Throughout the study adverse events and concomitant medication will be recorded. Other measures including EuroQol EQ-5D will be completed at Visit 1 and Visit 8..

**Number of Subjects:**

Approximately 280 patients may be screened to obtain 230 pateints who will be randomised in a 1:1 ratio to OXN / OXY PR. Each group will have 115 subjects.

**Screening Phase Inclusion Criteria:**

1. Males and females, at least 18 years or older with a diagnosis of cancer.
2. Females less than one year post-menopausal must have a negative urine pregnancy test recorded prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective method of contraception throughout the study. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistenly and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (hormonal), sexual abstinence or vasoectomised partner.
3. Subjects who are receiving WHO step II or Step III analgesic medication who have constipation induced, or worsened by their opioid medication, as shown by
   a) the subject's medical need of regular intake of laxatives to have at least 3 bowel evacuations per week, or having less than 3 bowel evacuations when not taking a laxative, respectively.
   b) the subject's self-assessment that their constipation was induced or worsened by their current pre-study opioid medication.
4. Documented history of moderate to severe, chronic cancer pain that requires around the-clock opioid therapy (starting dose of oxycodone PR between 20 -80 mg/day) and are likely to benefit from WHO step III opioid therapy for the duration of the study. Subjects must be willing to discontinue their current opioid analgesic routine.
5. Subjects are willing to discontinue pre study laxative medication and take study specific laxative medication.
6. Subjects taking daily fibre supplementation or bulking agents are eligible if they can be maintained on a stable dose and regimen throughout the study, and in the investigators opinion are willing and able to maintain adequate hydration.
7. Subjects willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinic visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.
8. Subjects already taking non-opioid analgesics and all other concomitant medications (including those for the treatment of depression) are eligible to take part in the study. However, all concomitant medications that are considered necessary for the subject's welfare should be continued at a stable dose throughout the double-blind phase of the study and under the supervision of the investigator.

9. Expected survival time > 3 months.
10. With capability of reading, understanding and signing inform consent form and compliance with protocol requirements.

**Exclusion Criteria:**

1. Subjects that require a dose >80 mg/day oxycodone PR at the start of the double-blind phase.
2. Any history of hypersensitivity to oxycodone, naloxone, morphine , bisacodyl, related products, and other ingredients.
3. Subjects with any situation in which opioids are contra-indicated, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, paralytic ileus.
4. Subjects with evidence of clinically significant gastrointestinal disease (e.g. paralytic ileus, peritnoneal carcinosis), significant structural abnormalities of the gastrointestinal tract (e.g. scarring, obstruction etc) either related or not related to the underlying cancer or disease progression.
5. Evidence of clinically significant cardiovascular, renal, hepatic or psychiatric disease, as determined by medical history, clinical laboratory tests, ECG results, and physical examination, that would place the subject at risk upon exposure to the study medication or that may confound the analysis and/or interpretation of the study results.
6. Abnormal aspartate aminotransferase (AST; SGOT), alanine aminotransferase (ALT; SGPT), r-glutamyltransferase (GGT) or alkaline phosphatase levels (>3 times the upper limit of normal) or an abnormal total bilirubin and/or creatinine level(s) (greater than 1.5 times the upper limit of normal).
7. Cyclic chemotherapy in the two weeks before the screening visit or planned during the core study that has shown in the past to influence bowel function. If subjects are having their first cycle of chemotherapy during the 2 weeks before the screening visit or during the double-blind phase of the study they should be excluded from the study.
8. Radiotherapy that, in the investigators opinion, would influence bowel function or pain during the double-blind phase of the study.
9. Subjects with known or suspected unstable brain metastases or spinal cord compression that may require changes in steroid treatment throughout the duration of the study.
10. Subjects with uncontrolled seizures.
11. Subjects with increased intracranial pressure.
12. In the investigator's opinion, subjects who are receiving hypnotics or other central nervoussystem (CNS) depressants that may pose a risk of additional CNS depression with opioid study medication.
13. Subjects with myxodema, not adequately treated hypothyroidism or Addisons disease.
14. Subjects who have a confirmed diagnosis of ongoing irritable bowel syndrome(IBS).
15. Surgery completed within 4 weeks prior to the start of the Screening Period, or planned surgery during the study that would influence pain or bowel function during the study or preclude completion of the study.
16. Subjects receiving opioid substitution therapy for opioid addiction (e.g. methadone or buprenorphine).
17. Active alcohol or drug abuse and/or history of opioid abuse.
18. Subjects suffering from diarrhoea and/or opioid withdrawal.
19. Subjects presently taking, or who have taken, naloxone ≤30 days prior to the start of the Screening Period.
20. Subjects who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry (defined as the start of the Screening Period), unless the subject is on data collection phase for Overall Survival.

**Criteria for entry to the Double-Blind phase**

Subjects continue to comply with the Screening Inclusion/Exclusion criteria.

**Withdrawal Criteria:**

1. If the subject demonstrates opioid withdrawal defined as a Modified Subject Opiate Withdrawal Scale (SOWS) score >26.
2. If a subject has a serious adverse event due to an opioid withdrawal syndrome.

3. If a subject meets at least one parameter of the Markedly Abnormal Laboratory values fulfilling at least one SAE criteria.
4. If a subject exceeds/falls below the normal ranges for vital signs fulfilling at least one SAE criteria.
5. If a subject requires greater than 120 mg OxyPR/OXN or 120 mg OxyPR/OXN plus more than the maximum Morphine Sulfate Tablets allowed by the protocol e.g. requires more than six rescue doses of Morphine Sulfate Tablets.
6. Regarding discontinuation criteria with respect to laxative use, overall the maximum allowed amount of bisacodyl should not exceed 5 dosages bisacodyl within 7 consecutive days. At the discretion of the investigator, the bisacodyl dose may be lowered. If there is no BM within 24 hours following the 72 h period after the most recent BM bisacodyl use may be repeated. If there is still no BM within 24 hours following the use of bisacodyl, an enema may be used. If there is still no BM following the use of the enema, the subject will be discontinued from the study.
7. If as subject demonstrates a clinically relevant reduction in vigilance fulfilling at least one SAE criteria.

**Concomitant Medication Including Rescue:**

All investigational drugs and devices are prohibited unless otherwise specified in the clinical protocol or directed by the Investigator, only after having received prior authorization from sponsor.

All other medication not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.

**Analgesics**

| Study Medication | Dosage Form | Unit Strength | Dosing Frequency | Mode of administration |
|---|---|---|---|---|
| Morphine Sulfate Tablets | Tablets | 10 mg | q4-6h PRN | Oral |

During the double-blind treatment phase, all subjects can receive Morphine Sulfate Tablets as rescue medication up to 6 times a day at a dose according to table 5 as recommendation.

At the discretion of the investigator, the rescue dose may be lowered if the subject experience side effects from the recommended dose or if after taking the recommended dose, the investigator/subject feels that the dose is higher than what may be required to provide adequate analgesia.

Stable doses of pre-study, non-opioid analgesics may be continued during the study. Any analgesic dosing during the double-blind treatment phase should remain stable. Opioid analgesics other than the study medication (i.e. OXN, OxyPR) and rescue medication (Morphine Sulfate Tablets) are not permitted.

- 6 rescue doses of Morphine Sulfate Tablets are the total maximum amount of rescue medication per day. Subjects who, on more than two consecutive days take >6 rescue doses should be discontinued. Note: 1 dose = 1 time rescue is taken and not 1 tablet if multiple tablets are taken (i.e. 3 tablets of 10 mg for a 30 mg dose).
- During the double-blind treatment phase, subjects, who consistently require 2 rescue doses of Morphine Sulfate Tablets per day should have their dose of OXN/OXYPR increased.
- During the double-blind phase subjects who are on the maximum daily dose of 120 mg Oxy PR/OXN and who regularly require more than 2 rescue doses per day should be discontinued.
- The maximum possible Oxycodone dose and equivalent morphine dose during the study is 120 mg Oxycodone PR per day plus 6 rescue doses of 180mg Morphine Sulfate Tablets per day, i.e. 120 Oxycodone PR plus180mg Morphine Sulfate Tablets per day.

In case other medication is taken by the subject after administration of the study drug, the investigator should record that on the case report form, including the name of drug(s), dosage and administration, the duration of administration, and the reason for administration.

**Laxatives, Anti-diarrhoeal Agents**

| Study Medication | Dosage Form | Unit Strength | Dosing Frequency | Mode of administration |
|---|---|---|---|---|
| Bisacodyl | Tablets | 5 mg | q3d prn*<br>(10 mg/day)# | Oral |

# At the discretion of the investigator the bisacodyl dose may be lowered (5mg) if the investigator/subject feels that the dose is higher than what may be required to provide an adequate bowel movement. If the dose is lowered to 5 mg, the lowered dose will be counted as a full single dose for this subject.

* Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication. On the day of randomization pre-study laxatives should be discontinued. If no bowel movement occurs within 3 days after the start of the double-blind phase, bisacodyl laxative intake will be commenced, which means that a laxative should be taken at that time. However, investigators can instruct their subjects that if they exhibit discomfort during this period they can take oral bisacodyl as a laxative earlier than after 3 days as required to treat constipation. After that first 3 day period, biscodyl tablets may be used no sooner than 72 h after the subjects' most recent bowel movement. However investigators can instruct their subjects that if they exhibit discomfort during the 72 hour period they can take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation. The maximum allowed number of bisacodyl intakes is 5 dosages within 7 consecutive days.

Overall the maximum allowed amount of bisacodyl should not exceed 5 dosages bisacodyl within 7 consecutive days. At the discretion of the investigator, the bisacodyl dose may be lowered. If there is no BM within 24 hours following the 72 h period after the most recent BM bisacodyl use may be repeated. If there is still no BM within 24 hours following the use of bisacodyl, an enema may be used. If there is still no BM following the use of the enema, the subject will be discontinued from the study.

Anti-diarrhoeals may be used throughout the study.

**Test Treatment, Dose, and Mode of Administration:**

| Study Medication | Dosage Form | Unit Strength | Dosing Frequency | Mode of administration |
|---|---|---|---|---|
| Oxycodone/naloxone prolonged-release (OXN) | Tablets | 5/2.5, 10/5, 20/10 and 40/20 mg OXN | Q12h | Oral |
| Matched placebo for OxyPR | Tablets | Matched placebos for 5,10,20 and 40 mg Oxy PR | Q12h | Oral |

During the double-blind treatment phase, subjects randomized to OXN treatment will receive blinded OXN and matched OXYPR placebo. Dosing is fixed and symmetrical (20, 30, 40, 60, 80, 100, and 120 mg/day Oxycodone prolonged release).

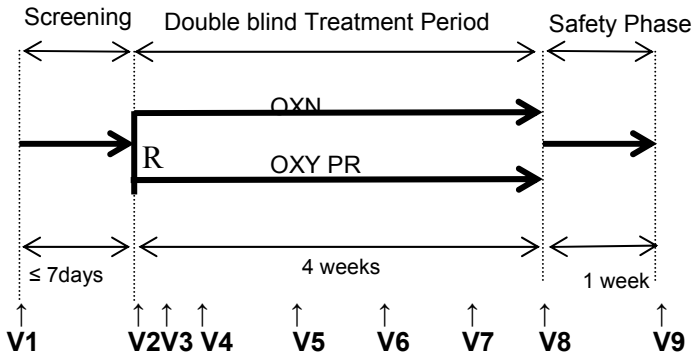
**Reference Treatment, Dose, and Mode of Administration:**

| Study Medication | Dosage Form | Unit Strength | Dosing Frequency | Mode of administration |
|---|---|---|---|---|
| Oxycodone prolonged-release (OxyPR) | Tablets | 5,10,20mg and 40 mg Oxy PR | Q12h | Oral |
| Matched placebo for OXN | Tablets | Matched placebos for 5/2.5,10/5,20/10 and 40/20mg OXN | Q12h | Oral |

During the double blind treatment phase, subjects randomized to OxyPR treatment will receive blinded OxyPR and matched OXN placebo. Dosing is fixed and symmetrical (20,30,40,60,80,100, and 120 mg/day Oxycodone prolonged release)

**Duration of Treatment:**
Pre-randomization Phase:
Screening Period: Prospective Assessment: ≤ 7 days
Double-Blind Phase:
Treatment Period: 4 weeks.
Safety Phase:
Safety follow up: 1 week

**Flow Scheme for Treatment plan**




**Treatment Schedule:**
**Pre-randomization Screening Phase (up to 7 days)**:
At Visit 1, after written informed consent is obtained, subjects undergo complete evaluation for study eligibility (i.e., all inclusion/exclusion criteria). Subjects who meet the Prospective Assessment Criteria can be randomized and enter the double-blind treatment phase of the study at visit 2.
**Double-blind Phase (4 weeks):**
At Visit 2, subjects who qualify for entry into the Double-blind Phase of the study will be randomized to Oxycodone/naloxone (OXN) or Oxycodone PR (OXYPR) (1:1). At the point of entry into the double-blind treatment phase, Investigators will change the subject's dose of pre-study opioid to a dose of Oxycodone PR. This change will be based on the subject's prior dose of opioid and whether subjects need an increase in opioid dose to control their pain. The subject's pre-study laxatives will be changed to study laxatives.Titration of study medication throughout the 4 week double-blind phase, if needed, is allowed by 10mg/day or 20mg/day Oxycodone PR. Subjects will receive double-blind study medication for up to 4 weeks.
Morphine sulphate tablets will be available as rescue medication. If subjects require 2 use of rescue medication per day, the investigator should increase the subject's dose of OXN/OxyPR up to a maximum of 120 mg Oxycodone PR per day.
**Safety Phase (1 week)**
Within one week following completion/discontinuation of the study (V8), the subjects will be followed up by telephone for assessment of any ongoing or new adverse events.

