SIGNATURE PAGE FOR PROTOCOL ONF16-CN-102

Protocol Number: ONF16-CN-102

Title: An Open-label, Single Dose, Randomized, Cross-over Study to Determine the Fasted State pharmacokinetics of Oxycodone from Oxycodone Tamper Resistant (OTR) Tablet 40 mg and OXYCONTIN® Tablet 40 mg in Chinese Subjects with Chronic Pain

Test Drug: OTR tablet 40 mg

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Regulatory Affairs Manager **Rainbow Bai** Mundipharma (China) Co., Ltd Beijing, China	 Signature Date
Medical Director, Greater China **Jane Zhang** Mundipharma (China) Co., Ltd Beijing, China	 Signature Date

SIGNATURE PAGE FOR INVESTIGATORS

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and China Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Investigators	Signature	Date

1. TITLE PAGE

Protocol Number: ONF16-CN-102

Title: An Open-label, Single Dose, Randomised, Cross-over Study to Determine the Fasted State pharmacokinetics of Oxycodone from Oxycodone Tamper Resistant (OTR) Tablet 40 mg and OXYCONTIN® Tablet 40 mg in Chinese Subjects with Chronic Pain

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

Test Drug: OTR tablet 40mg

Indication: Moderate to Severe Pain

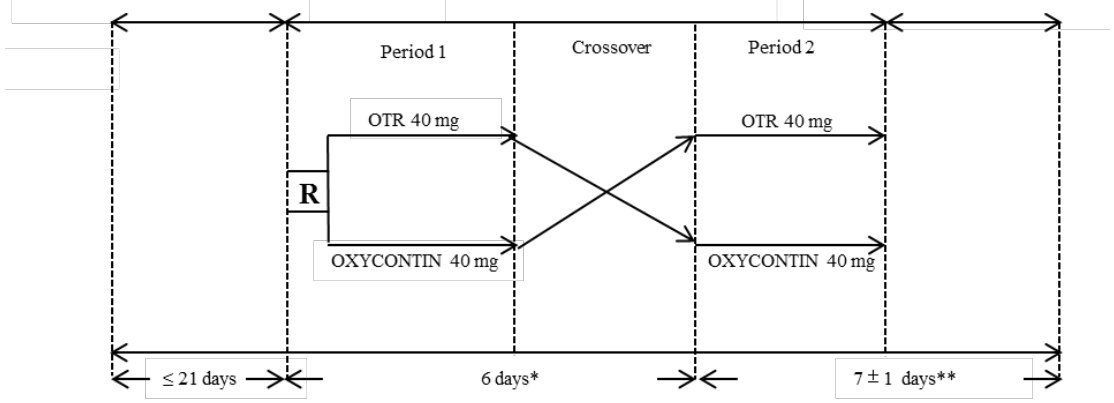
Phase: Phase 1

Release Date: 30-May-2016

GCP Statement: This study is to be performed in full compliance with ICH and all applicable local GCP and regulations. All required study documentation will be archived as required by Competent Authorities (CA).

2. CLINICAL PROTOCOL SUMMARY

Name of Sponsor: Mundipharma (China) Pharmaceutical Co. Ltd.	
Name of Generic Product: Oxycodone Hydrochloride Controlled-release Tablets	**Name of Active Ingredient:** Oxycodone hydrochloride
Protocol No.: ONF16-CN-102	**<EUDRACT><IND> No.:** NA
Short Title of the Study: OTR Tablet 40 mg Fasted-state Bioequivalence Study	
Full Title of the Study: An Open-label, Single Dose, Randomised, Cross-over Study to Determine the Fasted State Pharmacokinetics of Oxycodone from Oxycodone Tamper Resistant (OTR) Tablet 40 mg and OXYCONTIN® Tablet 40 mg in Chinese Subjects with Chronic Pain	
Investigators(s)/Centre(s): 1-2 Sites in China	
Study Initiation: Planned [Q4-2016]	**Phase of Development:** Phase 1
Objectives: **Primary** • To confirm the bioequivalence (BE) of OTR tablet 40 mg and OXYCONTIN tablet 40 mg in a fasted state. **Secondary** • To assess the safety of OTR tablet 40 mg and OXYCONTIN tablet 40 mg, when given to Chinese subjects with chronic pain in a fasted state.	
Study Design (Methodology): Open-label, single dose, randomised, cross-over study.	
Study Design Graphic:	



R = Randomization according to a Random Allocation Schedule (RAS) system
*: Starting from the 1st dosing to 2nd dosing
**: Starting from the 2nd dosing
IMP will be administered on Day1 of each period.
Crossover: Crossover to receive the alternative drug with a minimum of 6 days washout between two doses administration

Number of Subjects: A total of 38 subjects with histories of chronic pain will be randomized to receive the study drug to achieve 30 subjects (15 subjects per treatment sequence) to complete the study with valid pharmacokinetic (PK) data.

