1 TITLE PAGE

Protocol Number: **OXN08-CN-101**

Title: An open-label, randomized, single-dose, parallel group study to investigate the pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5)and20/10 mg (OXN 20/10) in Chinese patients with moderate to severe chronic non-malignant pain.

Sponsor: Mundipharma (China) Pharmaceutical Co., Ltd
Room 1808 Tower D CITC, 6A Jianguomen Wai Avenue, Beijing 100022, China
[Beijing, China] [zip code：100022]
[China]

Test Drug: Oxycodone/naloxone (OXN) prolonged release (PR) tablet

Phase: Phase I

Release Date: [25-Sep-2014]

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 SIGNATURE PAGE FOR INVESTIGATOR

Protocol Number: OXN08-CN-101

Title: An open-label, randomized, single-dose, parallel group study to investigate the pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5)and20/10 mg (OXN 20/10) in Chinese patients with moderate to severe chronic non-malignant pain.

Test Drug: Oxycodone/naloxone prolonged release tablet 5/2.5 (OXN 5/2.5)

Oxycodone/naloxone prolonged release tablet 20/10 (OXN 20/10)

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

Hu Pei

_____	_____	_____
Investigator	Signature	Date

Zeng Xiaofeng

_____	_____	_____
Investigator	Signature	Date

3 PROTOCOL SYNOPSIS

Name of Company: Mundipharma (China) Pharmaceutical Co., Ltd.		
Name of Finished Product: Targin®		
Name of Active Ingredient: Oxycodone hydrochloride (HCl) and naloxone HCl		
Protocol No.: OXN08-CN-101		
Title of the Study: An open-label, randomized, single-dose, parallel group study to investigate the pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5)and20/10 mg (OXN 20/10) in Chinese patients with moderate to severe chronic non-malignant pain.		
Investigator/Study Center: Dr. HU Pei , ,Zeng Xiaofeng/Peking Union Medical College Hospital, more sites might be included as necessary.		
Study Dates: 4Q 2013– 4Q 2014	**Study Status:** Planned	**Phase of Development:** Phase 1
Objectives: a. To determine the PK of oxycodone, naloxone and metabolites in Chinese patients. b. To assess, in a single dose investigation, the dose-proportionality of OXN.		
Methodology: An open-label, randomized, single-dose, parallel group study. The patients will be enrolled in sequence to receive one dose of either OXN 5/2.5, OXN 20/10.		
Number of Subjects: Planned: 24 subjects, each group (OXN 5/2.5, OXN 20/10) will have 12 subjects receiving OXN active treatment. More subjects will be enrolled if the completed subjects are less than 12 subjects in each group.		
Indication and Criteria for Inclusion: Chinese male and female patients with moderate to severe chronic non-malignant pain for OXN 5/2.5, OXN 20/10 single-dose study, aged 18 to 65 years.		

Criteria for Inclusion:

1. Adult Chinese patients with moderate to severe chronic non-malignant pain.
2. Male and female subjects with age range 18 to 65 years (including 18 and 65), body weight ≥ 45kg and BMI range 18 to 30 (including 18 and 30).
3. Patients who should rate their pain (Pain Intensity Scale -"average pain" over the last 24 hours) as ≥4 on 0-10 scale.
4. Patients, who are able to read, understand and sign written informed consent prior to study participation and are willing to follow the protocol requirements.
5. Females of childbearing potential and less than one year post-menopausal must have a negative serum pregnancy test during screening visit and at check-in and be non-lactating. In addition, they must be willing to use adequate and reliable 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 consistently and correctly such as sterilization, implants, injectables, combined oral contraceptives, some IUDs (intrauterine Device, hormonal), sexual abstinence or vasectomised partner.

Criteria for exclusion:

1. Females who are pregnant (positive β-human chorionic gonadotrophin [HCG] test) or lactating.
2. Use of opioid or opioid antagonist-containing medication in the 30 days before the start of the study.
3. Known sensitivity to oxycodone, naloxone, or related compounds.
4. Subjects with clinically unstable respiratory disease, dysfunction of the biliary tract, thyroid disease, adrenal cortical insufficiency, prostatic hypertrophy requiring intervention (medication or surgical) or renal artery stenosis, or any other medical condition, that, in the opinion of the investigator or the sub-investigator, precludes entry into this study.
5. Subject who have a past (within 5 years) history of malignant neoplasm including leukemia and lymphoma.
6. The electrocardiogram examination results are abnormal, in the opinion of the investigator or the sub-investigator, and are clinical significance.
7. Subjects with abnormal liver function (values exceed the upper limit of normal for AST, ALT or total bilirubin during the Screening Period) or abnormal renal function (values exceed the upper limit of normal for serum creatinine during the Screening Period).
8. Patients with a contraindication to the study medication.
9. Subjects who have a psychiatric disorder such that participation in the study may, in the opinion of the investigator or the sub-investigator, pose an unacceptable risk to the subject.

10. Subjects who have a current or past (within 5 years) history of substance or alcohol abuse, or subjects who give a positive result in drug abuse test during the Screening Period, or subjects who, in the opinion of the investigator or the sub-investigator, have demonstrated addictive orsubstance abuse behaviors.
11. Subjects with uncontrolled seizures or convulsive disorder.
12. Subjects who will receive any interventional therapy (surgery, paracentesis,etc) for arthritis during the study period.
13. History of or any current conditions that might have interfered with drug absorption, distribution, metabolism or excretion.
14. Any history of frequent nausea or emesis regardless of aetiology.
15. Participation in any clinical drug study during the 3 months preceding the initial dose in this study.
16. Use of any medication including vitamins, herbal and/or mineral supplements during the course of the study, other than Vitamin D, calcium supplements and continued use by females of contraceptive medication or HRT.
17. Consumption of alcoholic beverages within 48 hours before study drug administration, and refusal to abstain from alcohol until at least 48 hours after the last study drug administration.
18. Blood or blood products donated within 90 days prior to study drug administration or anytime during the study, except as required by this protocol.
19. Positive results of urine drug screen(for opioids, barbiturates, amphetamines, cocaine metabolites, methadone, diazepam and cannabinoids), alcohol breath test, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (Ab), human immunodeficiency virus (HIV) test or qualitative syphilis tests.
20. Patients with moderate to severe hypohemia (HGB<90g/L during the screening).

Concomitant Therapy:

Administration of medications (including vitamins, herbal and/or mineral supplements) other than the study drug will be prohibited from the start of the study to completion of the study, with the exception of Vitamin D, calcium supplements, continued use by females of contraceptive medication or HRT, and drug therapy for any adverse events that might develop.

In case other medication was taken by the subject after during the study, 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.

Paracetamol or NSAID's ibuprofen will be used as rescue medicine for patients who need the analgesic for pain relief. The maximum of Paracetamol allowed daily dose is 1.3g. The maximum of ibuprofen allowed daily dose is 1.2g. Ondansetron can be used before 30 minutes of study treatment, in the opinion of the investigator or the sub-investigator. If nausea, Ondansetron can be given at the discretion of the investigator after study treatment.Subjects will be withdrawn if they take any medicine affecting metabolism.

Study Restrictions:

During the study period, smoking, liquor, caffeine drinks and grapefruit juice will be prohibited. Acute exercise will also be prohibited during the study period. Study Restrictions (Food, Beverages, Alcohol, Caffeine and Smoking etc.) will be detailed in the full protocol for the study.

Test Treatment, Dose, and Mode of Administration:

Single dose: Oxycodone/naloxone PR tablet 5/2.5 mg (OXN 5/2.5), a PR combination tablet containing 5 mg of oxycodone HCl and 2.5 mg of naloxone HCl; oxycodone/naloxone PR tablet 20/10 mg (OXN 20/10), a PR combination tablet containing 20 mg of oxycodone HCl and 10 mg of naloxone HCl.
One OXN tablet shall be administered orally, at Day 1 (0 h).
OXN tablets are manufactured by Bard Pharmaceuticals Limited.

Batch number: PN3787 (5/2.5mg)，PN3952 (20/10mg).

Reference Treatment, Dose, and Mode of Administration:

Not applicable.

Duration of Treatment:

Screening is within 14 days before dosing on Day 1. There will be one study period. Subjects will be administered the study treatment on Day 1. Pharmacokinetic blood sampling and safety monitoring continued for up to 48 hours after dosing on Day 1. Subjects will have a post-study clinical evaluation at 48 h (±2 h) after their OXN dose.
Total duration of the study will be up to 17 days.
Single dose:

Screening and pre-dose examination: Day -14 to Day -2
Treatment duration: Day1 (0 h)
Safety Follow-up: Day 3 (48 h ± 2 h)

Treatment Schedule:

Each dose of OXN 5/2.5, OXN 20/10 will be given with 200 ml water to subjects in a standing position.