The Schedule of Visits and Procedures is presented in TABLE 1 of the protocol.

**Criteria for Evaluation: Analysis Populations**
The following data sets will be analyzed:
Enrolled Population
The enrolled population is defined as all subjects who signed informed consent.

Randomised Population
The randomised population is defined as all randomised subjects.

Full Analysis Population (FAP)
The full analysis population is defined as all randomised subjects who receive at least one dose of study medication (IMP) and have at least one post-baseline primary efficacy endpoint.

Per Protocol Population (PPP)
The Per Protocol Population is defined as all FAP subjects without major protocol violations. Major protocol violations will be agreed at the Determination of Subject Evaluability (DOSEA) meeting prior to database lock.

Safety Population
The safety population is defined as all randomised subjects who receive at least one dose of IMP and with at least one post-baseline safety assessment .

For the superiority test (bowel function) the Full-analysis population will be the primary analysis and the PP analysis will be performed for sensitivity reasons. For the non-inferiority test (pain) the PP population analysis will be the primary analysis and the FAS analysis will be the sensitivity analysis. All secondary endpoint will be analysed with the FAS population only, all safety analysis will use the DB safety population.
Efficacy Assessments:
Primary Efficacy Assessments:

- Bowel Function Index (BFI), recorded in the Case Report Form (CRF) at each assessment visit. The Bowel Function Index is the mean value of the 3 single items included in the BFI. Ease of defecation (numerical analogue scale [NAS], 0=easy/no difficulty; 100=severe difficulty); Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong); Personal judgment of constipation (NAS, 0=not at all, 100=very strong).
- Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's' pain (worst, least, average, right now), pain relief from medication and pain interference over the last 24 Hours.

• Secondary efficacy assessments:

- Amount of laxative medication use recorded at each assessment visit. Total number of bisacodyl tablets used per week, and the number of Bisacodyl tablets used per day will be recorded in the CRF.
- Amount (mg) of rescue medication used per day (24 hours) recorded on the OXY IR wallet.
- Modified Subjective Opiate Withdrawal Scale (SOWS) will be administered at Visits 1, 3, and 9..
- EQ-5D assessment at Visit 1 and 8.
- Number of bowel movements the subject has had in the last 7 days before the study visit and number of days the subject had a bowel movement in the last 7 days before the study visit.

Safety Assessments:

- Adverse events (collected via spontaneous reports, subject interview)
- Vital signs (at Visits 1, 2, 5, 6, 7 and 8)
- Clinical laboratory test results (at Visits 1,and 8)
- ECG (at Visits 1 and 8)
- Physical examination (at Visits 1 and 8)

**Statistical Methods**

*Sample Size and Power Considerations*

Approximately 280 patients may be screened to obtain 230 pateints who will be randomised in a 1:1 ratio to OXN / OXY PR. Each group will have 115 subjects randomized to ensure 105 patients in the FAS per group.

With 105 subjects in the FAS per treatment group the study has a power of 90% to detect a treatment difference of 12 on the BFI on a two-sided level of significance of α=0.05 assuming a common standard deviation of 26.

**EFFICACY ANALYSES**

# 3 TABLE OF CONTENTS

Page

# 4 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| BM | Bowel Movement |
| BFI | Bowel Functional Index |
| BPI-SF | Brief Pain Intensity-Short Form |
| BUN | Blood urea nitrogen |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| DCF | Data Clarification Form |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HR | Heart Rate |
| ICF | Inform Consent Form |
| ICH | International Conference on Harmonisation of Pharmaceuticals for Human Use |
| IEC | Independent Ethical Committee |
| IR | Instant Release |
| IVRS/IWRS | Interactive Voice Response System/ Interactive Web Response System |
| MedDRA | Medical Dictionary for Regulatory Affairs |
| NAS | Numerical Analog Scale |
| OXN | oxycodone / naloxone prolonged release tablet |
| Oxy PR | oxycodone prolonged release tablet |
| PI | Principal Investigator |
| PR | Prolonged Release |
| q12h | Every 12 hours |
| RBC | Red blood cell (count) |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SOPs | Standard operating procedures |
| WBC | White blood cell (count) |
| WHO | World Health Organisation |

# 5 STUDY CONDUCT AND OVERSIGHT

## 5.1 Sponsor

This study will be conducted by qualified Investigators under the Sponsorship of Mundipharma (China) Pharmaceutical Co.LTD

## 5.2 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and Contract Research Organisation (CRO), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as described in Section 15 of this protocol.

## 5.3 Investigators and Study Personnel

The study will be conducted at approximately 25 sites in China.

## 5.4 Randomisation

Randomisation will be completed using a validated system by the Sponsor in a 1:1 ratio. An interactive response technology (IRT) system will be employed to manage study treatment supply. Refer to Section 11.6 for details of how treatment is assigned.

## 5.5 Data Management

Data management and statistical analyses will be the responsibility of the Data Management and Statistics department at the selected CRO. Data collected via an EDC system as well as subject diaries, questionnaires and other external data, e.g. laboratory data, will be stored in a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. The Monitoring Plan and Data Management Plan will detail the data entry, cleaning, clarification, and validation procedures to be followed by all relevant study staff.

All data will be forwarded to the CRO and an electronic copy supplied to the site. Subjects will complete questionnaires and diaries which will be returned to the Investigator as detailed in Section 10. Laboratory data, vital signs, ECG and Adverse Events and concomitant medication data will be specified in the Data Management Plan.

## 5.6 Monitoring

The study will be monitored by qualified personnel from the CRO. The Monitoring Plan for the study will detail this process. The Investigator will allow monitoring, audit and inspection of the clinical, laboratory, and pharmacy facilities as required, to assure compliance with Good Clinical Practice and Good Laboratory Practice. The EDC system and subject's corresponding original medical records (source documents) are to be fully available for review by the CRO/Sponsor representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations and Good Clinical Practice. All records at the site are subject to inspection by the local competent authorities.

### 5.7 Medical Monitoring & Safety

The name of the Study Physician along with the telephone and fax numbers of the other contact persons at the Sponsor and CRO are listed in the study site file.

**5.8 Central Review/Central Laboratory/Bioanalytical Laboratory** There is no central review processes employed in the study. Local laboratories will be used for sample analysis for safety assessment.

## 6 INTRODUCTION

### 6.1 Therapeutic Area/Background

According to WHO's latest data show that it is estimated that by 2020, the global new cancer cases every year will reach about 15 million people, about a quarter of newly diagnosed patients, a third are treated patients and three-quarters of patients may be with pain. However, due to various reasons, thousands of pain patients did not receive regular treatment, suffering from severe pain.

Pain is a common symptom of cancer patients. The incidence rate of pain for cancer patients is about 60%~80%, where 1/3 for patients with severe pain. Cancer pain patients may survive for months or years, if without appropriate analgesic treatment, cancer pain can cause extremely serious influence on the quality of life of patients and their families. For example, cancer pain can lead to depression, fatigue, anxiety, insomnia, general condition deteriorated, and also a serious interference implementation of anticancer therapy.

### 6.2 Investigational Drug

#### Oxycodone prolonged release

Oxycodone prolonged release (OxyPR) is marketed by Purdue/Mundipharma/Napp and independent associated companies as OxyContin® /Oxygesic® in more than 50 countries for the treatment of moderate to severe pain (severe to most severe pain in Germany and concerned member states, but indication is country-specific) requiring around-the-clock opioid analgesia. Oxycodone was first introduced in the market as a prolonged release tablet at the end of 1995 in the US. Since then, the exposure in humans can be estimated as being approximately 50 million subject months. Oxycodone has been introduced into the market as a prolonged release formulation (Oxygesic) in Germany in 1998 and in China in 2004.

Opioid bowel dysfunction is an adverse drug reaction associated with OxyContin®/Oxygesic® and other opioid analgesics that limits the continuous treatment of pain subjects and is therefore one of the main reasons for insufficient pain therapy in general.

**Naloxone** is a narcotic antagonist used as a solution for injection in the treatment of opioid overdose. When administered orally, it can reduce opioid-induced constipation due to a local action in the gut. It has a high first-pass metabolism, which is an advantage as the laxative effect can be achieved due to the local action in the gut, without significant antagonism of the narcotic analgesic effect of the oxycodone. In a clinical investigation in 22 chronic pain subjects with opioid-related constipation (Meissner et al., 2000), oral naloxone immediate release was titrated individually depending on laxation and withdrawal symptoms up to a daily maximum dose of 36 mg (12 mg three times daily). In the majority of subjects the days with laxation were significantly increased and the days with laxative use significantly decreased. The mean naloxone dose was 17.5 ± 10.2 mg/day and the mean morphine dose was 232 mg/day. Nausea, restlessness and sweating were the most commonly observed side effects during the naloxone treatment. In some subjects, localized sensations of mild to moderate abdominal propulsions or cramps occurred shortly after naloxone administration. In additional studies, naloxone doses and treatment times varied substantially, but clinical findings suggest that oral naloxone doses below 2-4 mg are generally not effective (Meissner et al., 2000) and that daily naloxone doses of 50% of the corresponding morphine dose (including dosages above 100 mg morphine per day) can be tolerated (Latasch et al.,1997).

Please refer to prescription information of Oxycodone prolonged release

**Oxycodone/naloxone prolonged release (OXN PR)**

Oxycodone/naloxone prolonged release (OXN PR) is a prolonged release tablet consisting of oxycodone and naloxone in a 2:1 ratio. This ratio, when given in a prolonged release formulation, has been shown in the clinical Phase II study OXN2401 to provide sufficient analgesic activity measured by a pain scale (Numerical Analogue Scale (NAS)), similar to that of oxycodone combined with placebo naloxone, with an improved safety profile (Mueller-Lissner et al., 2007; Meissner et al.; 2008, Meissner et al., 2009). Naloxone prolonged release was well tolerated by the subjects in study OXN2401. OXN PR has been shown to provide effective analgesia while counteracting constipation (Simpson et al., 2008; Löwenstein et al., 2009; Reimer et al., 2009; Meissner et al., 2009; Vondrackowa et al., 2008). OXN PR (Targin®) was introduced into the German market in 2006. European regulatory procedures in 26 European countries for four dosage strengths (OXN5/2.5 mg PR, OXN10/5 mg PR, OXN20/10 mg PR and OXN40/20 mg PR twice daily) up to a maximum daily dose of OXN80/40 mg PR per day has been successfully completed. The Indication is: ‘Severe pain which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid-receptors locally in the gut’.

## 6.3 Study Rationale

In the UK, OXN PR is available for the treatment of pain under the tradename Targinact® since January 2009 (same tradename Targinact also in Cyprus, France, Belgium, Luxemburg, Slovenia and the Netherlands). In Norway, Sweden and Finland the tradename is Targiniq®. In all other concerned countries the tradename is Targin®. Furthermore OXN PR has also received Marketing Authorisation in Australia, Canada, China, Israel, New Zealand and Korea where the tradename is Targin®.

Since the launch of OXN PR as an analgesic into the market the exposure in humans can be estimated as being > 2 million patient months and the benefit of this combination therapy is

established. OXN PR provides an effective pain treatment together with an improved quality of life due to a reduced number of patients suffering from impeded bowel function compared to treatment with other opioids. OXN PR maintains the systemic opioid effects while naloxone counteracts the bowel function disorders that are typical for opioid treatment due to the local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone in the gut.

The mode of action of OXN PR is based on the particularly low oral bioavailability of naloxone (approx. 2%), which prevents that antagonist from having a significant impact on the central, analgesic properties of oxycodone. One possible obstacle to the development of higher strength OXN PR tablets would arise if the efficient extraction of naloxone by the liver was limited at higher strengths. However a single dose study (OXN1019) investigated the absolute bioavailability of naloxone following the administration of prolonged release naloxone tablets in healthy volunteers. It could be demonstrated that the low absolute bioavailability of naloxone was maintained up to a single dose of 120 mg oral naloxone. Therefore study OXN1019 provided evidence that the administration of OXN PR in daily doses up to OXN180/90 mg PR do not point to a specific risk.

In the clinical Phase III study OXN3401 it could be demonstrated that OXN PR has a superior analgesic efficacy compared to placebo and that the addition of naloxone does not negatively affect the analgesic efficacy of oxycodone PR (Vondrackova et al., 2008). Based on the clinical Phase III studies OXN3001 and OXN3006 it could be illustrated that OXN PR is superior to oxycodone PR alone, offering patients effective analgesia while significantly improving opioid-induced constipation (Simpson et al., 2008; Löwenstein et al., 2009). It was also showed similar results in a Phase III study in patients suffering from malignant pain (OXN2001).

The aim of the present study is to compare the effectiveness of OXN versus OXYPR in the management of chronic cancer pain by determining the improvement in symptoms of constipation –an adverse effect of opioid treatment, and also by assessing pain relief, safety and quality of life.

The study will follow the protocol, ICH- GCP, Chinese GCP and the applicable registration requirements

# 7 STUDY OBJECTIVES

## 7.1 Aim of the study

To assess the investigational drugs' effectiveness in relieving cancer pain and the improvement of adverse reaction of opioid -- symptoms of constipation.

## 7.2 Main Objectives

- To determine the improvement in symptoms of constipation in subjects with moderate to severe cancer pain receiving treatment with oxycodone/naloxone prolonged release tablets

(OXN) compared to oxycodone prolonged release tablets(OXY) based on the Bowel Function Index (BFI).

- To demonstrate the non-inferiority (comparability) of oxycodone / naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets (OXY PR) for the management of chronic cancer pain as assessed by the average pain of the Brief Pain Inventory (BPI).