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

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

1. Chinese male or female subjects with histories of chronic pain regardless of the aetiology, aged 18-55 years both inclusive
2. The average pain over the last 24 hours should be scored < 4 assessed with Numeric Rating Scales (NRS), when not receiving analgesics. The pain condition has been kept stable at least in the past 7 days prior to entering into the screening and is expected to be stable during the study duration
3. Body weight ≥45 kg and a body mass index (BMI) ≥18 and ≤28 kg/m^2
4. Karnofsky score of Performance Status ≥70
5. Willing to take all the food supplied while the subject is in the study unit
6. Be able to read, understand, and sign written Informed Consent Form (ICF) prior to study participation and be willing to follow the protocol requirements
7. Willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, some Intrauterine Device (IUD), sexual abstinence, or vasectomised partner
8. Female subjects, including those up to less than one year post-menopausal, must have a negative serum pregnancy test and be non-lactating.

Exclusion Criteria:

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

1. Subjects who are currently taking opioids or have used opioids in the past 14 days prior to receiving the study drug
2. Have hypersensitivity history to any opioids, naltrexone, naloxone, or related compounds or any contraindications as detailed in the OTR and OXYCONTIN tablet Summary of Product Characteristics
3. Histories of or any current conditions that might interfere with drug absorption, distribution, metabolism, or excretion
4. Subjects who are likely to have paralytic ileus or acute abdomen or to require an operation on abdominal regions
5. Subjects with biliary tract diseases, pancreatitis, prostatic hypertrophy, or corticoadrenal insufficiency
6. Subjects with respiratory depression, corpulmonale, or chronic bronchial asthma
7. Any history of seizures or symptomatic head trauma
8. Subjects with abnormal liver function (values exceeding the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin during the Screening Phase) or abnormal renal function (values exceeding the ULN for serum creatinine during the Screening Phase). Note: if the values of ALT, AST or total bilirubin are between 1 to 1.2 times of ULN and confirmed not clinically significant by the Investigators, the subject may be recruited after getting the approval from Sponsor.
9. Any other significant illness other than the primary disease of chronic pain during the 4 weeks preceding the entry into this study
10. Subjects who are unable to stop taking monoamine oxidase inhibitors during this trial period or time lapses less than 2 weeks since drug withdrawal prior to the study drug administration
11. Subjects who are currently taking tricyclic antidepressants or have used tricyclic antidepressants within 4 weeks prior to the study drug administration
12. Subjects who have used any medicinal product which inhibits Cytochrome P450 3A4 (CYP3A4) (e.g. troleandomycin, ketoconazole, gestodene, etc.) or induces CYP3A4 (e.g. glucocorticoids, barbiturates, rifampicin, etc.) within 4 weeks prior to the study drug administration
13. Subjects who have used any medicinal product which inhibits Cytochrome P450 2D6 (CYP2D6) (e.g. fluoxetine, quinidine, ritonavir, etc.) or induces CYP2D6 (e.g. dexamethasone, rifampicin, glutethimide, etc.) within 4 weeks prior to the study drug administration
14. Histories of smoking (being a smoker or an occasional smoker) within 45 days prior to the study drug administration and refusal to abstain from smoking during the study. According to World Health Organization (WHO), a smoker is defined as having smoked at least 1 cigarette per day continuously for more than 6 months and an occasional smoker is defined as having smoked for more than 4 times per week and less than 1 cigarette per day continuously for more than 6 months.
15. Subjects with histories of alcoholism or drug abuse. Alcoholism is defined as regular alcohol consumption exceeding 14 drinks/week (1 drink = 150 mL of wine or 360 mL of beer or 45 mL of hard liquor)
16. Consumption of alcoholic beverages within 48 hours before study drug administration, and refusal to abstain from alcohol for at least 48 hours after study drug administration

17. Refusal to abstain from food for 10 hours preceding and 4 hours following administration of the study drug and to abstain from caffeine or xanthine entirely during each confinement
18. Positive Hepatitis B Surface Antigen (HBsAg), anti-Hepatitis C Virus (HCV), anti-Human Immunodeficiency Virus (HIV), or syphilis antibody test result
19. Urine screening before study is positive for opioids, barbiturates, amphetamines, cocaine metabolites, methadone, benzodiazepines, phencyclidine, methamphetamine, or cannabinoids. Or alcohol breath test is positive
20. Any history of frequent nausea or emesis regardless of aetiology
21. Blood or blood products donated within 30 days prior to administration of the study drugs or anytime during the study, except as required by this protocol
22. Subjects who participated in a clinical research study within 30 days of study entry

Test Treatment, Dose, and Mode of Administration:

OTR tablet 40 mg. Oxycodone Hydrochloride Controlled-release Tablets containing 40 mg oxycodone hydrochloride, manufactured by Purdue Pharma L.P., U.S.