Criteria for Evaluation

Analysis Populations:
The enrolled population is defined as the group of individuals who provided informed consent.
The safety population is defined as the group of subjects who received at least one dose of study drug, and had at least one post-dose safety assessment.
The full analysis population for pharmacokinetic parameters is defined as the group of subjects who has at least one pharmacokinetic parameter post dose.

Pharmacokinetic Measures:
Blood samples for pharmacokinetic analysis will be taken as below schedule:
Single dose:
Pre-dose, 0.5h, 1.0h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 7h, 8h, 10h, 12h, 14h, 24h,28h,32h,36h,48h post dose. About 6 mL per sample. A total of 126 mL PK blood sample will be collected from each patient.

Safety: Safety will be assessed using adverse events (through subject interview and spontaneous reporting), clinical laboratory results, vital signs, physical examinations, and ECGs.

Bioanalytical Methods:
The plasma samples will be analysed for oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide using validated bioanalytical assays.

Pharmacokinetics:
Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide will be analyzed to determine the following pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, Cmax, tmax, Lambda_Z and t1/2 and so on.

Safety:
Safety will be assessed using adverse events (through subject interview and spontaneous reporting), clinical laboratory results, vital signs, physical examinations, and ECGs.

The adverse event will be reported according to MCPC procedures which will be mentioned in the full protocols.

All SAEs will be reported to MCPC within 24 hours. Medical doctors / research nurses who will be involved in the study will be trained on how to report SAEs accordingly. MCPC will report the SAE to MRL within the timeline that has been required in PVA between MRL and MCPC.

Statistical Methods:

Data will be tabulated, summarized, and plotted against time when appropriate.

Descriptive statistics of PK parameters AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, Lambda_z and $t_{1/2}$ of oxycodone, noroxycodone, oxymorphone, and noroxymorphone as well as naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide shall be analyzed by treatment group (naloxone-3-glucuronide will be the major metabolite of naloxone). The dose-proportionality of oxycodone and naloxone, metabolites(AUC_{0-t}, AUC_{0-INF} and C_{max}) will be analyzed using the linear mixed effect model (with treatment as the fixed term and subject as the random effect).

Safety Analyses: All safety data (ie, adverse events, vital signs, and laboratory tests) will be listed by subject and dosage group. Results of the vital signs and laboratory tests that are outside the normal range will be identified on the listings.

Sample Size Rationale: No formal sample size calculations will be performed. 24 subjects (12 in each dosage group) are regarded as sufficient according to CFDA regulation requirement. If subject withdraw from the study, subject replacement is needed.

4 TABLE OF CONTENTS

Page

5 LIST OF ABBREVIATIONS

OA	Osteoarthritis
AE	Adverse Event
ALT	Alanine transaminase (also SGPT)
AST	Aspartate transaminase (also SGOT)
MCPC	Mundipharma (China) Pharmaceutical Co., Ltd.
PUMCH	Peking University Medical College Hospital
AUCt	Area under the plasma concentration-time curve calculated from the time of dosing to the last measurable concentration
AUCINF	Area under the plasma concentration-time curve calculated from the time of dosing to infinity
Cmax	Maximum observed concentration
LambdaZ	Terminal phase rate constant
BMI	Body mass index
Bpm	Beats per minute
BUN	Blood urea nitrogen
CRA	Clinical Research Associate
CRF	Case report form
ECG	Electrocardiogram
DCF	Data Clarification Form
EDTA	Ethylenediaminetetraacetic acid
EC	Ethics Committee
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
HB_sAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IEC	Independent Ethics Committee
IRB	Institutional Review Board
CI	Confidence Intervals
mg	Milligram
Ml	Millilitre
LLN	Lower limit of the laboratory reference (normal) range
LNH	Classification according to whether the Laboratory test result was below (L), within (N), or above (H) the reference range
PR	Prolonged Release
RAS	Random Allocation Schedule
RBC	Red blood cell (count)
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetre mercury
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event
RBC	Red blood cell (count)
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction

t1/2Z	Apparent terminal phase half-life
tmax	Time from dosing to the maximum observed concentration
ULN	Upper limit of the laboratory reference (normal) range
WBC	White blood cell (count)
WHO	World Health Organisation
WHO-DD	WHO Drug Dictionary
TEAE	Treatment Emergent Adverse Events
MRL	Mundipharma Research Limited
PVA	Phamacovgilance Agreement

6 ETHICS

6.1Independent Ethics Committee

The protocol, any protocol amendments, the informed consent form (ICF) will be reviewed and approved by the study site's local independent ethics committee (IEC) before subjects are screened for entry. Verification of the IEC unconditional approval of the protocol will be transmitted to the Sponsor or its designee prior to the shipment of drug supplies to the study site.

6.2Ethical Conduct of the Study

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

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.

ICH Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use.

6.3Subject Information and Consent

All subjects will be provided with oral and written information describing the nature and duration of the study and data protection details. Each subject will be given a copy of the ICF and written information, as applicable. The subject will be asked to sign an ICF prior to any study specific procedures being performed. A sample subject ICF, and information sheet, will be included in the clinical study report (CSR) for this protocol.

This study will be conducted in accordance with national and local laws (e.g. China Regulation on the Control of Narcotic Drugs and Psychotropic Drugs).

7 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the sponsorship of Mundipharma (China) Pharmaceutical Co., Ltd at a Phase I study unit of Peking Union Medical College Hospital, Department of Clinical Pharmacology in China.

Dr Hu Pei, (Department of Clinical Pharmacology) and Zeng Xiaofeng(Department of Rheumatology)will be the Principal Investigator. study management and monitoring will be responsible by the sponsor.

The study will be coordinated and monitored by qualified personnel from Mundipharma (China) Pharmaceutical Co., Ltd. Pharmacokinetic analysis, Data management, statistical analyses and bioanalytical sample analysis will be the responsibility of Phase I unit, clinical Pharmacology researcher center, Peking Union Medical College Hospital.

8 INTRODUCTION

Mundipharma Research GmbH & Co. KG and its independent associate companies (NPRL and Purdue Pharma L.P) are developing a novel analgesic in a prolonged release tablet dosage form that combines the opioid agonist oxycodone with the opioid antagonist naloxone.

Oxycodone is an opioid analgesic available as a prolonged release formulation with indications ranging from moderate to severe pain.

The naloxone component in the fixed combination is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. In addition, due to the presence of the opioid receptor antagonist, naloxone, OXN PR tablets may decrease abuse liability versus single-entity modified-release opioids when the tablets are crushed for injection, or intranasal administration. Opioid therapy is a mainstay in the management of chronic pain. Prolonged release opioids have been shown to be effective agents in pain management; however, the ability to properly titrate and treat pain with opioids can be limited by adverse events. Opioid-induced constipation, is a frequently occurring and often severe adverse event in patients treated for pain with opioid therapy. Current therapy recommends the administration of laxatives; however, many patients discontinue opioid therapy because of ongoing problems with opioid-induced constipation. It is therefore advantageous to minimize the development of constipation or to reduce its severity. In this strategy, the high first-pass effect of naloxone is regarded as an advantage: the improvement in bowel function can be accomplished through the local action of naloxone in the gut, while the analgesic activity of oxycodone is not antagonized due to the low systemic availability of naloxone. The results of all clinical studies conducted so far indicated that the administration of prolonged release oxycodone and naloxone in combination was not associated with clinically important differences in analgesic efficacy, provided a patient benefit in terms of relief of constipation and was well tolerated.

A melt extrusion oxycodone/naloxone prolonged release tablet formulation with an oxycodone: naloxone ratio of 2:1. The two dose strengths to be used in this study are OXN5/2.5, and OXN 20/10, in which the number before the slash is the milligram amount of oxycodone hydrochloride and the number after the slash is the milligram amount of naloxone hydrochloride.

This study (OXN08-CN101) will investigate pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5), 20/10 mg (OXN 20/10) in Chinese chronic non-malignant patients with moderate to severe pain. Additionally, the pharmacokinetic dose-proportionality of OXN 5/2.5 and OXN 20/10 will be investigated.

9 STUDY OBJECTIVES

The objectives of this study are to assess pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5)and20/10 mg (OXN 20/10) in Chinese patients with moderate to severe chronic non-malignant pain.

To determine the PK of oxycodone, naloxone and metabolites in chinese patients.

To assess, in a single dose investigation, the dose-proportionality of OXN.

10 INVESTIGATIONAL PLAN

10.1Overall Study Design and Plan

It will be conducted to assess the pharmacokinetics of OXN 5/2.5 and OXN 20/10 tablets. Subjects will be allocated to a sequence of two strength group in accordance with a random allocation schedule (RAS) in a 1:1 ratio.