### 7.3 Other Objectives

- To compare the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN) to oxycodone prolonged release tablets(OXY PR) **based on laxative use.**
- To compare the management of chronic cancer pain of oxycodone / naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets (OXY PR) as assessed by r**escue medication use** recorded by subjects.
- To compare the management of chronic cancer pain of oxycodone / naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets (OXY PR) as assessed by Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's' pain (worst, least, right now), pain relief from medication and pain interference over the last 24 Hours. BPI will be assessed on V1, V2, V5, V6, V7 and V8.
- To assess safety of treatment with OXN compared with OXY based on the Modified Subjective Opiate Withdrawal Scale (SOWS), Adverse Events (AEs), Electrocardiograms (ECG) and laboratory tests.
- To assess quality of life based on EQ-5D

## 8 STUDY SUMMARY AND GRAPHIC

### 8.1 Overall Study Design and Plan

This is a multiple-center, randomized, double-blind, double-dummy, active-controlled, parallel group study using OXN 5/2.5mg, 10/5mg, 20/10mg or 40/20mg and Oxy PR 5mg, 10mg, 20mg and 40mg to treat moderate to severe, chronic cancer pain. Subjects with documented history of cancer pain that requires around-the clock opioid therapy will be included. Subjects must have a medical history of constipation that was induced by, or worsened by their opioid therapy.

This study is composed of three phases: a screening phase(<7 days) and a 4-week double-blind phase and follow up phase(1 week after last dose).

Following informed consent and screening, eligible subjects will be randomly allocated to one of the following treatments (in a ratio of allocation 1:1) via an IRT system.:

- Active oxycodone prolonged release tablets (OXYPR) and placebo oxycodone / naloxone (OXN)

prolonged release tablets.

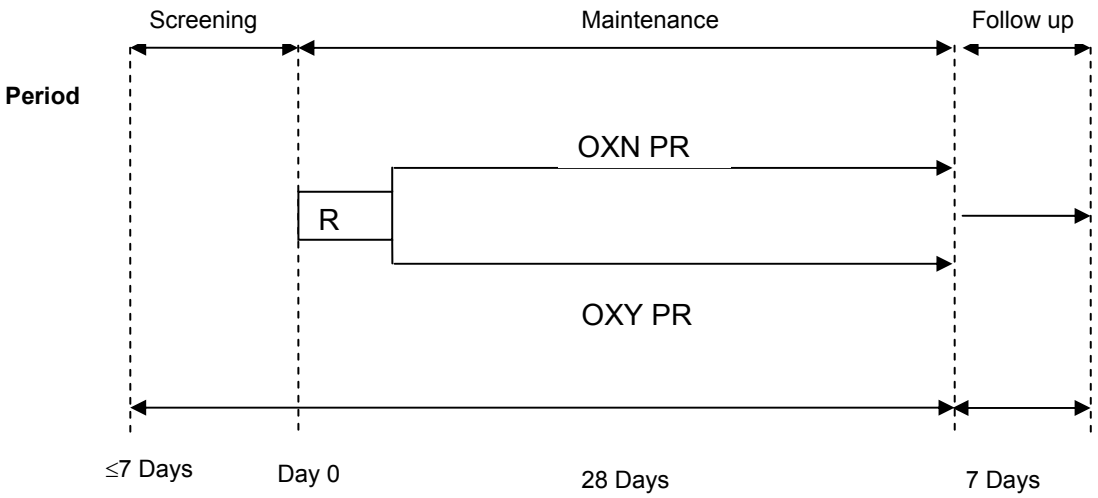
- Active oxycodone / naloxone prolonged release tablets (OXN) and placebo oxycodone prolonged release tablets (OXYPR).

At randomisation, the start of the double-blind phase, subjects will discontinue their current (pre study) opioid and change to an effective dose of study medication (OXYPR/OXN). Subjects will also stop taking any pre study laxatives at the time of randomisation and revert to the study laxative regime.

Approximately 280 patients may be screened to obtain 230 patients who will be randomised in a 1:1 ratio to OXN / OXY PR. Each group will have 115 subjects.

## 8.2 Study Diagram

**Figure 1 Study diagram for randomised double-blind study**




R = randomisation

## 8.3 Efficacy Parameters

### 8.3.1 Primary Efficacy Variable(s)

- Bowel Function Index (BFI) will be the mean of the following items (assessed at V1, V2, V5, V6, V7, V8):

  − Ease of defecation (numerical analogue scale [NAS], 0=easy/no difficulty; 100=severe difficulty)

  − Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong).

  − Personal judgment of constipation (NAS, 0=not at all, 100=very strong).

  Each of the above questions refers to the last 7 days for the subject.

- Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's' average pain over the last 24 Hours. BPI will be assessed on V1, V2, V5, V6, V7 and V8.
-

### 8.3.2 Secondary Efficacy Variable(s)

- To compare the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN) to oxycodone prolonged release tablets(OXY PR) based on laxative use.
- To compare the management of chronic cancer pain of oxycodone / naloxone prolonged release tablets (OXN) compared to oxycodone prolonged release tablets (OXY PR) as assessed by rescue medication use recorded by subjects.
- Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's' pain (worst, least, right now), pain relief from medication and pain interference over the last 24 Hours. BPI will be assessed on V1, V2, V5, V6, V7 and V8.
- To assess safety of treatment with OXN compared with OXY based on the Modified Subjective Opiate Withdrawal Scale (SOWS), Adverse Events (AEs), Electrocardiograms (ECG) and laboratory tests.
- To assess quality of life based on EQ-5D

# 9 SELECTION OF SUBJECTS

## 9.1 Number of Subjects

Approximately 230 subjects will be randomised to achieve 210 evaluable subjects in the Full analysis population. An adequate number of subjects will be screened in the screening period

to achieve this sample size. All subjects must have supplied written informed consent as per Section 15.3 prior to any study assessment or procedure taking place.

## 9.2 Inclusion Criteria

Subjects who are to be included in the study, are those who meet all of the following criteria:

1. Males and females, at least 18 years or older with a diagnosis of cancer.
2. Females less than one year post-menopausal must have a negative urine pregnancy test recorded prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective method of contraception throughout the study. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistenly and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (hormonal), sexual abstinence or vasoectomised partner.
3. Subjects who are receiving WHO step II or Step III analgesic medication who have constipation induced, or worsened by their opioid medication, as shown by

    a. the subject's medical need of regular intake of laxatives to have at least 3 bowel evacuations per week, or having less than 3 bowel evacuations when not taking a laxative, respectively.

    b. the subject's self-assessment that their constipation was induced or worsened by their current pre-study opioid medication.
4. Documented history of moderate to severe, chronic cancer pain that requires aroundthe-clock opioid therapy (starting dose of oxycodone PR between 20 -80 mg/day) and are likely to benefit from WHO step III opioid therapy for the duration of the study.Subjects must be willing to discontinue their current opioid analgesic routine.
5. Opioid medication continue at a stable or nearly stable dose in the investigator's opinion during the treatment.
6. Subjects are willing to discontinue pre study laxative medication and take study specific laxative medication.
7. Subjects taking daily Subjects taking daily fibre supplementation or bulking agents are eligible if they can be maintained on a stable dose and regimen throughout the study, and in the investigators opinion are willing and able to maintain adequate hydration.
8. Subjects willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled clinic visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing written, informed consent.
9. Subjects already taking non-opioid analgesics and all other concomitant medications (including those for the treatment of depression) are eligible to take part in the study. However, all concomitant medications that are considered necessary for the subject's welfare should be continued at a stable dose throughout the double-blind phase of the study

and under the supervision of the investigator. Regarding cyclic chemotherapy please see exclusion criteria list.

10. Subjects expected survived more than 3 months.
11. Subjects are able to read, understand and sign written informed consent prior to study participation and are willing to follow the protocol requirements.

### 9.3 Exclusion Criteria

Subjects to be excluded from the study are those who meet any of the following criteria:

1. Subjects that require a dose >80 mg/day oxycodone PR at the start of the double-blind phase.
2. Any history of hypersensitivity to oxycodone, naloxone, morphine, bisacodyl, related products, and other ingredients.
3. Subjects with any situation in which opioids are contra-indicated, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, paralytic ileus.
4. Subjects with evidence of clinically significant gastrointestinal disease (e.g. paralyticileus, peritnoneal carcinosis), significant structural abnormalities of the gastrointestinal tract (eg.scarring obstruction etc) either related or not related to the underlying cancer or disease progression.
5. Evidence of clinically significant cardiovascular, renal, hepatic or psychiatric disease, as determined by medical history, clinical laboratory tests, ECG results, and physical examination, that would place the subject at risk upon exposure to the study medication or that may confound the analysis and/or interpretation of the study results.
6. Abnormal aspartate aminotransferase (AST; SGOT), alanine aminotransferase (ALT; SGPT), r-Glutamltransferase (GGT), or alkaline phosphatase levels (>3 times the upper limit of normal) or an abnormal total bilirubin and/or creatinine level(s) (greater than 1.5 times the upper limit of normal).
7. Cyclic chemotherapy in the two weeks before the screening visit or planned during the core study that has shown in the past to influence bowel function. If subjects are having their first cycle of chemotherapy during the 2 weeks before the screening visit or during the double-blind phase of the study they should be excluded from the study.
8. Radiotherapy that, in the investigators opinion, would influence bowel function or pain during the double-blind phase of the study.
9. Subjects with known or suspected unstable brain metastases or spinal cord compression, that may require changes in steroid treatment throughout the duration of the study.
10. Subjects with uncontrolled seizures.
11. Subjects with increased intracranial pressure.
12. In the investigator's opinion, subjects who are receiving hypnotics or other central nervous system (CNS) depressants that may pose a risk of additional CNS depression with opioid study medication.

13. Subjects with myxodema, not adequately treated hypothyroidism or Addisons disease.
14. Subjects who have a confirmed diagnosis of ongoing irritable bowel syndrome.
15. Surgery completed prior to the start of the Screening Period, or planned surgery during the study that would influence pain or bowel function during the study or preclude completion of the study.
16. Subjects receiving opioid substitution therapy for opioid addiction (e.g. methadone or buprenorphine).
17. Active alcohol or drug abuse and/or history of opioid abuse.
18. Subjects suffering from diarrhoea and/or opioid withdrawal.
19. Subjects presently taking, or who have taken, naloxone, or participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days prior to the start of the Screening Period (except subject were in follow-up phase of survival data)
20. Subjects who are incapable of giving informed consent or complying with the protocol.

### 9.4 Criteria for Entry into the Double-blind Phase（the end of screening）

Subjects continue to satisfy Screening Inclusion/Exclusion criteria.

The exclusion criteria of Double-blind period are the same as the screening period.

# 10 ASSESSMENTS AND PROCEDURES

## 10.1 Schedule Overview

Table 1 Schedule of visits and procedures/ CRF modules for the study.

Schedule of Visits and Procedures

| **Phase Period** | **Pre-Randomization** | **Double-blind phase** | | | | | | | **Safety Phase** |
|---|---|---|---|---|---|---|---|---|---|
| | **Screening period** | **Treatment period** | | | | | | | **Safety Phase** |
| Duration | < 10 days | 4 weeks | | | | | | | 1 week |
| Study visit | V1 | V2[10] | V3 | V4 | V5 | V6 | V7 | V81 | V9 |
| Study day[2] | -10 to 0 | 0 | 1 | 3 | 7± 3 | 14± 3 | 21± 3 | 28± 3 | 35+ 3 |
| *Informed consent* | X | | | | | | | | |
| *Assess inclusion/ exclusion criteria* | X | (X) | | | | | | | |
| *Demography* | X | | | | | | | | |
| Physical examination | X | | | | | | | X | |
| *Vital signs measurements* | X | (X) | | | X | X | X | X | |
| *Medical history* | X | (X) | | | | | | | |
| *Assess prior and current medication use* | X | (X) | | | | | | | |
| *Clinical laboratory tests (hematology, chemistry, urinalysis)* | X | | | | | | | X | |
| pregnancy[3] | X | | | | | | | X | |
| *12-lead ECG* | X | | | | | | | X | |
| *Clinic visit* | X | (X) | | | X | X | X | X | |
| Telephone visit[4] | | | X | X | | | | | X |
| *Laxative medication use[5]* | | X | | | X | X | X | X | |
| *Question on bowel movements x2[6]* | X | (X) | | | X | X | X | X | |
| *Rescue medication use[7]* | | daily | | | | | | | |
| *Assess concomitant medication use* | | X | | | X | X | X | X | |
| *Bowel function index(BFI)[8]* | X | (X) | | | X | X | X | X | |
| *Brief pain inventory (BPI-SF)* | X | (X) | | | X | X | X | X | |
| *Modified SOWS* | X | | X | | | | | | X |

| Phase Period | Pre-Randomization | Double-blind phase | | | | | | | Safety Phase |
|---|---|---|---|---|---|---|---|---|---|
| | Screening period | Treatment period | | | | | | | Safety Phase |
| Duration | < 10 days | 4 weeks | | | | | | | 1 week |
| *EuroQol EQ-5D* | X | | | | | | | X | |
| *Adverse events (Non-elicited reporting)* | | X | X | X | X | X | X | X | X |
| Call IRT to enter/update subject status information | X | X | | | X | X | X | X | |
| Study medication dosing[9] | | X | | | X | X | X | X | |
| Study medication dispensation | | X | | | X | X | X | | |
| Drug accountability | | | | | X | X | X | X | |
| Randomization | | X | | | | | | | |
| Discontinuation/ end of study | | | | | | | | X | |

1. End of the double-blind phase completed at visit 8 or as soon as possible after early discontinuation from study medication.
2. The study visit window for Visit 1 ± 3 days and ± 3 days for Visits 5, 6, 7, 8 , +3 days for visit 9 Further visits to the study site will be conducted if considered necessary for the subject's welfare.
3. Urine test. Women of childbearing potential must have a negative pregnancy test prior to first dose of study medication.
4. Visits 3 & 4 are scheduled as telephone visits but can be completed as a clinic visit if required.
5. Laxative use in the last week to be recorded (total number of tablets per week and number of tablets per day)
6. Question 1. Number of bowel movements the subject has had in the last 7 days before the study visit
   Question 2. Number of days the subject had a bowel movement in the last 7 days before the study visit.
7. Recorded throughout the day for the rescue medication at the time of occurrence.
8. Includes subject assessments; ease of defecation, feeling of incomplete bowel evacuation, and personal judgment of constipation over the past 7 days.
9. If a subject needs to be titrated for adequate pain control the visit should be documented in the subject's source notes and the change in study medication dose will be recorded on the dosing CRF page at the next clinic visit
10 If screening visit and visit 2 are on the same day, do not duplicate the assessment completed on visit 1.