The OTR tablet 40 mg will be administered orally once on the morning of Day 1 of each period, in a fasted state.

Reference Treatment, Dose, and Mode of Administration:

OXYCONTIN tablet 40 mg. Oxycodone Hydrochloride Prolonged-release (PR) Tablets containing 40 mg oxycodone hydrochloride manufactured by Bard Pharmaceuticals Ltd., U.K.

The OXYCONTIN tablet 40 mg will be administered orally once on the morning of Day 1 of each period, in a fasted state**.**

Concomitant Medication Including Rescue:

Naltrexone Cover: Naltrexone hydrochloride will be administered orally with the study treatments to reduce opioid-related adverse events (AEs). Naltrexone tablets 50 mg will be administered 13 hours, 1 hour before, and 11, 23 hours after each dosing with the study treatment respectively (4 occasions for each period).

Ondansetron will be permitted for the treatment of nausea or vomiting based on the clinical judgement by the Investigators.

Paracetamol or ibuprofen will be used as rescue medicine for subjects who need the analgesic for pain relief. The maximum allowed daily doses of paracetamol and ibuprofen are 2.0 g and 1.2 g respectively.

Administration of medications (including vitamins, herbal and/or mineral supplements, CYP3A4 inhibitors and inducers, CYP2D6 inhibitors and inducers) other than the study drug will be prohibited from the start to the completion of the study, with the exception of Vitamin D, calcium supplements, and drug therapy for any AE that might develop.

In case other medications were taken by the subject during the study, the Investigators should record that on the case report form (CRF), including the name(s) of drug(s), dosage

and administration, the duration of administration, and the reason for administration.

During the study period, smoking, alcohol, caffeine drinks, and grapefruit juice will be prohibited. Acute exercise will also be prohibited during the study period. Study restrictions (food, beverages, alcohol, caffeine, smoking, etc.) are detailed in Section 10.6.

Duration of Treatment and Study Duration:

Screening should be within 21 days before the randomization. The randomized subjects will be administered the test and reference treatments in a randomized order. There will be two study periods, with a minimum of 6 days washout between the two doses. Subjects will cross over to receive the alternative study drug upon completing Period 1.

PK blood sampling will continue for up to 32 hours after dosing with the study treatment in each period. Subjects will stay in the unit for safety monitoring until 72 hours after each dosing of the study drug in each period. Subjects will have a safety follow-up visit via telephone at 7±1 days after the last dose of study drug in the case of completion or early discontinuation from the study.

Total duration of the study is up to 35 days.

Treatment Schedule (Procedure):

A single dose of study drug is administered to subjects in each period with a minimum of 6 days washout between two doses according to a RAS system. Each dose of study drug is given with 200 mL water to subjects in a standing position.

Eligible subjects will be randomized into one of the treatment sequences as below:

Treatment Sequence (n)	Period 1		Period 2
1 (n=19)	OTR tablet 40 mg	Washout	OXYCONTIN tablet 40 mg
2 (n=19)	OXYCONTIN tablet 40 mg		OTR tablet 40 mg

Naltrexone tablets (10 x 5mg) will be administered with 150 mL water to subjects in a standing position.

Subjects will fast from food (only water is permitted) for at least 10 hours prior to and at least 4 hours after each dosing. Subjects will also have restricted fluid for one hour prior to and one hour after each dosing.

Criteria for Evaluation:

Analysis Populations:

The **enrolled population** is defined as all subjects who signed ICF.

The **intent to treat (ITT) population** is defined as all randomised subjects.

The **safety population** is defined as all randomised subjects who receive at least one dose of Investigational Medicinal Product (IMP).

The **PK population** is defined as all subjects who received IMP and have at least one PK

concentration measurement.

Efficacy Assessment(s): NA

Drug Concentration Measurements:

Blood samples for determining oxycodone plasma concentration will be obtained for each patient at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 28, and 32 hours post each study drug administration.

For each sample, 4 mL of blood sample will be collected at the above time points. The total volume of blood to be collected from each patient for PK analysis will be approximately 152 mL.