Subjects will attend a screening visit within 14days of the first (OXN) dosing day (Day 1).
Eligible subjects will then check into the study unit on the day before OXN dosing (Day -2). Subjects will be administered their OXN dose the next 2 morning (Day 1), following an overnight fast.

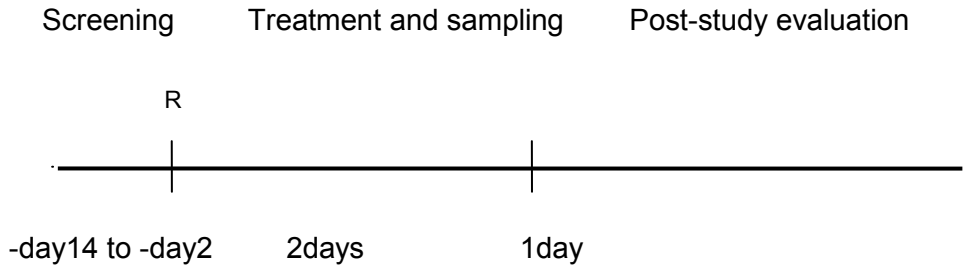
There will be 24 subjects with moderate to severe chronic non-malignant pain enrolled in this single-dose study, to be comprised of males and females aged 18-65 years. Blood samples will be collected in tubes containing the anticoagulant EDTA pre-dose and up to 48 hours after administration of OXN. Subjects remain in the study unit up to 48+2 hours after OXN dosing.

Vital signs (pulse, blood pressure, respiration rate) will be monitored pre-dose and then at 1, 2, 4, 6, 8, 12, 24, 36, 48 hours after OXN dosing. Auxiliary temperature will be monitored pre-dose, 24, 36, 48 hours after OXN dosing.

AEs will be recorded throughout the study. Subjects will attend a post-study evaluation 48±2 hours after OXN dosing (in the case of discontinuation from the study).

Figure1. Study Diagram

Single dose：



Screening period: -day14 to -day2
Treatment and sampling period: 2 days
Group A: oxycodone/naloxone PR tablet 5/2.5 mg, 1 tablet
Group B: oxycodone/naloxone PR tablet 20/10 mg, 1 tablet
Post-study evaluation: 1 day

10.1.1Screening Period（day-14today-2）

Subjects will be screened within14 days before Day 1 of OXN dosing. Safety evaluations, as detailed in Section 10.4, will only be carried out after the subject signs the study-specific ICF, and eligibility criteria are met.

10.1.2Treatment Phase

Subjects will receive a single dose of OXN 5/2.5 mg or 20/10mg in this study period in accordance with the RAS.

10.1.2.1.Days -2- check-in

Subjects will report to the study unit on the day before 2 days of OXN dosing.

10.1.2.2. Days -1– the day before OXN dosing

BPI-SF evaluations will be performed in accordance with Table 1. Subjects will undergo drug, alcohol screening and safety assessment according to Table 1 and Section 10.4.1.2. (If screening visit and treatment day less than 7 days, do not duplicate the assessment completed on screening visit.)

10.1.2.3. Days 1– OXN dosing day

Subjects will receive a single dose of OXN on the morning of Days 1. Safety assessments and blood sampling for pharmacokinetics analysis will occur as detailed in Table 1 and Section 10.4.1.3.

10.1.2.4. Days 2, 3

Subjects will remain in the study unit until the 48-hour procedures have been completed (morning of Day 3). They will then be discharged from the study unit. Safety monitoring and blood sampling for pharmacokinetic analysis will be carried out according to Table 1 and Section 10.4.1.4.

10.1.2.5. End-of-Study Procedures

Subjects will attend a post-study evaluation 48±2 hours after OXN dosing (in the case of discontinuation from the study). Safety evaluations will be performed in accordance with Table 1 and Sections 10.4.1.5.

10.2 Discussion of Study Design, Including Choice of Treatments and Appropriateness of Measurements

The blood sampling regimen has been designed in an attempt to adequately detail the pharmacokinetic profile of oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide. Based on earlier studies involving OXN, it is unlikely that the plasma concentrations of each of the analytes will be

sufficient to enable a quantitative pharmacokinetic analysis. Therefore, the primary focus will center on oxycodone and naloxone-3-glucuronide.

The confidence intervals that will be calculated in this study relate to the (dose-corrected) ratios of AUC and Cmax (i.e. 20/10 vs 5/2.5 mg strengths).

The study includes all the safety measures expected of a study in chronic non-malignant pain subjects.

10.3 Selection of Study Population

A total of 24 chronic non-malignant pain subjects, both male and female will be randomized to receive study medication with the aim that 24 subjects will complete the study and provide valid pharmacokinetic data. More subjects will be enrolled if the completed subjects are less than 12 subjects in each group.

10.3.1Inclusion Criteria

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

1. Adult Chinese patients with moderate to severe chronic non-malignant pain.
2. Male and female subjects with age range 18 to 65 years, (including 18 and 65) body weight ≥ 45kg and BMI range 18 to 30(including 18 and 30).
3. Paitents who should rate their pain (Pain Intensity Scale -“average pain” over the last 24 hours) as ≥4on 0-10 scale.
4. Patients, who are able to read, understand and sign written informed consent prior to study participation and are willing to follow the protocol requirements.
5. Females of childbearing potential and less than one year post-menopausal must have a negative serum pregnancy test during screening visit and at check-in and be non-lactating. In addition, they must be willing to use adequate and reliable 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 consistently and correctly such as sterilization, implants, injectables, combined oral contraceptives, some IUDs (intrauterine Device, hormonal), sexual abstinence or vasectomised partner.

10.3.2Exclusion Criteria

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

1. Females who are pregnant (positive β-human chorionic gonadotrophin [HCG] test) or lactating.
2. Use of opioid or opioid antagonist-containing medication in the 30 days before the start of the study.
3. Known sensitivity to oxycodone, naloxone, or related compounds.
   .
4. Subjects with clinically unstable respiratory disease, dysfunction of the biliary tract, thyroid disease, adrenal cortical insufficiency, prostatic hypertrophy requiring intervention (medication or surgical) or renal artery stenosis, or any other medical condition, that, in the opinion of the investigator or the sub-investigator, precludes entry into this study.

5. Subject who have a past (within 5 years) history of malignant neoplasm including leukemia and lymphoma.
6. The electrocardiogram examination results are abnormal.
7. Subjects with abnormal liver function (values exceed the upper limit of normal for AST, ALT or total bilirubin during the Screening Period) or abnormal renal function (values exceed the upper limit of normal for serum creatinine during the Screening Period).
8. Patients with a contraindication to the study medication.
9. Subjects who have a psychiatric disorder such that participation in the study may, in the opinion of the investigator or the sub-investigator, pose an unacceptable risk to the subject.
10. Subjects who have a current or past (within 5 years) history of substance or alcohol abuse, or subjects who give a positive result in drug abuse test during the Screening Period, or subjects who, in the opinion of the investigator or the sub-investigator, have demonstrated addictive orsubstance abuse behaviors.
11. Subjects with uncontrolled seizures or convulsive disorder.
12. Subjects who will receive any interventional therapy (surgery, paracentesis) for arthritis during the study period.
13. History of or any current conditions that might have interfered with drug absorption, distribution, metabolism or excretion.
14. Any history of frequent nausea or emesis regardless of aetiology.
15. Participation in any clinical drug study during the 3 months preceding the initial dose in this study.
16. Use of any medication including vitamins, herbal and/or mineral supplements during the course of the study, other thanVitamin D, calcium supplements and continued use by females of contraceptive medication or HRT.
17. Consumption of alcoholic beverages within 48 hours before study drug administration, and refusal to abstain from alcohol until at least 48 hours after study drug administration.
18. Blood or blood products donated within 90 days prior to study drug administration or anytime during the study, except as required by this protocol.
19. Positive results of urine drug screen(for opioids, barbiturates, amphetamines, cocaine metabolites, methadone, diazepam and cannabinoids), alcohol breath test, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (Ab), human immunodeficiency virus (Anti-HIV) test or qualitative syphilis tests.
20. Patients with moderate to severe hypohemia (HGB<90g/L during the screening).