## 10.2 Screening/Baseline Period

After confirming the subject's initial study eligibility, the following procedures/evaluations will be performed after the subject signs informed consent. No study procedure will be completed until the subject has given written informed consent

**Visit 1 (≤ 10 days):**

- Informed consent
- Inclusion/exclusion criteria
- Demography
- Physical exam

- Vital signs
- Medical history
- Prior and current medication use
- Clinical laboratory tests (hematology, chemistry, urinalysis)
- Pregnancy test (urine) if applicable
- 12-lead ECG
- Complete 2 questions on bowel movement
- Bowel Function Index BFI (Appendix 2)
- Brief Pain Inventory Short Form BPI-SF© (Appendix 1 )
- Modified Subjective Opiate Withdrawal Scale SOWS (Appendix 3)
- EuroQol EQ-5D (Appendix 4)

**Screening failures**

For subjects who are screening failures, the visit date should be registered in the IRT System and screening failure reason should be also be collected in the IRT system .

A subject will be considered a screen failure if the subject signs the ICF but withdraws from the study before receiving any study treatment. Data for screen failures will be collected in the source documentation at the site; however, the subject number , date of consent and screen fail reason and adverse events will be captured in the EDC system .

## 10.3 Randomisation-Visit 2 (Day 0)

Randomisation will be completed once all inclusion and exclusion criteria are verified. Visit 2 can be on the same day of visit 1 or up to 10 days later and will be completed by IRT. Refer to Section 11.6 for further details.

**Visit 2(Day 0)**

- Check Inclusion/exclusion criteria
- Check medical history unchanged
- Vital signs
- Laxative use

- Complete 2 questions on bowel movement
- Concomitant medication and therapy
- Bowel Function Index BFI (Appendix 2)
- Brief Pain Inventory Short Form BPI-SF© (Appendix 1 )
- Modified Subjective Opiate Withdrawal Scale SOWS (Appendix 3)
- Adverse Events

**Other procedures:**

- Call IRT to update the subject status information
- Randomisation to double-blind treatment

**Dispense:**

- Double-blind study medications, OXYPR/OXN, rescue medication (morphine sulphate tablet), and laxative (bisacodyl)
- Subject Questionnaires required for Visit 3 and Visit 4

## 10.4 Treatment Period- Visit 3, 4, 5, 6, 7 and 8

**Visit 3(Day 1) and Visit 4(Day 3) Telephone Visits** (Clinic visits can be performed at the discretion of the investigator and the same assessments as scheduled are to be completed)

The following evaluations will be performed at Visit 3 and 4, which occurs 1 and 3 days after Visit 2:

- Site Study Staff to call the subject to determine whether the subject needs to be titrated to a higher/lower dose study medication
- Record rescue medication use
- Adverse Events

Subject Completes:

- Modified Subjective Opiate Withdrawal Scale SOWS(only on Visit 3)

**V5，V6 和 V7**

The following evaluations will be performed at Visit 5, 6, 7 and recorded on the eCRF:

- Call IRT to update subject status information

Vital signs

Complete 2 questions on bowel movement

—Question 1：number of bowel movements the subject has had in the last 7 days before the study visit；

—Question 2. Number of days the subject had a bowel movement in the last 7 days before the study visit.

Laxative use

Record rescue medication use

Concomitant medication and therapy

Bowel Function Index BFI（BFI）

Brief Pain Inventory Short Form BPI-SF©（BPI-SF）

Study Medication Dosing change if needed

Adverse Events　Study Medication Dispensation

Drug Accountability

**Visit 8( Day 2, at time of study completion or early discontinuation)**

Physical exam

Vital signs

Clinical laboratory tests (hematology, chemistry, urinalysis)

Pregnancy test (urine) if applicable

12-lead ECG

Complete 2 questions on bowel movement (see section above for V5-V7 for wording)

Laxative use

Record rescue medication use

Concomitant medication and therapy

Bowel Function Index BFI（BFI）

Brief Pain Inventory Short Form BPI-SF©（BPI-SF）

EQ-5D

Adverse events

Drug accountability

Call IVRS to update subject status information

## 10.5 Follow-Up Period-Visit 9

Subjects that complete the Treatment Period or who discontinue treatment with IMP(s) early will be followed up no earlier than 7 days after the subject's last dose of IMP.

**Visit 9(Telephone Visit)**

Modified Subjective Opiate Withdrawal Scale（SOWS）

Adverse Events

## 10.6 End of Study

Subjects that complete the treatment Period will carry out Completion/Discontinuation Visit (v8) procedures in accordance with Table 1

## 10.7 Early Discontinue/Withdrawal from Study

The Investigator(s) or subjects themselves may stop study treatment at any time for safety or personal reasons. If possible, the subject will attend clinic to complete end-of-study procedures (Visit 8).

Subjects who do not tolerate the study medication will be discontinued from the study. Site study staff members will discontinue the subject from the study and the subject will return to the clinic to complete Visit 8 and to be provided with appropriate therapy according to standard care.

For subjects who prematurely stop participation in the study, Investigators will question subjects about their primary reason for discontinuing from the study, which will be recorded in the electronic Case Report Form. Site study staff members will follow subjects after the last dose of study medication for 7 days to collect non-serious adverse events, for 30 days to collect serious adverse events and obtain non-serious adverse event outcome information, and for serious adverse events, until the event resolves, or the event or sequelae stabilize.

# 11 STUDY TREATMENTS AND CONCOMITANT THERAPIES

## 11.1 Study Treatments (IMPs and NIMPs)

### 11.1.1 Test Investigational Medicinal Product(s), Dose and Mode of Administration

In double-blind phase, subjects randomized to test treatment group will take OXN and matching placebo of OXYPR. The dosage would be fixed and symmetrical (20/10, 30/15, 40/20, 60/30, 80/40,100/50 or 120/60 mg/day of oxycodone/naloxone)

**Table 1 Investigational Drug Identity**

| Test Treatment, | **Dosage Form** | **Strength** | **Dosing Frequency** | **Mode of Administration** |
|---|---|---|---|---|
| Oxycodone /naloxone prolongedrelease (OXN) | Tablets | 5/2.5，10/5，20/10 and40/20mg OXN | Q12h | Oral |
| Matched placebo for OXYPR | Tablets | Matching placebos for 5,10, 20 and 40 mg OXYPR tablets | Q12h | Oral |

### 11.1.2 Reference Investigational Drug, Dose and Mode of Administration

Subjects randomized to reference treatment group will take OXY PR and matching placebo of OXN. The dosage would be fixed and symmetrical(20, 30, 40, 60, 80,100 or 120mg/day)

**Table 3 Reference Investigational Drug Identity**

| Study Medication | Dosage Form | Strength | Dosing Frequency | Mode of Administration |
|---|---|---|---|---|
| Oxycodone Prolonged release (OXY PR) | Tablets | 5，10，20 and 40mg Oxy PR | Q 12 h | Oral |
| Matched placebo for OXN | Tablets | 5/2.5，10/5，20/10 and40/20mg OXN placebo | Q 12 h | Oral |

### 11.1.3 Non-Investigational Medicinal Product (NIMP), Dose and Mode of Administration

The rescue medications are not Investigational Medicinal Products. Rescue medications include Analgesics and Laxative treatment and will be supplied by the Sponsor.. Table 4 and 6 listed the analgesics and laxative rescue medication accordingly.

**Table 4 Analgesics Rescue Medication dosage and mode of administration**

| **Rescue Medication(Pain)** | **Dosage Form** | **Strength** | **Dosage Frequency** | **Mode of Administration** |
|---|---|---|---|---|
| Morphine Sulphate | Tablet | 10 mg | P.R.N, q4-6h | Oral |

| | | | | |
|---|---|---|---|---|
| Tablets | | | | |

During the double-blind treatment phase, all subjects can receive Morphine Sulphate Tablets as rescue medication up to 6 times a day at a dose(based on calculation of ratio for morphine and oxy IR) according to table 5.

At the discretion of the investigator, the rescue dose may be lowered if the subject experiences side effects from the recommended dose, or if after taking the recommended dose the investigator/subject feel that the dose is higher than what may be required to provide adequate analgesia.

- During the double-blind treatment phase, subjects, who consistently require more than 2 rescue doses of morphine sulphate tablets per day should have their dose of OXN/OXYPR increased.
- The maximum possible Oxycodone dose during the study is 120 mg per day plus 6 rescue doses of 30mg morphine sulphate tablets per day, i.e. 120 Oxycodone PR plus 180mg morphine sulphate tablets per day
- During the double-blind phase subjects who are on the maximum dose of 120 mg OXYPR/OXN and who regularly require more than 2 rescue doses per day should be discontinued.
- 6 rescue doses of morphine sulphate tablet is the total maximum amount of rescue medication per day. Subjects who, on more than two consecutive days take >6 rescue doses should be discontinued.

Stable doses of pre-study, non-opioid analgesics may be continued during the study. Any analgesic dosing during the double-blind treatment phase should remain stable.

Opioid analgesics other than the study medication (i.e. OXN, OXYPR) and rescue medication (Morphine Sulphate Tablet) are not permitted during the double-blind phase.

For further information refer to below table for Rescue Dose.

**Table 5 Rescue Dose (based on calculation of ratio for morphine and oxy IR)**

| Dose Level of daily maintenance dose of OXN/OXY | Morphine sulphate tablets Rescue Dose (Per Dose) |
|---|---|
| L1(20mg) | 10 mg（1 Tablet） |
| L2(30mg) | 10 mg（1 Tablet） |
| L3(40mg) | 20 mg（2 Tablet） |
| L4(60mg) | 20 mg（2 Tablet） |
| L5(80mg) | 30 mg（3 Tablet） |
| L6(100mg) | 30 mg（3 Tablet） |
| L7(120mg)[1] | 30 mg（3 Tablet） |

1. If the daily dose over the maximum possible oxycodone dose during the study is 120 mg per day plus 6 rescue doses of morphine sulphate tablets per day, the subject should discontinued from the study.

**Laxatives, Anti diarrhoeal Agents**

Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication. On the day of randomisation pre study laxatives should be discontinued. If no bowel movement occurs within 3 days after the start of the double-blind phase, bisacodyl laxative intake will be commenced, which means that a laxative should be taken at that time. However investigators can instruct their subjects that if they exhibit discomfort during this period they can take oral bisacodyl as a laxative earlier than after 3 days as required to treat constipation. After that first 3 day period, bisacodyl tablets may be used no sooner than 72 h after the subjects' most recent bowel movement. However investigators can instruct their subjects that if they exhibit discomfort during the 72 hour period they can take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation. The maximum allowed number of bisacodyl intakes is 5 dosages within 7 consecutive days.

Overall the maximum allowed amount of bisacodyl should not exceed 5 dosages bisacodyl within 7 consecutive days. At the discretion of the investigator, the bisacodyl dose may be lowered. If there is no BM within 24 hours following the 72 h period after the most recent BM bisacodyl use may be repeated. If there is still no BM within 24 hours following the use of bisacodyl, an enema may be used. If there is still no BM following the use of the enema, the subject will be discontinued from the study.

**Table 6 Laxatives Rescue Medication dosage and mode of administration**

| **Rescue Medication** | Dosage Form | **Unit Strength Dosing** | **Dosing Frequency** | **Mode of Administration** |
|---|---|---|---|---|
| Bisacodyl | **Tablets** | 5mg | q3d PRN （10mg/day）# | Oral |

# At the discretion of the investigator the bisacodyl dose may be lowered (5 mg) if the investigator/subject feel that the dose is higher than what may be required to provide an adequate bowel movement. If the dose is lowered to 5 mg the lowered dose will be counted as a full single dose for this subject.

Antidiarrhoeals may be used throughout the study.

## 11.2 Study Treatments to be Supplied

The Sponsor will package the study treatments. Each subject will receive either OXN and matched placebo of OXYPR or OXYPR and matched placebo of OXN. In addition to the IMP subjects will also receive rescue medication for analgesia and laxative treatment if needed.

Investigational and reference drugs will be supplied in labelled containers by the Sponsor.

| **IMP** | **Dosage form** | **strength** | **Manufacture site** |
|---|---|---|---|
| OXN PR | Tablets | 5/2.5mg,<br>10/ 5mg,<br>20/10mg<br>40/20mg | Bard Pharmaceutical ltd., UK |
| Matched placebo of OXY PR | Tablets | 5mg,<br>10mg,<br>20mg<br>40 mg | |
| OXY PR | Tablet | 5mg,<br>10mg,<br>20mg<br>40 mg | |
| Matched placebo of OXN | Tablet | 5/2.5mg,<br>10/5mg,<br>20/10mg<br>40/20mg | |

The Product Release Certificate(s) for the IMP(s) will be included in the clinical study report for this protocol. The study treatment will be supplied in packs labelled to meet the national requirements and will include a unique pack identifying number.

## 11.3 Dosing Schedule

### 11.3.1 Starting dose of IMP

At Visit 2, qualified subjects with confirmed opioid related constipation will stop their pre study opioid and will be randomised in a 1:1 allocation ratio to the double-blind study medication (i.e. OXN or OXYPR) taken every 12 hours which will be titrated to an effective analgesic dose.

The starting dose of oxycodone PR will be based on the subject's prior dose of opioid (see Appendix 5 Guidance table for identifying the starting dose of oxycodone PR based on pre-study opioid use) and whether subjects need an increase in opioid dose to control their pain.

The related dose level based on approximately calculation by investigator will be selected as starting dosage. Start dose of eligible subjects (in the opinion of the investigator) for treatment is at least ***20mg/da***y oxycodone PR to a maximum of ***80 mg/day*** oxycodone PR.

Subjects requiring a start dose of > 80 mg oxycodone PR should be excluded from the study (e.g. >200 mg Morphine).

.

### 11.3.2 Titration and Maintain dose of IMP

#### Titration

During the double-blind phase study medication will be titrated up to a maximum of 120 mg/day of oxycodone PR in a double-blind, double-dummy manner to obtain good pain control.

Open label morphine sulphate tablets will be available to subjects as rescue medication throughout the double-blind treatment phase. Morphine sulphate tablets will be taken at a dose according to Table 5 as recommendation, and will be taken as required by subjects to treat breakthrough pain. A maximum of 6 doses of Morphine sulphate tablets can be taken in 24 hours (e.g. for a subject on 120 mg/day oxycodone PR then the maximum dose of Morphine sulphate tablets would be 180 mg/day). For further information see Appendix 5.

If a subject regularly requires more than ***2 uses*** of rescue medication per day, the investigator should increase the subject's dose of double-blind medication by 10mg/day or 20mg/day of OXN/OXYPR.

If a subject requires greater than 120 mg/day OXY/OXN or 120 mg/day OXY/OXN plus more than the maximum Morphine sulphate tablets allowed by the protocol e.g. regularly requires more than two rescue doses of Morphine sulphate tablets, then the subject must be withdrawn from the study.

**Daily Maintained dose level**

| Dose Level | Daily maintenance dose of OXN | Daily maintenance dose of OXY |
|---|---|---|
| L1 | 20/10 mg | 20mg |

| | | |
|---|---|---|
| L2 | 30/15 mg | 30mg |
| L3 | 40/20mg | 40mg |
| L4 | 60/30 mg | 60mg |
| L5 | 80/40 mg | 80mg |
| L6 | 100/50 mg | 100mg |
| L7[1] | 120/60 mg | 120mg |

1 Subjects requiring a start dose of > 80 mg oxycodone PR should be excluded from the study (e.g. >200 mg Morphine).

## 11.4 Dose Modification/Discontinuation of NIMP

### Analgesia

During the double-blind treatment phase, all subjects can receive morphine sulphate tablets as rescue medication up to 6 times a day at a dose according to Table 5.

At the discretion of the investigator, the rescue dose may be lowered if the subject experience side effects from the recommended dose, or if after taking the recommended dose, the investigator/subject feels that the dose is higher than what may be required to provide adequate analgesia.

- During the double-blind treatment phase, subjects, who consistently require 2 rescue doses of morphine Immediate-release Tablets per day should have their dose of OXN/OXY increased.
- The maximum possible Oxycodone dose during the study is 120 mg per day plus 6 rescue doses of 30mg morphine sulphate tablets per day, i.e. 120 Oxycodone PR plus 180mg morphine sulphate tablets per day
- 6 rescue doses of morphine sulphate tablets are the total maximum amount of rescue medication per day. Subjects who, on more than two consecutive days take >6 rescue doses should be discontinued.
- During the double-blind phase subjects who are on the maximum daily dose of 120 mg Oxy PR/OXN and who regularly require more than 2 rescue doses per day should be discontinued.

*Stable doses of pre-study, non-opioid analgesics may be continued during the study. Any analgesic dosing during the double-blind treatment phase should remain stable. Opioid analgesics other than the study medication (i.e. OXN, OxyPR) and rescue medication (*morphine sulfate *Tablets) are not permitted.*

•

In case other medication is taken by the subject after administration of the study drug, the investigator should record that on the case report form, including the name of drug(s), dosage and administration, the duration of administration, and the reason for administration.

### Laxatives, Anti-diarrhoeal Agents

1. Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication.
2. On the day of randomization pre-study laxatives should be discontinued.
3. If no bowel movement occurs within 3 days after the start of the double-blind phase, bisacodyl laxative intake will be commenced, which means that a laxative should be taken at that time.
   However, investigators can instruct their subjects that if they exhibit discomfort during this period they can take oral bisacodyl as a laxative earlier than after 3 days as required to treat constipation.
4. After that first 3 day period, biscodyl tablets may be used no sooner than 72 h after the subjects' most recent bowel movement. However investigators can instruct their subjects that if they exhibit discomfort during the 72 hour period they can take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation.
5. The maximum allowed number of bisacodyl intakes is 5 dosages within 7 consecutive days.

At the discretion of the investigator the bisacodyl dose may be lowered (5mg) if the investigator/subject feels that the dose is higher than what may be required to provide an adequate bowel movement. If the dose is lowered to 5 mg, the lowered dose will be counted as a full single dose for this subject.

Overall the maximum allowed amount of bisacodyl should not exceed 5 dosages bisacodyl within 7 consecutive days.

If there is no BM within 24 hours following the 72 h period after the most recent BM bisacodyl use may be repeated. If there is still no BM within 24 hours following the use of bisacodyl, an enema may be used. If there is still no BM following the use of the enema, the subject will be discontinued from the study.

Anti-diarrhoeals may be used throughout the study.

## 11.5 Method of Administration

The blinded study medication (i.e. OXN or OXYPR) will be administered orally, prescribed q12h. The open-label rescue medication (i.e. morphine sulphate tablets) will be administered orally, prescribed q4-6 hours as required for breakthrough pain. The open-label laxative medication (i.e. bisacodyl) will be administered orally, prescribed q3 days as needed. Investigators will instruct their subjects that if they exhibit discomfort during the 72 hours period they can take oral bisacodyl as a laxative earlier than 72 hours after their most recent BM for the treatment of constipation.

## 11.6 Treatment Assignment

Treatments are masked in a double-dummy fashion, whereby subjects to receive OXN are given OXN and OXYPR placebo, and subjects to receive OXYPR are given OXYPR and OXN placebo.

Treatment assignments will be randomised within blocks of fixed size. If possible, no stratification will be done.

The randomisation scheme will be reviewed and approved by a statistician at the Sponsor's site and locked after approval. Randomisation data will be kept strictly confidential within the Clinical Supplies Department, accessible only to authorised persons until the time of unblinding. The randomisation scheme and identification for each subject will be included in the clinical study report.

## 11.7 Blinding

The study medication (OXN or OXYPR) will be packaged in a double-blind, double-dummy manner, rendering the active tablets indistinguishable from the matched placebo tablets. During the double-blind phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the Investigators, investigational site personnel, and the Sponsor's and CRO's staff, will be blinded to the medication codes. Randomisation data will be kept strictly confidential, filed securely by the Sponsor, and accessible only to authorized persons per Sponsor's Standard Operating Procedures (SOPs) until the time of unblinding. Emergency unblinding will be done via the IRT system. Unblinding is not to be done unless an actual emergency occurs and knowledge of the subject's randomisation code may affect his/her medical treatment. If possible, before breaking the blind, the Investigator should consult with the Sponsor's Medical Monitor to ascertain the necessity of breaking the code. A record will be made of the date, time and reason for breaking the blind.

## 11.8 Treatment Compliance/Drug Accountability

The Investigator and study staff will be responsible for the accountability and record maintenance of all clinical supplies (dispensing, inventory, and returns) following Sponsor instructions and will adhere to GCP guidelines as well as applicable country specific regulations. Subjects will be asked to return all unused medication and used medication containers at each visit of treatment period to evaluate medication compliance. At each visit the Investigator must check and document subjects' compliance with taking study treatment(s).

Under no circumstances will the Investigator allow the study treatment(s) to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled and currently participating in the study.

## 11.9 Concomitant Therapies (Permitted and Prohibited)

All medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the Investigator.

For subjects who receive study medication, concomitant medications and therapies, including over-the-counter medications and non-pharmacological treatments such as physiotherapy, that are ongoing as of the date of informed consent will be recorded on the Concomitant Therapy section of the eCRFs.

The Concomitant Therapy CRF will be maintained and updated throughout the subject's participation in the study for any new therapies of changes to existing therapies. The dose of these concomitant medications taken during the double-blind period should be kept constant until study completion. The use of such concomitant medications should be approved in advance by the Sponsor, when possible. The Investigator will record the adverse event for which the concomitant medication was administered on the CRF.

Analgesia and laxative will be permitted for the treatment of breakthrough pain and opiated constipation as described in Section 11.4.

### 11.10 Shipping, Handling, Storage, and Destruction/Return

All study treatments will be supplied to the Principal Investigator by the Sponsor via a local warehouse contracted by the Sponsor. Drug supplies must be kept in an appropriate secure area (e.g. locked cabinet/pharmacy) and stored according to the conditions specified on the drug labels. Specific laws relating to the handling and storage of [narcotics/chemotherapeutics] must be followed, and this will be the responsibility of the Investigator [or designee such as pharmacist] (e.g. ).

Investigational site personnel must maintain an accurate and timely record of the receipt of all clinical supplies, dispensing of study treatments to the subject, collection of unused supplies returned by the subject and subsequent return of unused or expired study treatment to the Sponsor. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study treatment dispensing/return reconciliation log, (c) study treatment accountability log, and (d) all shipping service receipts. All forms will be provided by the Sponsor's selected CRO. Any comparable forms that the site wishes to use must be approved by the Sponsor. A copy of these records must be given to the Sponsor at the end of the studyThe supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or Competent Authority (CA).

All unused study treatment(s), including empty containers, are to be returned to the investigational site personnel by the subject to the Sponsor designated warehouse termly and no later than the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. The investigational site personnel must not destroy any study treatment labels or any partly used or unused study treatment supply until directed by the Sponsor or designee following accountability checks. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel or designee, study treatment that is to be returned to the Sponsor designated warehouse must be sealed with tamper-evident seals and shipped back to the Sponsor designated warehouse following [all local regulatory and shipment laws/the Pharmacy manual/IRT guidance.

## 12 REFERENCE VALUES

## 12.1 Physical/Vital Sign Assessments

Vital signs (e.g. blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiration rate, temperature, and weight measurements will be obtained at the visits designated on the Schedule of Visits and Procedures (Table 1). Blood pressure and pulse rate will be measured after the subject has been sitting for 3 minutes.

Each clinically notable vital sign abnormality has to be recorded on the AE section of the eCRF . Additionally, if the change in vital signs qualifies as a SAE it has to be reported to the CRO/Sponsor using the SAE data form .

## 12.2 Laboratory Assessments

All scheduled clinical laboratory tests will be performed by local laboratories. Local laboratories will perform tests to qualify subjects for entry into the study and relative safety assessment. Laboratory certification will be included in the clinical study report for this protocol as appendix. The Schedule of Visits and Procedures (Section 10.1) shows the time points at which blood and urine samples will be collected for clinical laboratory tests.

| | Items |
|---|---|
| Hematology | RBC， haemoglobin, haematocrit, platelets and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils). |
| Biochemistry | sodium, potassium, chloride, bicarbonate, Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin, blood urea, creatinine, glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin, uric acid. |
| Urinalysis | pH, protein, glucose, ketone, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity |

A laboratory abnormality may qualify as an AE or SAE as described in Section 13.7 Additionally, if the abnormality qualifies as a SAE it must be reported to the Sponsor using the SAE data form.

Values out of the lower normal range do not automatically lead to an exclusion of the subject from the study. The decision to discontinue a subject from the study due to bilirubin or creatinine levels below the lower limit of normal should be based on the medical judgement of the Investigator. Microscopic urinalysis will only be performed when certain parameters of the macroscopic urinalysis show abnormal results.

### 12.3 Additional Assessments Reference Ranges

## 13 SAFETY ASSESSMENTS

Safety assessments will be recorded from the point at which the Informed Consent is signed. These will consist of:

- monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), observed or volunteered, regardless of treatment group or suspected causal relationship to the IMP. This includes reactions, interactions, accidents, illnesses, misuse and abuse.
- monitoring haematology, blood chemistry, and urine values at visits 1, 8;
- periodic measurement of vital signs at visits 1,2,5,6,7,8;
- physical examinations at visits 1,8
- 12-lead ECGs at visits 1,8;

The obligations and responsibilities with regards to collection, distribution and onward reporting of adverse events and reactions to the appropriate regulatory bodies, committees and other investigators will be carried out in accordance with local regulations and are documented in a separate Safety Plan.

### 13.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

**An Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can be:

- Any unfavourable and unintended sign/syptom (including reactions from overdose, abuse, incorrect use of any treatment, or interaction)
- Any new disease or exacerbation of an existing disease (e.g. increase in frequency or worsening in nature)
- Any deterioration in measurements of laboratory values or other clinical tests (e.g. ECG, vital signs or X-ray) that results in symptoms, a change in treatment, or discontinuation from the IMP
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline
- Other medical events regardless of their relationship to the IMP, such as accidents, falls and any injuries resulting from them.

**A Serious Adverse Event (SAE)** is any AE that:

- results in death
- is life-threatening (i.e. the subject was at immediate risk of death from the AE as it occurred)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who was exposed to the IMP)
- is a medically important event or reaction.

Assessment of medically important events:

The Investigator **must** check the list of Important Medical Events (supplied in the Investigator Site File) to determine whether criteria for a SAE is met. Additionally, any event not on this list, but that the Investigator determines is medically important (e.g. if it jeopardises the patient or requires intervention to prevent a serious outcome) should be reported as an SAE.

An SAE must be reported ***immediately*** (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period. Any SAE with a suspected causal relationship to the IMP occurring at any other time after completion of the study must be promptly reported.