10.4 Study Methods

10.4.1.Schedule of Visits and Procedures

Table1. Schedule of Visits and Procedures/ CRF Modules (parameters in italics will be collected in the CRF)

Phase	Pre-treatment	Treatment																										
Visit Name and Number	Screening	Study Period																										Pre-study medical[1]
Day	Within 14days	Day -2	Day -1	Day1																		Day 2				Day 3	3 days after OXN dosing
Hours	within-336	Check -in		Pre-dose	0	0.5	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	14	24	28	32	36	48	48±2
Informed consent	X																									
Demography & BMI	X																									X(weight)
Inclusion/Exc. Criteria	X																									
Med. history & current Med condition	X																									
Vital Signs[2]	X			X			X		X				X		X		X		X		X			X		X
Adverse Events[3]	X	x	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
X-ray(in the opinion of the investigator)	X																									
Concomitant Therapy	X	x	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[4]	X																									X
Haematology, Blood, Chemistry, Urinalysis	X																									X
Virology[5]	X																									
ECG	X																									X
β-hCG Pregnancy Test[6]	X		X																							X
Urine Drug, Alcohol Breath Test	X		X[8]																							
OXN Dosing					X																					
BPI-SF[7]	X		X-X	X			X		X		X		X		X		X	X	X		X-X				X	
Blood Samples				See Table 2 for blood sampling schedule																								
Discharge from study																												X

1. Post-study evaluation 48±2 hours after OXN dosing (in the case of discontinuation from the study).
2. Pulse rate, respiration rate, blood pressure. Axillary temperature will be recorded at pre study screening, pre-dose, at 24, 36, 48 hours post-dose.
3. AEs will be recorded from the time a subject provides their informed consent at screening until 3 days after OXN dosing. Throughout the study, subjects will be asked to volunteer AEs to investigators.
4. Full physical examinations will be carried out at screening and at post-study evaluation. (or new AE happens).
5. Anti-HIV, HBsAg, Hepatitis C antibody,hepatitis B core antigen (anti-HBc), qualitative syphilis test.
6. Serum β-HCG pregnancy test at screening and check-in (Serum FSH for more than one year postmenopausal females), urine pregnancy test at post study(except females who confirmed by Serum FSH). (If necessary, in the opinion of the investigator or the sub-investigator, Female using IUDs will receive a pelvic ultrasound, to confirm the location of the IUDs.)
7. Brief Pain Inventory- Short Form (BPI-SF) (Cleeland, 1991) will be assessed at pre-dose,1h,2h,3h,4h,6h,8h,10h,12h,14h on day1, and BPI-SFwill be assessed at the same time point on day-1 and day2 . In addition to the first inquiry of each morning, subjects only need to answer the BPI-SF.
8. If screening visit and treatment day less than 7 days, do not duplicate the assessment completed on screening visit.

Table 2: PK blood sampling schedule

Phase	Treatment																				
Day	1																2				3
Hour	Pre-dose	0.5	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	14	24	28	32	36	48
Blood Sampling (6 mL)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

10.4.1.1Screening Period - Screening Visit (V1, Days -14 to -2)

The following evaluations will be performed after the subject signs the study specific informed consent form:

- Inclusion/exclusion criteria
- Demography
- Body Mass Index (BMI)
- Medical history
- Physical examination
- 12-lead ECG
- X-ray(if any, in the opinion of the investigator or the sub-investigator, X-ray may be arranged to confirm the damage of jonit.)
- Vital signs (supine blood pressure, supine respiration rate, supine pulse rate, axillary temperature, height, and weight)
- Urine drug (opioids, barbiturates, amphetamines, cocaine metabolites, methadone, diazepam and cannabinoids), alcohol breath test
- Haematology, blood biochemistry, and urinalysis
- Virology (Anti-HIV, HBsAg, Hepatitis C antibody, Anti-syphilis test)
- Serum β-hCG pregnancy test for females of child-bearing potential (Serum FSH for more than one year postmenopausal females. If necessary, in the opinion of the investigator or the sub-investigator, Female using IUDs will receive a pelvic ultrasound, to confirm the location of the IUDs.)
- Concomitant therapy

10.4.1.2. Days -2 - Day-1(Table1)

- Subjects will be provided with meals and snack, to be eaten.
- Inclusion/exclusion criteria will be verified at check-in. Subjects will be asked how they have been feeling since their last visit, whether they have taken any prescribed or over the-counter medications, or any vitamins or mineral supplements or herbal products since their screening visit, and whether they have abstained from alcohol during the previous 2 days (within 48 hours before the scheduled study drug dosing).
- Subjects will provide a urine sample for a test of drugs of abuse and a breath test for alcohol. The results for all of these tests must be negative prior to study drug dosing.
- Subject will be randomized to treatment.
- BPI-SF
- Subjects must begin fasting >8 hours prior to OXN dosing.
- Subjects must follow the restrictions detailed in Sections 10.4.3 throughout the study.

10.4.1.3. Days 1

- Vital signs will be obtained pre-dose and a brief medical assessment will be performed, as applicable.
- A venous blood sample (6mL) will be drawn from each subject pre-dose for the determination of baseline oxycodone, naloxone, and metabolites plasma concentrations.
- Study drug will be administered to each subject according to Section 10.5.
- Subjects will remain in a semi-supine position for 4 hours after they have received their dose of OXN.(except go to bathroom or other activities related on the study)
- Pharmacokinetic blood samples (6mL) will be obtained as specified in Table 1 and Section 10.4.2.
- BPI-SF
- Vital signs will be obtained post-dose according to Table 1 and Section 10.4.6.2.
- Safety will be monitored as specified in Table 1 and Section 10.4.6&10.4.7.

- Food and beverages will be provided in accordance with Section 10.4.3.1.

10.4.1.4. Days 2-3

- Blood samples (6 mL) for pharmacokinetic analysis will be obtained as specified in Table 1 and Section 10.4.2.
- BPI-SF
- Vital signs will be obtained according to Table 1 and Section 10.4.6.2.
- Safety will be monitored as specified in Table 1 and Section10.4.6&10.4.7.
- Food and beverages will be provided in accordance with Section 10.4.3.1.

10.4.1.5. End-of-Study

Subjects will attend a post-study evaluation 48±2 hours after OXN dosing, 48±2 hours after OXN dosing in the case of discontinuation from the study. The following safety evaluations will be carried out:

- review of adverse events
- review of concomitant therapy
- physical examination
- 12-lead ECG
- vital signs (supine blood pressure, supine pulse rate, respiration rate, axillary temperature and weight)
- hematology, biochemistry, and urinalysis
- Urine pregnancy test (female subjects except post menopausal females confirmed by Serum FSH)
- Subjects will be discharged after the 48-hour procedures are completed.

10.4.2 Pharmacokinetic Sample Collection

Beginning on Days 1 serial blood collections (6 mL each) will be obtained at the following times: at baseline (0 h; within 30 minutes prior to OXN dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6,7,8, 10, 12, 14, 24, 28, 32, 36, 48 hours after OXN dosing. In total there will be 126 mL blood taken for pharmacokinetic analysis.

10.4.3. Study Restrictions

10.4.3.1. Food and Beverages

Menus will be standardized while subjects are inpatients in the study unit. The menus will follow the arrangement of study unit. However, the menus for each day need not be identical. Subjects must consume only the food given to them while in the unit. Food and water will be restricted as follows:

- **Days -2 (check-in) -** Subjects will be given meals and snack following check-in to the study unit on 2 day before OXN dosing. They will fast (only water is permitted) for at least 8 hours prior to OXN dosing.
- **Days 1(dosing) -** Subjects will fast (only water is permitted) for at least 4 hours after OXN dosing. Subjects will also have restricted fluid (200 mL water at time of OXN dosing) from 1 hour before OXN dosing until 1 hour after OXN dosing. From 1 hour after OXN dosing there will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurements. A low fat lunch (<30% fat), dinner, and an evening snack will be provided at 4, 10, and 14 hours after OXN dosing. Drinks of decaffeinated tea or

decaffeinated coffee will be supplied with meals (if any).

- **Day 2**: Breakfast will be provided 24 hours after OXN dosing. Lunch, an evening meal, and a snack will be provided 28, 34, and 38 hours after OXN dosing, respectively. There will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurements.
- **Days 3 (discharge) -** Breakfast will be optional after all study procedures have been completed.

10.4.3.2. Alcohol, Caffeine, and Smoking Restrictions

Subjects must abstain from alcohol for 48 hours before they check in to the study unit for each study period. Caffeine or xanthine containing food or beverages will not be permitted while subjects are in the study unit. Smoking is not permitted at any time during the study.

10.4.4. Efficacy Assessments

Not investigated.

10.4.5. Pharmacokinetic Measurements

10.4.5.1. Drug Concentration Measurements

Blood samples for determining analyte concentrations will be obtained for each subject during the period; pre-dose (within 30 minutes before OXN dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6,7, 8, 10, 12, 14, 24, 28, 32, 36, 48 hours (21 blood samples per study period) after OXN dosing. Blood will also be drawn, where appropriate, at the first report of a serious or severe unexpected adverse event and at its resolution.