The following **mandatory information** must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Protocol number

- Site number

- Subject number

- AE

- IMP(s)

- Investigator's name and contact details

Causality assessment should be completed as soon as possible.

Follow-up information should be actively sought until the SAE has resolved or sequelae have stabilised. Additional information e.g. hospital reports or death certificates, may be requested by the Sponsor and should be anonymised/pseudonymised before transmission and subsequently filed in the Investigator Site File.

The medical safety of the subject is of paramount importance when discussing study continuation.

## 13.2 Reporting of Adverse Events

See also Appendix Section 6.

Reporting period – Events will be recorded from the point at which the Informed Consent is signed until 7(+3) days after the subject leaves the study. This includes new AEs that are reported in the 7(+3) days following the subject's completion/discontinuation visit. Any AE that is still ongoing 7(+3) days after the completion/discontinuation visit will have an outcome of 'ongoing' in the CRF, however the Investigator will continue to follow up ongoing AEs and record information in the source documents. SAEs will be followed until the event resolves or the event or sequelae stabilise and this information will be reported to the Sponsor using the SAE Data Form.

Medical conditions that are diagnosed at the screening visit will *only* be documented as adverse events if they are known to have started or are suspected to have started after the subject has signed the informed consent form. All other medical findings at the medical examination at the screening visit will be documented as medical history. Medical judgement should be exercised to estimate if a condition is likely to have started between the signing of the informed consent and the date/time of the physical examination.

If the Investigator becomes aware of a SAE after the completion of the study (after the 7(+3) days follow up period), which may have been caused by an IMP or NIMP used in the study, they should report it to the Sponsor by phone, fax or e-mail.

Screen failures - For subjects who are screen failures, AEs will be recorded on the AE Screen Failure Log.

For subjects who receive at least one dose of study medication - All AEs will be collected on the AE section of the EDC. In addition, a note should be made in the source documentation of the subject.

SAE - All SAEs will be collected on the AE section of the EDC in 24 hours after the investigator is informed and flagged as serious. All SAEs information shall be collected and recorded in the SAE Data Form in the EDC. Investigators should evaluate the relevance of every SAE case with the investigated drug.

Reporting term - A cluster of signs and symptoms that results from a single cause or that could form a diagnosis should be reported as a single AE.

Contact - The drug safety commissioner's contact phone number/fax number and email address will be stored in the Investigator Site File. Questions relating to Drug Safety and Pharmacovigilance should be addressed to this number or e-mailed.

### 13.3 Causality Assessment

The question of the relationship of an AE to the IMP should be determined by the Investigator after thorough consideration of all facts that are available.

Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, underlying conditions in the study population, exclusion of other causes, and/or absence of alternative explanations.

The Investigator will be asked if a **reasonable possibility of a causal relationship** to the IMP is suspected**.**

- "Yes" should be selected if there are facts (evidence) or arguments to suggest a causal relationship.
- "No" should be selected if there are no facts (evidence) or arguments to suggest a causal relationship.

Please note that causality assessment of adverse events in the EDC only relates to the IMP(s) named in Chapter 5.

If an AE is related to a non-investigational medicinal product or concomitant therapy only, and not an interaction or effect of the IMP, the causality assessment will be "No" (no reasonable possibility of a causal relationship to IMP).

### 13.4 Severity Assessment

The Investigator (or medically qualified designee) will evaluate the comments of the subject and the response to treatment to judge the severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health and will be assessed according to the following criteria:

**Mild:** Awareness of sign, symptom, or event, but easily tolerated.

**Moderate:** Discomfort enough to cause interference with usual activity and may warrant intervention.

**Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

Note: A severe adverse event will not necessarily be a serious adverse event.

Any medication necessary for the treatment of an adverse event must be recorded on the Concomitant Therapy Section of the EDC (and, if applicable, on the SAE Data Form).

## 13.5 Outcome Evaluation

The terms and definitions below are for the evaluation of final AE result:

- **Ongoing:** The AE is continuing at the end of the study (last study visit).
- **Recovered:** the subjects has fully recovered from the adverse event. With no residual effects.
- **Recovered with sequelae**: the subject has residual effects of the adverse event. Therapy may or may not be given for the adverse event.
- **Death**: Requires a SAE report to the sponsor with all relevant information as to the cause of death (within 24 hours from learning of death).
- **Lost to follow up**: All communication with the subject has ceased

## 13.6 Pregnancy

Pregnancy occurring in a subject (or a male subject's female partner) during a clinical study must be reported to the investigator, who will report to the drug safety specialist of Mundipharma (China) Pharmaceutical Co., Ltd. in 24 hours using the Pregnancy Notification Form. The CRO will contact the investigator to confirm significant pregnancy information i.e. AEs during pregnancy, the pregnancy outcome, and any events to 3 months post-partum. All the follow up information about the pregnancy will be reported to the drug safety specialist of Mundipharma (China) Pharmaceutical Co., Ltd. in 24 hours after being notified.

## 13.7 Laboratory Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- **They result in a change in IMP schedule of administration** (change in dosage, delay in administration, IMP discontinuation, **or other medical or treatment intervention** (e.g. anaemia requiring transfusions or hyperglycaemia requiring potassium supplement))
- They are considered as **clinically significant** by the Investigator,
- They meet the markedly abnormal criteria

Where possible, the AE description should be the diagnosis rather than the abnormal laboratory value. The same is true if abnormal values reflect a worsening of an underlying condition. **Abnormal laboratory values that are present at Screening are not AEs** (unless they are a consequence of a Screening procedure). Where an Investigator does not deem an abnormal (or

markedly abnormal) laboratory value to be clinically significant, the reason must be clearly document in the source notes (e.g. normal fluctuation of the disease).

### 13.8 Vital Signs and Physical Examinations

AEs from vital sign or physical examination assessments include any changes, values or findings (abnormalities):

- which result in medical intervention
- and/or is deemed by the Investigator as **clinically significant**
- and/or meets the clinically notable abnormal criteria (see appendix 7).

### 13.9 ECG Adverse Events

A simultaneous 12-lead resting ECG will be obtained at visit 1 and visit 8. For consistency, the same physician should read all ECGs from one subject. Abnormal test findings as judged by the Investigator as clinically significant should be recorded as AEs.

### 13.10 Other Safety Considerations/Risk Management

Preventable medication administration errors with an IMP are a potential safety issue and must be reported immediately to the Sponsor/CRO as a protocol deviation. Examples of these include:

- Overdose - This must always be reported, and may additionally (but not always) meet the criteria for an AE/SAE.

- Drug Abuse - Defined as intentional excessive and persistent or sporadic use of a medicinal product which is accompanied by harmful physical or psychological effects. Drug abuse is always a medically important event and subject to immediate SAE reporting.

- Drug Diversion - Defined as study treatment that is sold or given to other persons either deliberately or accidentally. This may include accidental misdirection of study supply into mainstream hospital supplies. Adverse events in persons other than the subject after drug diversion will be processed in the Sponsor's drug safety database.

Any packaging or labelling that has been identified as causing potential risk (e.g. due to similarity with other products or unclear instruction) must be immediately reported to the Sponsor.

### 13.11 Product Quality Complaint

Product quality complaint means any suspicion of a the product fault related to the production, labeling or packaging, including the dissatisfaction about the reliability of product characteristics, quality, duration, labeling and package integrity. Product quality complaint possibly exerts

influence on the product safety and treatment. It is of great importance to protect the subjects, researchers and sponsor by reporting and analyzing any product quality complaint information obtained in the clinical research timely and accurately and it is approved by the world supervision organization. .

### 13.11.1 Process

As long as obtaining the product quality complaint events, the investigator should report the product complaint events information to the sponsor within the shortest time possible.

As for the serious product quality complaint caused by the product fault or serious adverse events, the investigators must report to the sponsor within the timeline of the seriously adverse event (please refer to the section about reporting of the seriously adverse events). If required by the sponsor, the sample of the doubtful product must be saved for further investigation.

### 13.11.2 Contacting the sponsor about the product quality

The name (and the contact phone) of sponsor to be contacted if any product quality complaint have been listed in the contact information page; such information will be provided as independent document.

### 13.12 Overdose

Symptoms of oxycodone overdose may include miosis, respiratory depression, somnolence progressing to stupor, skeletal muscle flaccidity, bradycardia as well as hypotension. Coma, non-cardiogenic pulmonary edema and circulatory failure may occur in more severe cases and may lead to fatal outcome.

Clinical symptoms suggestive of an oxycodone overdose may be treated by the administration of opioid antagonists (e.g. naloxone hydrochloride 0.4-2 mg intravenously). Administration should be repeated at 2-3 minute intervals, as clinically necessary. It is also possible to apply an infusion of 2 mg naloxone in 500 ml of 0.9% sodium chloride or 5% dextrose (0.004 mg/ml naloxone). The infusion should run at a rate aligned to the previously administered bolus doses and to the patient's response.

Consideration may be given to gastric lavage.

Supportive measures (artificial ventilation, oxygen, vasopressors and infusions) should be employed, as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary. Fluid and electrolyte metabolism should be maintained.

Symptoms of a naloxone overdose alone are unlikely due to the low bioavailability of oral naloxone. Withdrawal symptoms due to an overdose of naloxone should be treated symptomatically in a closely-supervised environment.

# 14 STATISTICAL ANALYSES

All data analyses will be performed by the CRO after the study is completed and the database is released for unblinding. Statistical programming and analyses will be performed using SAS and/or other validated statistical software as required.

## 14.1 Statistical Methodology and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan (SAP), which will be finalised prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

## 14.2 Statistical Considerations

All data will be listed by treatment group.

In general, continuous data will be summarised by treatment group using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarised by treatment group as the number and percentage of subjects in each category.

The assumptions of the statistical models (e.g. normality) will be assessed.

Further details of statistical methods and analyses will be documented in the SAP.

## 14.3 Analysis Populations

**Enrolled Population**
The enrolled population is defined as all subjects who signed informed consent.

**Randomised Population**
The randomised population is defined as all randomised subjects.

**Full Analysis Population (FAP)**
The full analysis population is defined as all randomised subjects who receive at least one dose of study medication (IMP) and have at least one post-baseline primary efficacy endpoint.

**Per Protocol Population (PPP)**

The Per Protocol Population is defined as all FAP subjects without major protocol violations. Major protocol violations will be agreed at the Determination of Subject Evaluability (DOSEA) meeting prior to database lock.

**Safety Population**
The safety population is defined as all randomised subjects who receive at least one dose of IMP and with at least one post-baseline safety assessment.

For the superiority test (bowel function) the Full-analysis population will be the primary analysis and the PP analysis will be performed for sensitivity reasons. For the non-inferiority test (pain) the PP population analysis will be the primary analysis and the FAS analysis will be the sensitivity analysis.
All secondary endpoint will be analysed with the FAS population only, all safety analysis will use the DB safety population.

## 14.4 Protocol Violations and Deviations

The following protocol violations may exclude a subject from the PPP:

1) Failure to comply with the inclusion/exclusion criteria.

2) Being non-compliant with study treatments.

3) Taking any prohibited concomitant therapies.

Additional factors excluding subjects from inclusion in the PPP may be included in the SAP for the study. Major protocol violations will be agreed at the Determination of Subject Evaluability (DOSEA) meeting prior to database lock. Further details will be documented in the SAP.

## 14.5 Sample Size and Power Considerations

Approximately 280 patients may be screened to obtain 230 patients who will be randomised in a 1:1 ratio to OXN / OXY PR. Each group will have 115 subjects randomized to ensure 105 patients in the FAS per group.

With 105 subjects in the FAS per treatment group the study has a power of 90% to detect a treatment difference of 12 on the BFI on a two-sided level of significance of $\alpha$=0.05 assuming a common standard deviation of 26.

## 14.6 EFFICACY ANALYSES

Summary statistics of efficacy variables will be produced. These will be sorted by treatment group (oxycodone, oxycodone/naloxone, combined), visit number where appropriate, and country (alphabetically) where appropriate. Statistics to be reported for continuous variables are: sample size, mean, SD, SE, range, median. For categorical variables, counts and percentages will be reported. The primary analysis population is the Full Analysis population, secondary analyses will use the per-protocol population.

Primary Efficacy Analyses

The analysis of the primary endpoint uses an ANCOVA comparing the treatments at final vist using LOCF for missing values, adjusted for baseline observation. The full analysis population is the primary population for this BFI analysis, the per-protocol population will be analyzed as well.

Additional sensitivity analyses will be performed. A MMRM model will be used that has fixed effects for visit, treatment within visit, baseline; random intercept over subjects; an unstructured covariance matrix over the visits. The comparison between treatments at final visit will be reported. A similar model will be estimated that assumes a constant treatment effect over visits.

For average pain uses an ANCOVA comparing the treatments at final vist using LOCF for missing values, adjusted for baseline observation. The per-protocol population is the primary population for this pain analysis, the Full-Analysis population will be analyzed as well.

Other Efficacy Analyses

For all other endpoints the summary statistics will be produced as described in section “Efficacy Analyses”. Only exploratory statistical comparisons will be made for these endpoints using the Full-Analysis population..

## 14.7 Subject Disposition

The number and percentage of subjects in each population will be summarised by treatment group and overall for subjects in the enrolled set. Reasons for exclusion from the PPP will also be summarised.

The number and percentage of subjects enrolled and the primary reason for screen failure will be summarised for subjects in the enrolled population.

The number and percentage of subjects that complete the study and the primary reason for discontinuation will be summarised for subjects in the randomised population.

The number and percentage of subjects enrolled from each country and site will be summarised for subjects in the randomised population.

## 14.8 Demographic/Baseline Analyses

Demographic and baseline variables will be summarised by treatment group and overall for subjects in the Full Analysis Population.

Age, weight, height, and body mass index will be summarised as continuous data. Gender and race will be summarised as categorical data.

Current medical conditions will be summarised by System Organ Class and Preferred Term.

## 14.9 IMP Analyses

IMP will be summarised as treatment exposure.

Treatment exposure will be defined as the number of days on IMP. This will be calculated as the number of days between the first and last dose of IMP. Treatment exposure will be summarised by treatment group as continuous data.

## 14.10 Concomitant Medications Analyses

Concomitant medications will be assigned an 11-digit code using the World Health Organisation Drug Dictionary (WHO-DD) drug codes of version Q4/2012. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification.

The number and percentage of subjects taking concomitant medications will be summarised by ATC anatomical class, pharmacological class, pharmacological sub-class and treatment group for subjects in the FAP.

## 14.11 Safety Analyses/Adverse Outcomes

Safety data that will be evaluated includes adverse events (AEs), laboratory values, vital signs, and ECGs. Safety data will be summarised by treatment group and overall for subjects in the safety population. All safety data will be listed.

## 14.12 Analysis of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system version 15 and summarized by System Organ Class (SOC) and preferred term for each event.

Only treatment emergent AEs will be summarised. A treatment emergent AE will be defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP. This will also include AEs with an onset date up to and including 7 days after the last dose of IMP.

The number and percentage of subjects reporting any AE will be summarised by the 'preferred term' nested within the SOC. In addition, the number of reported AEs will be summarised.

AEs will be summarised by worst severity and relationship to IMP. In addition, severe AEs, AEs leading to death, serious AEs, AEs leading to discontinuation from study, AEs requiring additional therapy, AEs leading to dose reduction, and AEs leading to dose interruption will be summarised.

The most frequent AEs (preferred term ≥ 5% in any treatment group) will be summarised for the double-blind phase. These will also be presented graphically using a dot plot and a caterpillar plot within which the percentage of subjects reporting each of the most common AEs will be presented alongside the odds ratio (and associated 95% CI) for comparing the incidence of AEs.

## 14.13 Analysis of other Safety Parameters

**SOWS Values:** SOWS change from baseline to visit 3 and visit 9 will be summarised as continuous data. Scatter plots will be produced for SOWS comparing baseline and Visit 3 values.

**Laboratory Values:** Clinical laboratory data to be summarised includes haematology, blood chemistry, and urinalysis.

| | Items |
|---|---|
| Hematology | RBC， haemoglobin, haematocrit, platelets and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils). |
| Biochemistry | sodium, potassium, chloride, bicarbonate, Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin, blood urea, creatinine, glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, globulin, uric acid. |
| Urinalysis | pH, protein, glucose, ketone, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity |

Clinical laboratory results recorded at each visit and change from baseline to each visit will be summarised as continuous data for each parameter. Each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Results will be summarised using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than).

Clinical laboratory values after first dose of IMP will be evaluated for markedly abnormal values. The number and percentage of subjects reporting markedly abnormal values will be summarised for each parameter by treatment group. Each subject can be counted once in the parameter high and the parameter low categories, as applicable. Scatter plots will be produced for each laboratory parameter comparing baseline and end of study values.

**Vital Signs:** Vital sign parameters to be summarised include systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and temperature.

Vital sign results recorded at each visit and change from baseline to each visit will be summarised as continuous data for each parameter.

Vital sign results for each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Vital sign results will be summarised using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than).

Vital sign values after first dose of IMP will be evaluated for clinically notable abnormalities. The number and percentage of subjects reporting clinically notable abnormalities will be summarised for each parameter by treatment group. Each subject can be counted once in the parameter high and the parameter low categories, as applicable.

Scatter plots will be produced for each vital sign parameter comparing baseline and end of study values

**ECG:** Only Clinically significant ECG findings as determined by the Investigator will be reported.

### 14.14 Other Special Tests

None planned.

## 15 ETHICS & REGULATORY

### 15.1 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and CRO, which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

1. Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
2. ICH E6 Guideline for GCP and subsequent notes for guidance (CPMP/ICH/135/95) European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).
3. European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.
4. GCP Directive 2005/28/EC
5. Chinese GCP, 2003

This study will be conducted in accordance with national and local laws (e.g. drug and narcotics laws) of the countries where study sites are located.

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH Good Clinical Practice to which the protocol conforms as well as all governing local regulations and principles for medical research.

**15.2** Ethical and Regulatory Review

The protocol, any protocol amendments, the patient information sheet (PIS), informed consent form (ICF) and any study related information or documents issued to subjects for recruitment, data recording etc., will be reviewed and approved along with other required documents by the central Ethics Committee (EC) and local ethical committee if applicable before subjects are screened for entry. The ECs should be constituted and functioning in accordance with ICH E6, Section 3.2, and any local regulations. A list of the EC(s) that provided a positive opinion for this study will be included in the clinical study report for this protocol.

A signed letter of positive opinion regarding the study from the EC Chairman must be sent to the Investigator who will provide the CRO with a copy prior to study start and the release of any study treatment to the site by the Sponsor or its designee (ICH E6). The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the EC of any reportable adverse events (AEs) per ICH guidelines and local EC standards of practice.

SAEs should be reported to the EC in accordance with local regulatory requirements.

In the case of early termination/temporary halt of the study, the Investigator should notify the EC and CA within 15 days and a detailed written explanation of the reasons for the termination/halt should be given. If the EC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the EC to the Sponsor and selcted CRO.

At the end of the study, the Sponsor or selected CRO should notify the EC and CA within 90 days. The end of the study will be the date of the last scheduled study visit for the last subject in the study. The Sponsor will always also provide the EC/CA with a summary of the study's outcome.

## 15.3 Subject Information and Consent

Informed consent should be obtained by means of a patient information sheet (PIS) and Informed Consent Form (ICF), prepared in accordance with ICH E6 Section 4.8.10 and applicable local regulations, written in non-technical language. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be

informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the patient information sheet (PIS) and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

The original signed ICF for each subject will be verified by the Sponsor/CRO monitors and kept in the study centre investigational site files. This applies for any additional ICFs signed (e.g. for re-consent).

### 15.4 Data Protection and Human Tissue Sampling

Data protection will be carried out in accordance with the Principles of the Data Protection Act (1998) 95/46/EC. This will apply to all study data in whatever format it is collected and recorded.

Any scan data, imaging, ECGs etc., collected for the trial will be retained in the patient's notes held with the Investigator. No scans need to be sent for central review.

Samples collected for the purpose of safety or bioanalytical analysis will not be retained after analysis.

### 15.5 Quality Assurance & Inspection Requirements

This study will be organised, performed, and reported in compliance with the protocol, Standard Operating Procedures (SOPs) of the Sponsor [and CRO]. ICH E6 defines Quality Assurance (QA) as 'all those planned and systemic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements'. Sponsor QA activity will be undertaken as outlined in the study audit plan. Section 5.19.3(b) of ICH E6 states that the audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to competent authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects and any identified problem(s). QA activities may be outsourced to CROs or independent consultants. The investigator is required to support audit activities, to be available to the auditors upon request and to permit the auditor direct access to source data/documents.

A CA/authorised third party may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a CA, the Investigator must inform the Sponsor immediately that this request has been made.

## 16 STUDY MANAGEMENT RECORDS & PUBLICATION

## 16.1 Protocol Amendments

The Investigator should not implement any deviation from, or changes to the protocol without agreement by the Sponsor and prior review and documented approval from the EC (ICH E6 4.5.2).

Any change to the protocol requires a written substantial or non-substantial protocol amendment. Substantial protocol amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require approval by the applicable ECs of all sites and, in some countries, by the CA. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the [Clinical Leader/Study Physician/Medical Monitor] must be notified promptly and the EC for the site must be informed in accordance with the policy of the EC approving the study, local regulations and policies. Changes affecting only administrative aspects of the study do not require substantial protocol amendments or EC approval, but the EC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the EC detailing such changes.

## 16.2 Record Maintenance and Retention

- 

Neither a subject's name nor initials are to appear on documents transmitted to the Sponsor in order to maintain confidentiality. Additional anonymisation/pseudonymisation laws as applicable by country will also be adhered to.

Use the following text if an EDC system is being used.

In order to provide the Sponsor/CRO with accurate, complete, and legible data, the following criteria are to be maintained:

Source documents will be completed according to a source document agreement outlining all the data that is to be collected in the source documents throughout the study.

EDC entries should be made as close to the visit of the subject as possible.

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of EDC, Investigator's Brochure, regulatory agency registration documents, ICFs, and EC correspondence.

The site should plan on retaining study documents for approximately 15 years after completion of the study. This will include copies of the EDC data.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of

permanently retaining the study records. Records retained will be stored independently of the Sponsor, and the Sponsor will not be permitted direct access to this data.

## 16.3 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with ICH E6, Section 4.

There are to be no waivers to the Inclusion/Exclusion criteria and no Investigator-led deviations from the schedules and procedures set out within this protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation may be ineligible for analysis and may compromise the study.

Any unintentional deviation or violation that is discovered should be reported to the Sponsor/CRO immediately. Any deviation of violation that may have an impact upon subject's safety or suitability for the study should be reported to, and discussed with the Medical Monitor.

Subjects who have not signed an IRB/EC approved ICF cannot receive study medication.

The Investigator and research team must comply with the 13 principles of ICH GCP and all applicable local regulatory laws and regulations.

## 16.4 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time, however not without good cause. Reimbursement for expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees will be made. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgement so dictate. In such an event, final settlement of the grant-in-aid will be adjusted pro rata, and the Investigator will refund the excess of payments made in advance. The Investigator will notify the EC in case of study discontinuation. Study records must be retained as noted above.

## 16.5 Retention of Tissue Samples

Not Applicable

## 16.6 Registration and Publication of Study Summary and Results

If a study design is of the type required for registration in a public database as detailed in the guidance on www.clinicaltrial.gov or www.ClinicalTrialResults.org the study will be registered on a public database according to the Sponsor's SOPs. As a general guide phase 1, exploratory and post marketing studies will not require registration.

Following the end of the study the results should be published within a year of product approval for newly registered products, or within a year of completion of the clinical study report (CSR) if the product is already approved. If results are intended for publication in a peer review scientific

journal, no detailed results will be published on a public database beforehand.

The site may publish or present the results of this protocol subject to the protection of any patentable rights of the Sponsor or its nominee(s) and subject to the protection of the Sponsor's confidential information. The Sponsor will be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review of confidential or patentable information. Upon notice by the Sponsor, however, that the Sponsor reasonably believes that a patent application claiming an invention relating to the IMP(s) made during the performance of the study will be filed prior to such publication, such publication may be delayed for an additional 30 days or until any patent application or applications have been filed, whichever will first occur.

For multi-site studies, it is mandatory that the first publication be based on data obtained from all analysed subjects; therefore Investigators participating in multi-site studies must agree not to present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Publication of clinical trial results may include the presentation of such work at national and international congresses, symposia, professional meetings, peer-reviewed journals, and via other appropriate channels. Named authors and contributors to such publications shall be determined by the Sponsor in accordance with both the Company Publication Policy and the criteria as outlined by standard authorship guidelines. Selected Investigators, Consultants and Scientific Advisors may be invited to be named authors on such publications by the Sponsor. If the Investigator/Consultant/Scientific Advisor agrees to participate in the publication as an author, they will be asked to participate in the creation of all versions of the document(s) in question prior to submission or public dissemination. The Sponsor will ensure that any reasonable comments made by the invited author will be incorporated into the publication and that the named author will consent to the publication of the final version of the document. The copyright associated with any publication will be and shall remain the sole property of the Sponsor, unless or until the copyright of the document is transferred to the scientific peer-reviewed journal prior to and as part of the publication process.

# 17 REFERENCE LIST

**1. 2011 NCCN Cancer pain guideline**

**2. OXN IB version 8**

**3. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad MedSingapore. 1994; 23(2): 129-38.**

**4. Frank L, Kleinman L, Farup C, Taylor L and Miner Jr P. Psychometric validation of a Constipation Symptom Assessment Questionnaire. Scand J Gastroenerol 1999; 34: 870-877.**

**5. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987; 13: 293-308.**

**6. Xu JG, Yu SY, Narcotic drugs and psychotropic drugs of standardized clinical application and management Beijing: People's Medical Publishing House, 2007**