At each time of blood sampling, 6mL venous blood will be drawn from a forearm vein into a tube containing K2 EDTA anticoagulant. All samples should be processed according to the sample handling procedures described in Appendix 12.1.1.

10.4.5.2. Pharmacokinetic Metrics

In case of no protocol deviation during the trial which affects PK endpoint variables (such as AUC and Cmax) (such as missing doses), all subjects will be included in the PK analysis set.

The following PK parameters shall be calculated using the non-compartment analysis method within the software Phoenix WinNonlin 6.3 (Pharsight Corp., Mountain View, CA, USA).

Parameters	Definitions	Calculation methods
$AUC_{0\text{-}inf}$	The area under the plasma concentration-time curve from time 0 to infinity	$AUC_{0\text{-}inf}$ =$AUC_{0\text{-}t}$+(Clast/Lambda_z), where Clast is the corresponding blood concentration at the last measurable time point Tlast.
$AUC_{0\text{-}t}$	The area under the plasma concentration-time curve from time 0 to the last	Linear/ log trapezoidal method

	measurable concentration (Clast)	
Cmax	Maximum plasma concentration	It shall be obtained directly from observation data.
Lambda_z	Elimination rate constant [1/ hr]	The elimination rate constant shall be calculated using the linear regression of log-linear concentration-time curve. The time point can be included only if corresponding linearity decreases.
T1/2	Half-life of elimination [hr]	T½=ln(2)/Lambda_z. The time point can be included only if corresponding linearity decreases.
Tmax	Time to peak blood concentration [hr]	Time to peak blood concentration present for the first time on the time axis shall be obtained from observation data.
AUC_%Extrap	The percentage AUC extrapolated [%]	The percentage of area under the plasma concentration-time curve from the last measurable concentration time point after dosing *t* to infinity in $AUC_{0\text{-}inf}$

Descriptive statistics of PK parameters of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone), naloxone and its metabolites (naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide) shall be analysed by dose group. The descriptive statistics includes mean, standard deviation, coefficient of variation, minimum and maximum (geometric mean shall be indicated, if any).

The mean (Mean ± SD) concentration-time curves of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone), naloxone and its metabolites (naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide) shall be drawn by dose group.

The dose-proportionality of oxycodone and naloxone, metabolites ($AUC_{0\text{-}t}$, $AUC_{0\text{-}INF}$ and C_{max}) will be analysed using the linear mixed effect model (with treatment as the fixed term and subject as the random effect).

10.4.6.Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and Serious Adverse Events (SAEs); pre-study and post-study haematology, blood chemistry, urine values, and ECGs; regular measurement of vital signs, and physical examinations.

During the study period, subjects must be monitored while they are in the study unit, by the study unit staff. The Investigator or Co-investigator must remain in the study unit for at least 8 hours after dosing and during normal working hours, for each study period.

Throughout the study, subjects will be reminded to immediately report AEs experienced during the study to the medical staff. These will be recorded in the CRFs and reported according to Sections 10.4.7.

Throughout the study, if any vital sign falls outside the normal range and is considered potentially clinically significant or clinically significant, it will be repeated. If the value remains outside the normal range and is considered clinically significant by the Investigator, or Co-investigator, the event will be recorded in the AE section of the CRF. If appropriate, the subject's further participation in the study should be discussed with the CRA or Medical Monitor at the Sponsor. As at any time during the study, if the Investigator considers that continuation in the study is not in the subject's best interests, the subject will be discontinued from the study. If the Investigator or Co-investigator considers the result not to be of clinical significance, the subject may continue in the study and an explanation will be recorded in the source data.

If the subject is discontinued from the study, the full details should be conveyed to the CRA immediately (see Section 10.4.7.1 for details relating to the reporting of AEs).

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.

Day 1

- Pre-dose vital signs (supine blood pressure, supine pulse rate, respiratory rate, and axillary temperature).
- Pre-dose medical evaluation to confirm suitability for dosing.
- Post-dose vital signs (supine blood pressure, supine pulse rate, respiratory rate，and) at 1, 2, 4, 6, 8 and 12 hours.

Day 2

- Vital signs (supine blood pressure, supine pulse rate, respiratory rate) at 24, and 36 hours.
- Axillary temperature will be recorded at 24 and 36 hours.

Day 3

- Vital signs (supine blood pressure, supine pulse rate, respiratory rate) at 48 hours.
- Axillary temperature will be recorded at 48 hours.
- Medical evaluation at 48±2 hours after dosing.

See Table 1 for the timing of safety evaluations during the study period:

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.

10.4.6.1. Laboratory Measurements

Clinical laboratory tests during the pre-study and post-study will be performed by a local laboratory. Laboratory certification as available will be included in the clinical study report for this protocol.
Table 1presents the clinical laboratory tests to be performed.

10.4.6.2. Vital Sign and Weight Measurements

Vital sign measurements (blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiration rate, and axillary temperature) will be obtained at the visits designated on the Schedule of Visits and Procedures (Table 1). Blood pressure and pulse will be measured after the subject has been supine for 3 minutes. Weight will be recorded pre and post-study.

10.4.6.3. Medical History and Physical Examinations

Medical history will be taken at screening. Physical examinations will be performed at the pre study and post-study. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF. Only changes from screening physical examination findings that meet the definition of an adverse event will be recorded on the Adverse Events CRF. Medical evaluations will be performed prior to study drug administration and 48±2 hours after dosing.

10.4.6.4. Electrocardiograms (ECGs)

The 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be obtained at the visits designated on the Schedule of Visits and Procedures (Table1). ECGs will be performed after the subject has been supine for 3 minutes. The ECGs will be evaluated by the study investigator or a designate. ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant abnormal findings will be reported as adverse events.

ECG recordings will be made at the following time points:
- At the screening
- At the end-of-study

10.4.7. Adverse Events (AEs) and Serious Adverse Events (SAEs)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject who is administered a medicinal product and which does not necessarily have to 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.

10.4.7.1. Reporting of Adverse Events

See also SAE flow chart in Appendix Figure1.

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 immediately(within 24 hours)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 CRF. 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 CRF and flagged as serious. The invwstigator should complete a seperate paper SAE Data Form and forward to the sponsor within 24 hours any information related to onset of SAEs in the subjects participating in the study. 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.

10.4.7.2. 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 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 the causality assessment of adverse events in the CRF only relates to the IMP(s) named in section13.1.

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).

10.4.7.3.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 CRF (and, if applicable, on the SAE Data Form).

10.4.7.4.Pregnancy

Pregnancy occurring in a subject (or his partner) enrolled in the trial must be reported to the investigator, who will forward it to the drug safety specialist of Mundipharma (China) Pharmaceutical Co., Ltd. within 24 hours using the paper Pregnancy Notification Form. The sponsor will contact the investigator to confirm significant pregnancy-related information (i.e., AEs during pregnancy, the pregnancy outcome, and any events to 3 months post-partum). All follow up information about the pregnancy will also be reported to the drug safety specialist of Mundipharma (China) Pharmaceutical Co., Ltd. within 24 hours.

10.4.7.5.Laboratory Abnormalities

All clinical laboratory tests will be performed by a local laboratory.
Table 2 presents the clinical laboratory tests to be performed.

Table3. Clinical Laboratory Tests

Category Parameters

Category	Parameters
Haematology	RBC, hemoglobin, hematocrit, platelets, and WBC with differential(neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	Electrolytes Sodium, potassium, chloride, bicarbonate
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, gamma glutamyl transferase (GGT)
Renal function parameters	blood urea, creatinine
Other	Glucose (fasting), calcium, albumin, cholesterol, triglycerides,phosphorus, lactate dehydrogenase (LDH), total protein, uric acid
Urinalysis	pH, protein, glucose, ketone, occult blood, specific gravity
Urine microscopy (if required)	RBC, WBC, casts, crystals

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,

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).

10.4.7.6.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 table 3).

Table4 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.		

10.4.7.7.ECG Adverse Events

A simultaneous 12-lead resting ECG will be obtained both during the Screening Phase and the end of the study. 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.

10.4.7.8.Other Safety Considerations/Risk Management

Preventable medication errors related to an IMP which occur at the time of drug's administration are a potential safety issue and must be reported immediately(within 24 hours) to the Sponsor 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 the study supply into mainstream hospital supplies. Adverse events in persons (other than the subjects enrolled in the study) after drug diversion will be entered into 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(within 24 hours) to the Sponsor.

10.4.8.Product Quality Complaint

Product quality complaint means any suspicion of product fault related to the production, labeling or packaging(including dissatisfaction about reliability of product characteristics, quality, duration, labeling and package integrity). A product quality complaint may possibly influence both product safety and treatment administered to subjects enrolled in the study. Hence,it is of great importance to protect subjects, researchers and other involved personnel by reporting and analyzing any product quality complaint information in a timely and accurate manner, as approved by the world supervision organization.

10.4.8.1.Process

As long as obtaining product quality complaint events, the investigator should report product complaint events information to the sponsor immediately (within 24 hours).

As for serious product quality complaints caused by product's fault or serious adverse events, the investigators must report them to the sponsor within the timeline of seriously adverse event (please refer to section10.4.7.1). If required by the sponsor, a sample of the doubtful product must be saved for further investigation.

10.4.8.2. Contacting the sponsor about the product quality

The name (and contact details) of the sponsor's representative to be contacted in case of any product quality complaint are listed in the contact information page; such information is provided as independent document.

10.4.9. Completion/Discontinuation of Subjects

When a subject completes the study or discontinues from the study, the end-of-study procedures will be followed and protocol-specified information will be collected. However, a subject may elect to discontinue from the study at any time for safety or personal reasons. The Completion/Discontinuation page of the CRF will be completed accordingly.

10.5. Treatments

10.5.1. Treatments Administered

The treatments administered in this study are presented below:
Test treatments
Oxcodone/Naloxone PR tablets 5/2.5 (OXN 5/2.5) and Oxcodone/Naloxone PR tablets 20/10(OXN 20/10).
The randomization for medication numbers will be generated by MCPC.
Subjects will be randomly assigned to Treatment A or Treatment B before thefirst administration of the study drug on Day 1. The treatment will be administered orally as follows:
Treatment **A:** one tablet of OXN 5/2.5 in a fasted state
Treatment **B:** one tablet of OXN 20/10 in a fasted state

10.5.2. Packaging, labeling and re-supply

Drug supplies will be provided by MCPC. The clinical trial supply consists of containers with trial- and centre identification that hold the trial medication. The study medications will be contained in a specific medication pack. Each medication pack will contain an appropriate amount of drug (in blister wallet cards) for dosing. The clinical supplies will be labelled with the following as appropriate:
• Study number
• Name of product and strengths or identification code
• Pharmaceutical dosage form, quantity of dosage units
• Directions for use(for clinical trial use only)
• Caution Statement
• Sponsor name and address
• Storage conditions
• Expiry date
• Number of batch
Label examples are given in the Investigator Site File (ISF).
All drug supply(including unused and partially used study medication)will be fully accounted for. Unused study medication will be returned to sponsor for destruction.

10.5.3. Drug Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory and record keeping) following Sponsor's instructions and adherence to GCP guidelines as well as China Regulation on the Control of Narcotic Drugs and Psychotropic Drugs.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study.
An accurate and timely record of the receipt of all clinical supplies, dispensing of study drug to the subject, collection of unused supplies returned by the subject, and subsequent return of unused study drug to the Sponsor must be maintained. This includes, but may not be limited to:
(a) documentation of receipt of clinical supplies
(b) study drug dispensing/return reconciliation log
(c) study drug accountability log
(d) all shipping service receipts.
All forms will be provided by the Sponsor. Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, a representative of the CFDA. All unused study drug, including empty containers, are to be returned to the Sponsor at the conclusion of the study, unless provision is made to the Sponsor for destruction of supplies and containers at the investigational site. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, study drug that is to be returned to the Sponsor must be sealed with tamper-evident seals and shipped back to the Sponsor following all local regulatory and shipment laws.

PUMCH must retain samples when bioavailability/ bioequivalence testing has been performed under contract with a sponsor. Retained samples will retain according to PUMCH's lab related Sops, which states that each reserve test drug and reference standard sample will

- consist of a sufficient quantity to permit CFDA to perform all the release test standards required in the application five (5) times,
- be adequately identified so the reserve samples can be positively identified as having come from the same samples as used in the bioavailability/bio-equivalency studies,
- be stored under conditions that will maintain the samples' integrity, identity, strength, quality and purity, and be retained for at least five years following the date on which the application or supplemental application is approved, or, if the application is not approved, at least five years following the date of completion of the bioavailability/bioequivalence study.

10.5.4. Method of Assigning Subjects to Treatment Sequences

Subjects will be assigned to treatment using a pseudo-random number generator in a computer program. The method avoids bias by using a chance mechanism. The randomization scheme and identification for each subject will be included in the CSR for this protocol.

10.5.5. Removal of Subjects from Therapy or Assessment

The Investigator(s) or subjects themselves may decide to stop the study treatment at any time for safety or personal reasons. If appropriate, a subject who discontinues from the study treatment will be monitored for subsequent protocol-specified safety procedures. A subject that discontinues from the study for any reason may be replaced at the discretion of the Sponsor. To keep the completed subjects are at leat 12 subjects in each group.

10.5.6. Dosing Schedule

This study is an open-label design, and each subject will receive 1 tablet of OXN 5/2.5 or OXN 20/10 according to the RAS prepared by a computer program.

10.5.7. Method of Administration

Each dose of OXN will be given with 200 mL water to subjects in a standing position.
The oral cavity will be checked by the study site personnel to ensure that the dose has been swallowed.

10.5.8. Blinding

Not applicable.

10.5.9. Concomitant Therapy

For subjects who receive the study drug, any concomitant medications(including over-the counter medications) and therapies that are ongoing as of the date of the informed consent will be recorded on the Concomitant Therapy CRFs and must be approved by the sponsor. Administration of medications other than the study drug will be prohibited from the start of the study to completion of the study, with the exception of Vitamin D, calcium supplements, continued use by females of contraceptive medication or HRT.and drug therapy for any adverse events that might develop. The Investigator will record the adverse event for which the concomitant medication was administered on the Adverse Events CRF.

Paracetamol or NSAID's ibuprofen will be used as rescue medicine for patients who need the analgesic for pain relief. Maximum allowed daily dose of paracetamol is 1.3g. Maximum allowed daily dose of ibuprofen is 1.2g.

Ondansetron can be used before 30 minutes of study treatment, in the opinion of the investigator or the sub-investigator. If nausea, Ondansetron can be given at the discretion of the investigator after study treatment.Subjects will be withdrawn if they take any medicine affecting metabolism.

Female subjects who require prescription of HRT or contraceptives will continue their medication, in accordance with their primary care physician's instructions, throughout the study.

10.5.10. Treatment Compliance

Records of study drug and doses administered will be kept for the whole duration of the study. The CRAs will review drug accountability the during investigational site visits and at when the study is completed.

10.6. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor's qualified compliance auditing team, which is an independent function from the study conduct team.

10.6.1. Data Collection

Promasys ® system will be used to design electronic CRF and database in accordance with the study protocol. Data administrators will responsible for develop data management plans. Investigator will enter source data according SOP. There is a one-to-one relationship between source data and CRF. Investigator will enter required information source documents. When a discrepancy results in corrected source data, data that is corrected will be struck through with a single line, initialed, and dated. The completed original CRF researchers will be stored by investigator for 5 years and then transfer to the sponsor.

10.6.2. Clinical Data Management

The internal quality control of entered and collected Source documents will be apply to ensure validity and accuracy of the clinical database. Data will be entered using the dual independent entry by investigators or authorized investigators, electronic data from the central laboratory will be input using SAS® Programming, to ensure the reversibility of source data. CRAs will visit investigational site as frequently as documented in the monitoring plan to review the CRFs for completeness and accuracy against the source documents, the data administrator will verify the validity and accuracy of data after double entry and data input. CRA and data administrator can get into a dispute with the data of eCRF, investigator responsible for query answering and /or correct data of eCRF or source documents, all changes will be carried out in the Audit Trail function. Investigators will explain the reason for modifications in written form; the system will save the data information before and after modification. All data query have been clarified or resolved, data administrator will lock the database after get the written confirmation investigator and the sponsor.

10.6.3. Bio-analytical Data Management and Quality Control

Samples and sample Log Forms will be sent to Bioassay Lab (East Campous), Phase I Unit Clinical Pharmacology Research Center, Peking Union Medical College Hospital by the Investigator samples' analysis. Analyses will be performed by means of validated bioanalytical methods. Details on the analytical methodology, method of validation, and the analytical within-study quality control procedures will be included in the clinical study report.

10.7. Statistical Methods

Data analyses will be performed by the department of Statistics of PUMCH after the studycompletion and database lock.

10.7.1. Statistical and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan, which will be finalized prior database lock,and will be included in the clinical study report.