# 18 APPENDICES

## Appendix 1 BPI-SF

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

### Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

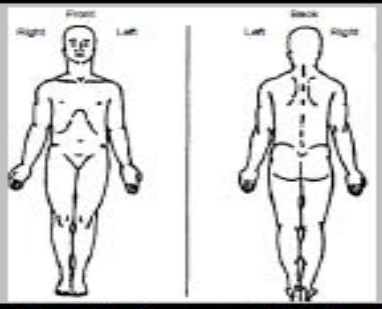
Name: _____ _____ _____

Last First Middle Initial

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

1. Yes 2. No

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




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

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

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

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

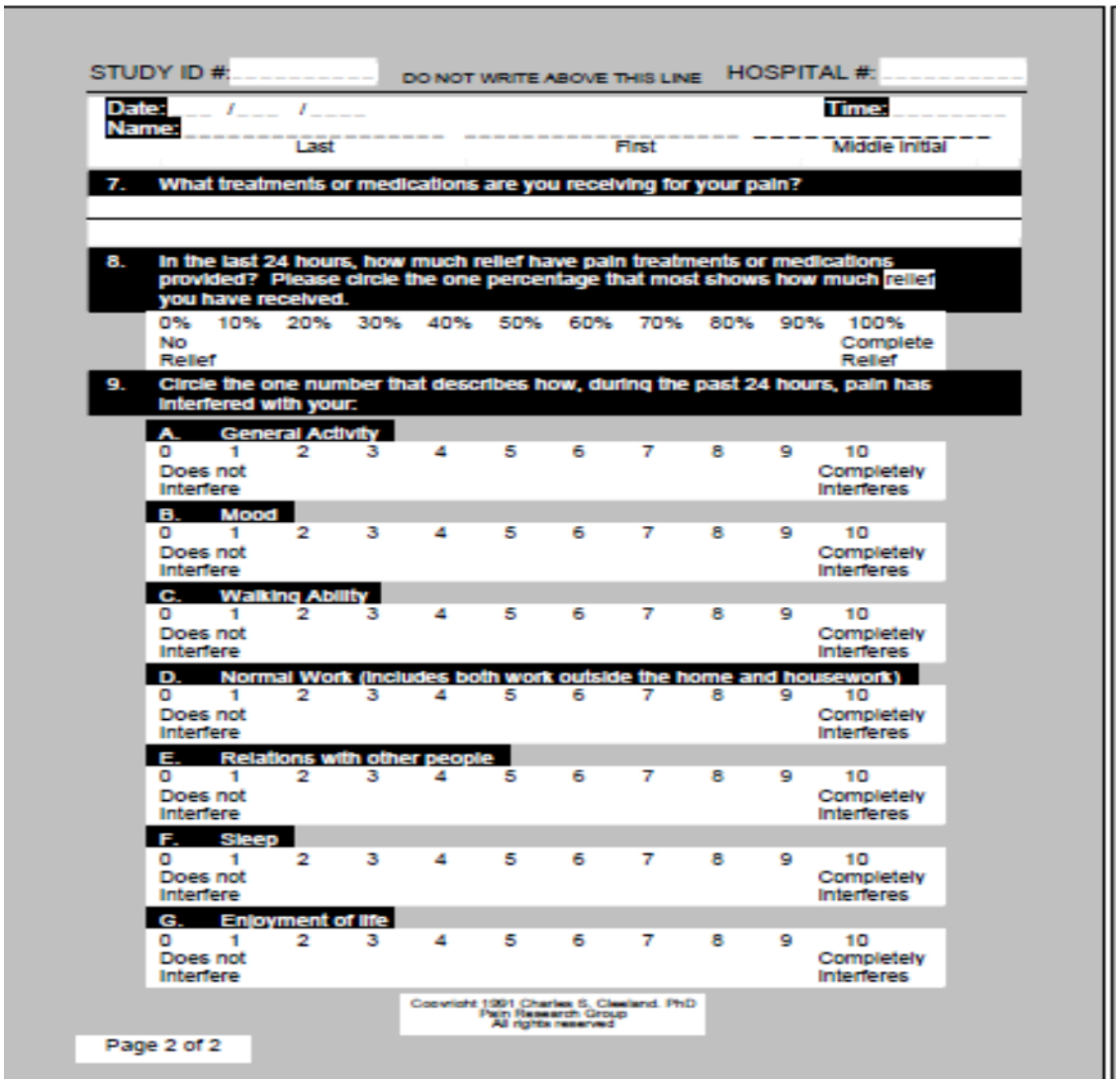
5. Please rate your pain by circling the one number that best describes your pain on the average.

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

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

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

Page 1 of 2



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

Date: ___ / ___ / _____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

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

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

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

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

**A. General Activity**

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

**B. Mood**

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

**C. Walking Ability**

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

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

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

**E. Relations with other people**

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

**F. Sleep**

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

**G. Enjoyment of life**

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



Page 2 of 2

# Appendix 2 BFI

**Bowel Function Index (BFI): Instructions for Use**

Instructions for study personnel on the administration of the BFI to study subjects

The Bowel Function Index (BFI) is a 3-item questionnaire to measure constipation from the patient's perspective. Study personnel should ask subjects the BFI questions. The BFI is not intended to be given to the subject for completion on their own (self-administration), not even if study personnel explain how the measure should be completed. The BFI should always be administered to the subject by study personnel.

| |
|---|
| Instructions for administering each item of the BFI are indicated in the grey sections below each item. |

Ask subjects each question. If the subject does not understand the question, study personnel may provide clarification as indicated below each question in the grey sections of the measure below. Study personnel should enter each answer provided by the subject in the appropriate section of the case record form (CRF). To avoid any form of response bias, study personnel must not lead the subjects in their answers (e.g. study personnel should not provide examples of answers to a given question).

| **Bowel Function Index (BFI)** |
|---|
| Please complete all items in this assessment. |
| 1. Ease of defecation (NAS) during the last 7 days according to patient assessment:<br>0 = easy / no difficulty<br>100 = severe difficulty<br>***Ask the subject***: *"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*<br>***If the subject requires clarification, ask***: *"During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"* |
| 2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:<br>0 = not at all<br>100 = very strong<br>***Ask the subject***: *"During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"*<br>***If the subject requires clarification, ask***: *"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"* |
| 3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:<br>0 = not at all<br>100 = very strong<br>***Ask the subject***: *"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*<br>***If the subject requires clarification, ask***: *"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"* |

## Appendix 3 SOWS

### Modified Subjective Opiate Withdrawal Scale (SOWS)

To let us know how you feel at this moment, place an **"X" on the line** next to the number **(0, 1, 2, 3 or 4)** that best describes how you feel **RIGHT NOW.**

| | Not at All | A Little | Moderately | Quite a Bit | Extremely |
|---|---|---|---|---|---|
| 1. I feel anxious. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 2. I feel like yawning. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 3. I'm perspiring. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 4. My eyes are tearing. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 5. My nose is running. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 6. I have goose flesh. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 7. I am shaking. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 8. I have hot flashes. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 9. I have cold flashes. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 10. My bones and muscles ache. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 11. I feel restless. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 12. I feel nauseous. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 13. I feel like vomiting. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 14. My muscles twitch. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |
| 15. I have cramps in my stomach. | 0)____ | 1)____ | 2)____ | 3)____ | 4)____ |

(Handelsman et al., 1987)

## Appendix 4 EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

| | |
|---|---|
| I have no problems in walking about | ❑ |
| I have some problems in walking about | ❑ |
| I am confined to bed | ❑ |

**Self-Care**

| | |
|---|---|
| I have no problems with self-care | ❑ |
| I have some problems washing or dressing myself | ❑ |
| I am unable to wash or dress myself | ❑ |

**Usual Activities** (*e.g. work, study, housework, family or leisure activities)*

| | |
|---|---|
| I have no problems with performing my usual activities | ❑ |
| I have some problems with performing my usual activities | ❑ |
| I am unable to perform my usual activities | ❑ |

**Pain/Discomfort**

| | |
|---|---|
| I have no pain or discomfort | ❑ |
| I have moderate pain or discomfort | ❑ |
| I have extreme pain or discomfort | ❑ |

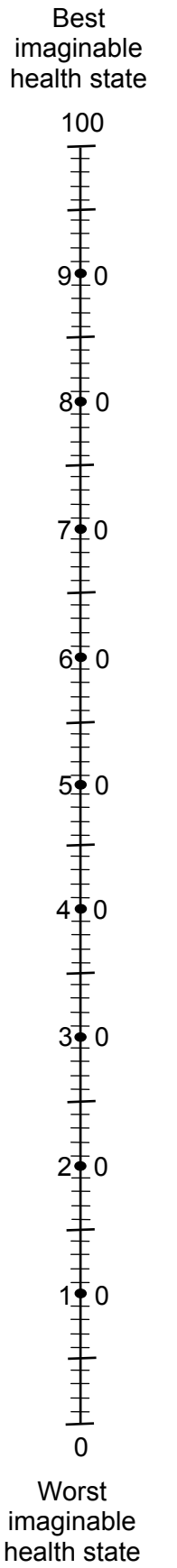
**Anxiety/Depression**

| | |
|---|---|
| I am not anxious or depressed | ❑ |
| I am moderately anxious or depressed | ❑ |
| I am extremely anxious or depressed | ❑ |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own health state today**

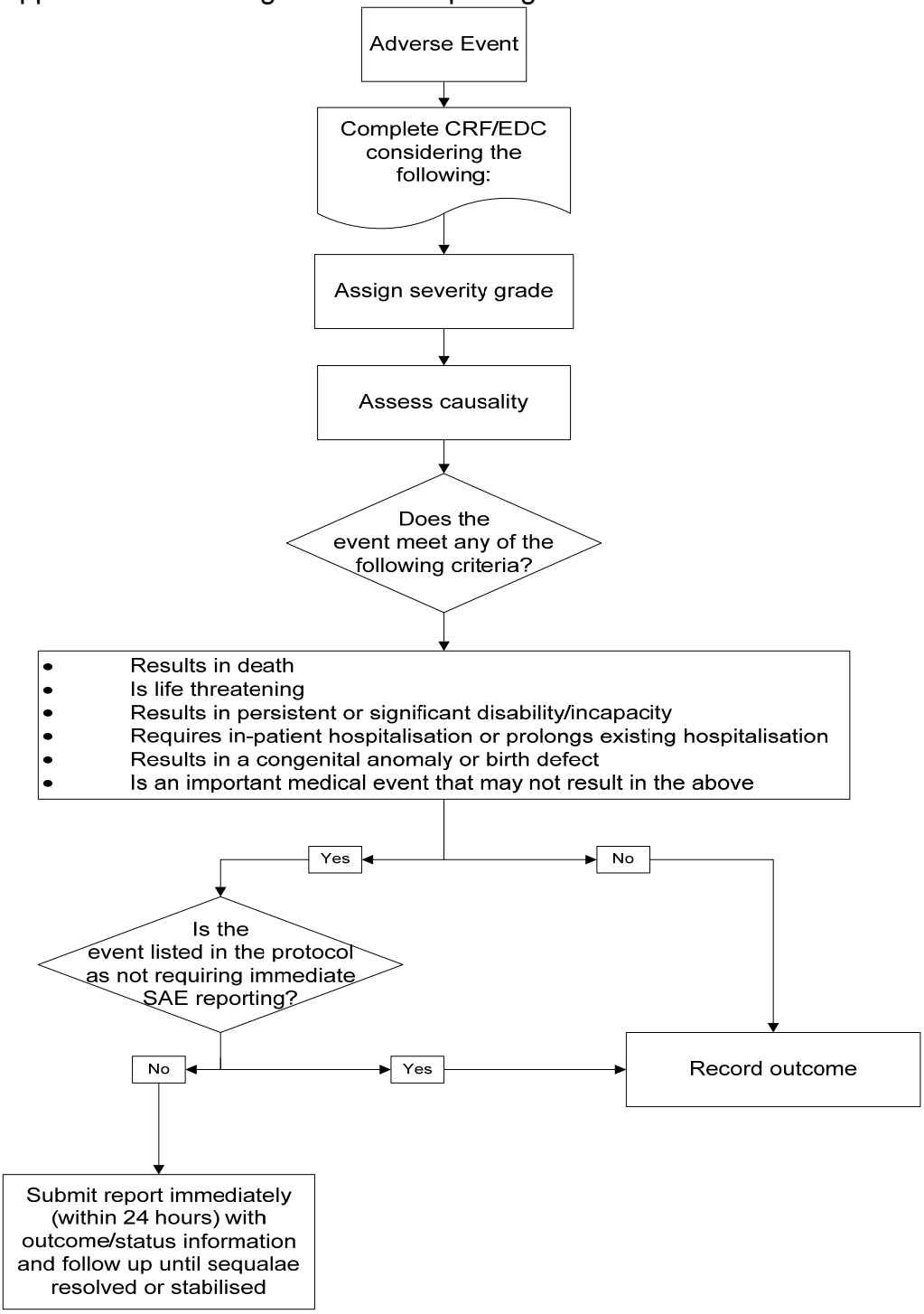


## Appendix 5 Guidance table for identifying the starting dose of oxycodone PR based on pre study opioid use.

| Opioid Dose Range | Guidance Pre-Study Opioid Examples Total Daily Dose | Total Daily Dose Study medication Start Dose at treatment Period[3] |
|---|---|---|
| Low Dose | Morphine up to 80 mg<br>Hydromorphone up to 10 mg<br>Dextropropoxyphene<br>Dihydrocodeine<br>Tramadol<br>Fentanyl 25 µg/hour<br>Buprenorphine Patch[1] 35 µg/hour<br>Buprenorphine Patch[1] 52.5 µg/hour | 20 - 40 mg OxyPR |
| Medium Dose | Morphine > 80 - 160 mg<br>Hydromorphone > 12 mg<br>Fentanyl 50 µg/hour<br>Buprenorphine Patch[1] 70 µg/hour | 40 - 60 mg OxyPR |
| High Dose[2] | Morphine 160 - 200 mg<br>Hydromorphone > 20 mg<br>Fentanyl 75 µg/hour | 60 - 80 mg OxyPR |

1 Buprenorphine Patch is the 3 day Transtec Patch
2 Subjects requiring a start dose of > 80 mg oxycodone PR should be excluded from the study (e.g. >200 mg Morphine).
3 The subjects study medication is to be reviewed the following day (telephone visit) to assess if an increase or decrease in study medication is required.
Please note; this table is for guidance only.

## Appendix 6 Flow diagram for AE reporting



## Appendix 7 Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

| Vital Sign Parameter | Value | Change From Baseline[a] |
|---|---|---|
| Systolic blood pressure | ≥ 180 mmHg | Increase of ≥ 20 mmHg |
| | ≤ 90 mmHg | Decrease of ≥ 20 mmHg |
| Diastolic blood pressure | ≥ 105 mmHg | Increase of ≥ 15 mmHg |
| | ≤ 50 mmHg | Decrease of ≥ 15 mmHg |
| Pulse rate | ≥ 120 bpm | Increase of ≥ 15 bpm |
| | ≤ 50 bpm | Decrease of ≥ 15 bpm |
| Respiration rate | < 8 breaths/minute | - |
| | > 24 breaths/minute | - |

[a]Both value and change from baseline criteria must be met to qualify as a clinically notable vital sign abnormality.