10.7.1.1. Analysis Populations

The enrolled population is defined as the group of individuals who provided informed consent. The safety population is defined as the group of subjects who received at least one dose of study drug, and had at least one post-dose safety assessment. The full analysis population for

pharmacokinetic parameters is defined as the group of subjects who has at least one pharmacokinetic parameter post dose.

10.7.1.1.1. Demographic/Baseline Analyses

The safety population will be used to summarize and list the demographic and baseline variables.

Age, height, weight, and body mass index will be summarized as continuous data. Gender and race will be summarized as categorical data. Descriptive summaries will also be done by gender if there is a minimum of five subjects for each gender.
Medical history and concurrent medical conditions will be listed.

10.7.1.1.2. Study Drug

Drug dosage and levels are fixed in this study. Compliance checks will be carried-out by study site staff at the time of dosing.
The number of subjects taking each study treatment will be summarized in the safety population.

10.7.1.1.3. Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO-DD) drug codes. A listing of concomitant medications by drug and drug class will be included in the clinical study report for this protocol.
Concomitant medications will be listed for subjects in the safety population.

10.7.1.2. Pharmacokinetic Analyses

Plasma concentration data and pharmacokinetic metrics will be listed for subjects in the safety population.

Plasma concentration data for each analyte will be summarized descriptively by time-point and treatment for subjects in the safety population. Individual and mean plasma concentrations for each analyte will also be plotted over time for each treatment.

Pharmacokinetic metrics (AUC_{0-t}, AUC_{0-inf}, Cmax, tmax, LambdaZ and t1/2Z) for each analyte will be summarized descriptively by treatment and gender for subjects in the full analysis population for pharmacokinetic metrics. To have a valid pharmacokinetic metric, a subject must not experience emesis within 12 hours after OXN dosing.

The linear relationship between exposure (AUC_{0-t}, AUC_{0-INF} and C_{max}) of oxycodone and naloxone-3-glucuronic acid and dose shall be analyzed using the linear mixed effect model (with treatment as fixed term and subject as random effect) (the specific method will be given in the statistical analysis plan).

The primary investigation for the treatments are:
• The PK of Oxycodone from OXN 5/2.5,OXN 20/10
• The PK of Naloxone glucuronide from OXN 5/2.5,OXN 20/10

To assess dose-proportionality of OXN 20/10 vs. OXN 5/2.5 the following secondary comparisons will be performed:
• Oxycodone from OXN 20/10 vs. OXN 5/2.5
• Naloxone glucuronide from OXN 20/10 vs. OXN 5/2.5

In addition, metabolite: parent ratios of AUCt, and where possible AUCINF will be summarized using number, mean, standard deviation, minimum and maximum.

10.7.1.3. Safety Analyses

Assessment of safety will be performed for all subjects who receive at least one dose of study drug and for whom at least one post-dose safety observation is recorded (the safety population). Safety data that will be evaluated include adverse events (including changes from baseline in physical examination findings), clinical laboratory results, vital signs, and ECGs. All safety data will be listed for subjects in the safety population.

10.7.1.3.1. Adverse Events

Adverse events will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA).Adverse events will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all adverse events will be contained in the data listings of the clinical study report for this protocol.
Adverse events will be summarized by presenting, for each treatment group, the incidence of adverse events. The incidence of adverse events will be based on the numbers and percentages of subjects with adverse events. Although a MedDRA term may be reported more than once time for a subject, that subject will be counted only once in the incidence count for that MedDRA term.
Data for adverse events will be analysed using the treatment emergent signs and symptoms (TESS) philosophy. Treatment emergent signs and symptoms are defined as adverse events that:
• emerge during treatment, having been absent at pre-treatment (baseline), or
• re-emerge during treatment, having been present at baseline but stopped prior to treatment, or
• worsen in severity during treatment relative to the pre-treatment state, when the adverse event is continuous.

Only treatment emergent adverse events from the study will be summarized.

10.7.1.3.2. Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol.

10.7.1.4. Vital Signs

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range. Reference (normal) ranges for vital sign parameters will be included in the Clinical Study Report for this protocol.
Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and Axillary temperature) will be summarized by treatment and time-point for the safety population and listed.

Table5. Reference Range for Vital Sign Values

Vital Sign Parameter	Range
Systolic blood pressure	90–140 mmHg
Diastolic blood pressure	50–90 mmHg
Pulse rate	60–100bpm
Respiration rate	12–20 rpm
Temperature	≤ 37°C

10.7.1.5. ECG Changes

ECG data will be obtained in the screening period and at the post-study medical (and, where appropriate, if a subject experiences an AE, TEAE, or SAE). ECGs will be classified as clinically significant or not clinically significant.
ECG data will be evaluated on an individual basis for each subject. Clinically significant results will be recorded on the CRF and identified on the ECG listing.

10.7.2. Sample Size and Power Considerations

No formal sample size calculations will be performed. 24 subjects (12 in each dosage group) are regarded as sufficient according to CFDA regulation requirement. If subject withdraw from the study, subject replacement is needed.

10.7.3. Interim Analysis

No interim analysis is planned.

11. PROCEDURES AND INSTRUCTIONS

11.1. Ethics and Good Clinical Practice

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. The protocol, informed consent, and appropriate related documents must be reviewed and approved by an IRB/IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations eg approvals and notifications as required of the IRB/IEC. Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.
A signed letter of study approval from the IRB/IEC Chairman must be sent to the Principal Investigator with a copy to the Sponsor prior to study start. If the IRB/IEC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.
Study progress is to be reported by the Sponsor to the IRB/IEC annually (or as required) according to local regulatory obligations. SAEs should also be reported by the Sponsor to the IRB/IEC in strict accord with local regulatory requirements.
At the end of the study, the sponsor should notify the IEC within 90 days. The Sponsor should also provide the IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the Investigator should notify the IEC within 15 days and a detailed written explanation of the reasons for the termination/halt should be given.

11.2. Subject Information and Informed Consent

As part of providing the informed consent document, the Investigator must explain to each subject (or guardian/legally authorized representative) 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.
This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. No subject can enter the study before his/her written informed consent has been obtained.
An unsigned copy of an IRB/IEC and Sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 3, and all applicable local regulations and provided to the Sponsor. Each subject must sign an approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each subject will be verified by the Sponsor and kept in the study center's investigational site files; a signed copy will be given to the subject.

11.3. Administrative Procedures

11.3.1. Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.
Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs of all investigational sites. 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. Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB/IEC detailing such changes.

11.3.2. Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol. There are to be no Investigator-initiated deviations from the protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation maybe ineligible for analysis and may compromise the study. On occasion, a subject whose medical condition does not exactly conform to the specifications of the protocol but who could potentially benefit from study participation may be considered for enrollment by the Sponsor if the Investigator first reviews the situation with the Sponsor. In these cases, the potential subject's participation will be discussed with the Sponsor personnel prior to the subject signs the informed consent and the exemption for study enrollment will be sent in writing to the investigational site by the Sponsor. The investigational site will retain a copy of this document.

If the Investigator learns at any time after informed consent that a subject does not meet protocol specifications for study participation, he/she will call the Sponsor immediately. Subjects who have not signed an IRB/IEC approved ICF cannot receive study drug. The Investigator and research team must comply with ICH E6 principles and all applicable local regulatory laws and regulations.

11.3.3. Monitoring Procedures

The Sponsor's CRA will maintain contact with the Investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Good Clinical Practices. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with ICH regulations. All records at the investigational site are subject to inspection by the local regulatory authority.
In accord with ICH E6, Section 6.10, source documents include, but are not limited to the following:
• Clinic, office, hospital charts;
• Copies or transcribed health care provider notes which have been certified for accuracy after production;
• Recorded data from automated instruments such as Interactive Voice-response Systems, x-rays, and other imaging reports, e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, Polysomnographys, pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives);
• Pain, quality of life, medical history questionnaires completed by subjects;
• Records of telephone contacts;
• Diaries or evaluation checklists;
• Drug distribution and accountability logs maintained in pharmacies or by research personnel;
• Laboratory results and other laboratory test outputs, e.g., urine pregnancy test result documentation;
• Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs;
• CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source.

11.3.4. Recording of Data

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained:
• All entries are to be typed or printed using a black ink ballpoint pen.
• There are to be no erasures, write-overs, use of correction fluid or tape, and the original entry must remain legible.
• Errors are to be corrected by placing one line through the error. The correct entry should appear next to the error, dated, and initialed by the responsible person making the change. The name of anyone making corrections must appear on the Site Signature Log collected at the beginning of the study and as study assignments change throughout the conduct of the study. Each error is to be corrected separately.
• The Investigator must sign and date the CRF where noted. A signature stamp may not be used.
• Changes to a CRF that has been previously signed by the Investigator must be initialed and dated by the Investigator after the change is made. Changes made to CRFs via data clarification forms issued by the Sponsor must likewise be signed by the Investigator. Neither

a subject's name nor initials are to appear on documents transmitted to the Sponsor in order to maintain confidentiality.

11.3.5. Retention of Records

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 CRFs, Investigator's Brochure, regulatory agency registration documents, eg, ICFs, and IRB/IEC correspondence. In addition, the Sponsor will send a list of treatment codes by study subject to the Investigator after the clinical database for this study has been secured. The investigational site should plan on retaining study documents for approximately 5 years after completion of the study according to local regulations.
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.

11.3.6. Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department may conducts audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH Good Clinical Practices and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

11.3.7. Handling of Study Drug

All study drugs will be supplied to the Principal Investigator by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, double-locked cabinet) and stored according to the conditions specified on the drug labels. The Investigator must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.
The assigned CRA will review these documents along with all other study conduct documents at appropriate intervals during visits to the investigational site once study drug has been received by the investigational site.
All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator must not destroy any drug labels or any partly used or unused drug supply. At the conclusion of the study and as appropriate during the course of the study, the Investigator will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor's CRA and to the Sponsor's address provided in the Investigator folder at each site.

11.3.8. Publication of Results

The investigational 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 study drug 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 multicenter studies, it is mandatory that the first publication be based on data obtained from all analyzed subjects; therefore Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Authorship of communications arising from pooled data will be determined by both contribution to the scientific design, conduct, and interpretation of the study and by mutual agreement and will include selected members from investigational sites as well as Sponsor personnel.

11.3.9. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. 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 judgment 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 IRB/IEC in case of study discontinuation. Study records must be retained as noted above.

12. APPENDICES

12.1. Pharmacokinetic Sample Handling and Shipping

12.1.1. Sample Procurement and Processing

Blood samples, 6 mL each, will be drawn into tubes containing K2 EDTA solution, an anticoagulant. It is important for the assay to obtain a full 6-mL blood sample. Samples should be centrifuged within 30 minutes of collection. Following centrifugation (1500g, 4°C, 15 min.), the harvested plasma will be pipetted equally into two polypropylene labeled tubes and frozen at -20°C and below. If the required volume of blood cannot be collected, a minimum of 1.4 mL of plasma must be transferred into the first tube and the remaining volume transferred to the second tube. Prior to freezing, each plasma sample will be identified by protocol number, subject number, specimen matrix (plasma) and nominal time of sampling etc.

12.1.2. Sample Transportation

At the end of the 48-hour blood collection in the treatment period, one set of samples (primary) and second set (back-up samples) packed in sufficient dry ice will be sent to Bioassay Lab (East Campus), Phase I Unit clinical Pharmacology researcher center, PUMCH(No1,Shuaifuyuan, Dongcheng District, Beijing, 100730 P.R. China). Sample Transportation will performed in accordance with bioassay lab's Sops.

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OXN1017- An open-label, multiple-dose, parallel group study to compare the steady-state pharmacokinetics of oxycodone and naloxone from an oxycodone/naloxone (OXN) prolonged release (PR) tablet 10/5 mg in healthy elderly and younger subjects. Mundipharma, 2007

OXN1403-An open-label, single-dose, 4-treatment, 4-period, randomized crossover study in healty subjects to assess the pharmacokinetic and bioavailability characteristics of three different strengths of a fixed combination OXN and a combination of Oxygesic® plus Nalocion CR.Mundipharma, 2005

OXN1018-An open-label, single-dose, 4-treatment, 4-period, randomized crossover study in healthy subjects to assess the pharmacokinetics of oxycodone and naloxone after administration of an oxycodone/naloxone prolonged release tablet 5/2.5 mg (OXN 5/2.5) in a fed and fasted state, an oxycodone hydrochloride prolonged release tablet 5 mg in a fasted state, and oxycodone hydrochloride immediate release liquid 5 mg and naloxone hydrochloride liquid 2.5 mg in a fasted state. Mundipharma, 2007

OXN IB version 8

Figure 1:Flow diagram for AE reporting

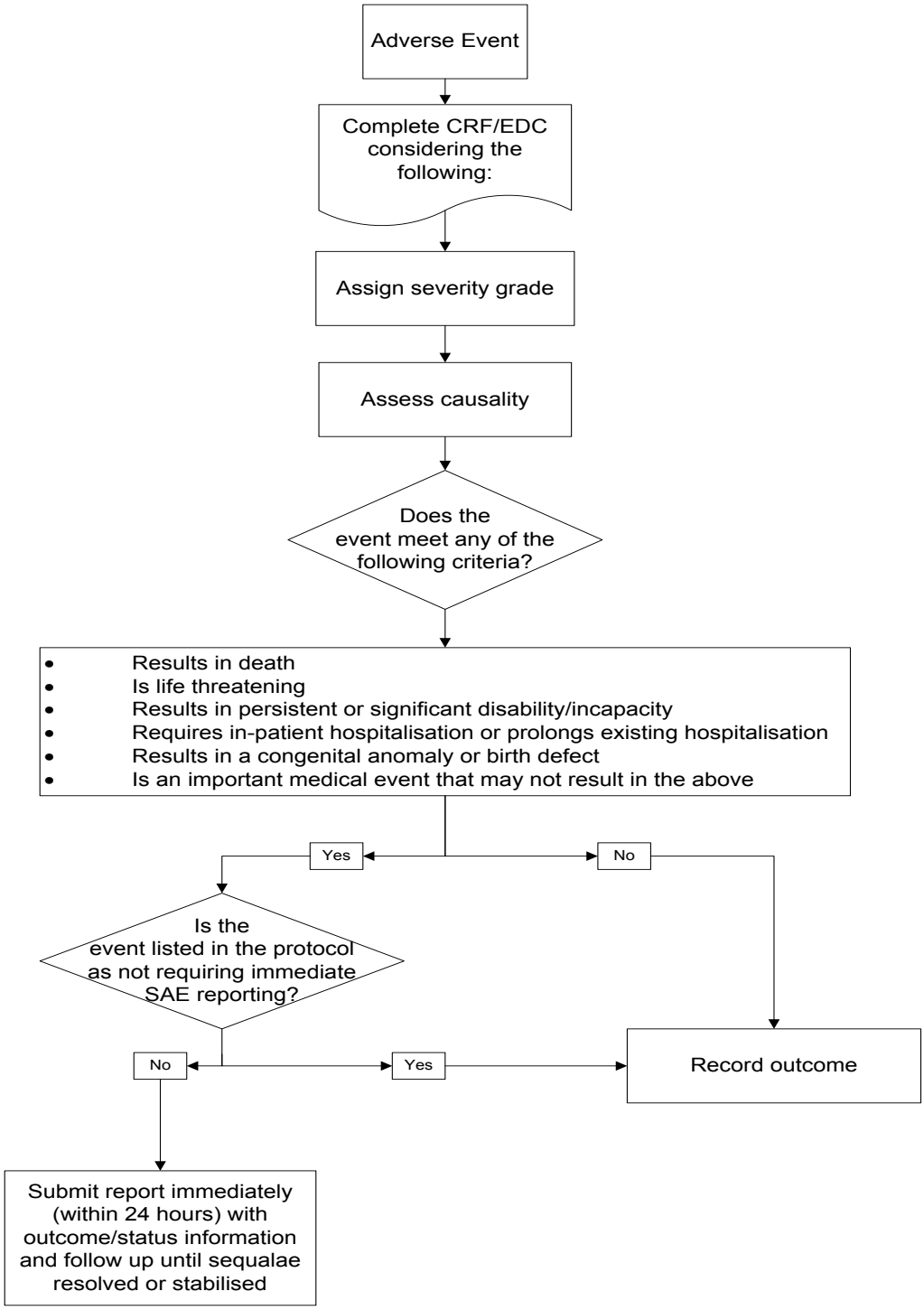
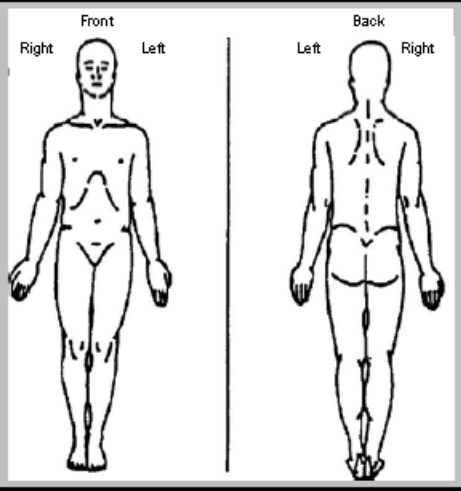


Figure2： Brief pain inventory – Short Form (BPI-SF)

Date： Time:

Name:

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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