If subjects experience vomiting within 12 hours after dosing of the study treatment, no further PK blood sampling will be undertaken for the rest of the study period.

Blood samples, 4 mL each, will be drawn into tubes containing K_2EDTA anticoagulant. After procurement, samples should be kept in a cool environment, preferably in a container of ice water, until processing. Samples must be centrifuged within 30 minutes of collection. Following centrifugation (1500 g, 4℃, 15 minutes), the plasma will be transferred, via pipettes, into two labelled polypropylene tubes, and stored at -20℃ within one hour of collection.

Bioanalytical Methods:

The plasma samples will be analysed by a validated bioanalytical assay for oxycodone.

PK Parameters:

AUCt, Area under the plasma concentration-time curve calculated from the time of dosing to infinity (AUCINF), terminal phase rate constant (LambdaZ), apparent terminal phase half-life (t1/2Z), Cmax, and time from dosing to the maximum observed concentration (tmax) for oxycodone.

AUCt will be calculated using the linear trapezoidal method. Where possible, LambdaZ will be estimated using those points determined to be in the terminal log-linear phase. T1/2Z will be determined from the ratio of ln 2 to LambdaZ. The areas under the plasma concentration-time curve between the last measured point and infinity will be calculated from the ratio of the final observed plasma concentration (Clast) to LambdaZ. This will be added to the AUCt to yield AUCINF.

Cmax and tmax will be obtained directly from the reported data.

PK parameters will be determined using actual sampling times. All PK parameters calculations will be conducted using the Phoenix WinNonlin, Version 6.2 or later.

Pharmacodynamic Measurements: NA

Safety Assessments:
Safety will be assessed by AEs, clinical laboratory results, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and axillary temperature), physical examination, and electrocardiogram (ECGs) in the safety populations.

AEs will be recorded through spontaneous reporting from the time subjects provide their informed consent at screening until 7±1 days after the last dose of study drug, and through open questioning at each study visit. The subject's AEs will be categorized into Preferred Term (PT) and associated System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAE) will be defined as AEs that start or increase in severity after the administration of OTR tablet 40 mg or OXYCONTIN tablet 40 mg. When the Investigators identify a serious adverse event (SAE), a completed SAE data form signed and dated must be forwarded to Mundipharma China within 24 hours.

Statistical Methods:

Efficacy Analyses: NA

Interim Analyses: NA

PK Analyses:
Plasma concentration data and PK parameters will be listed for subjects in the enrolled population.

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

PK parameters (AUCt, AUCINF, Cmax, tmax, LambdaZ, and t1/2Z) for analyte oxycodone will be summarised descriptively by treatment for subjects in the PK population.

The comparison will be OTR tablet 40 mg in a fasted state (test) vs. OXYCONTIN tablet 40 mg in a fasted state (reference).

Primary Analysis:
The primary analysis will be for PK parameters AUCt and Cmax and for analyte oxycodone. Analysis of Variance (ANOVA) with fixed effect terms for treatment, period, sequence, and subject within sequence for ratio of means (using log scale) will be used to compare the test and the reference treatments. BE of test and reference will be concluded for a PK parameter of analyte oxycodone if the 90% Confidence Interval (CI) for the ratio (test/reference) falls completely within the BE acceptance range of 80.00% to 125.00%. BE of test and reference will be declared at all if it can be concluded for AUCt and Cmax, respectively.

Secondary Analysis:
The primary analysis will be repeated for the PK parameter AUCINF and for analyte oxycodone.

The statistical analyses will exclude PK parameters for which any of the following criteria apply: vomiting within 12 hours after dosing, incorrect dosing, incomplete plasma profile which cannot adequately detail the parameter, pre-dose concentration > 5% of Cmax, R^2 < 0.85.The validity of PK data will be discussed further and evaluated during the data review meeting at the end of the study. In accordance with BE guidelines, only subjects that provide valid PK data for both the test and reference treatments will be included in the statistical analysis.

Safety Analyses:

All safety summaries will be based on the safety population.

AEs will be classified into standardised terminology from the verbatim description (Investigators term) according to MedDRA Coding Dictionary to give a SOC and PT for each event.

An overall summary of TEAEs will be provided by treatment group. The number and percentage of subjects reporting TEAEs will be summarised by the PT nested within the SOC. In addition, the number of reported TEAEs will be summarised.

TEAEs will be summarised by worst severity and relationship to IMP. In addition, severe TEAEs, TEAEs leading to death, SAEs, and TEAEs requiring additional therapy will be summarised.

Clinical laboratory parameters and vital signs will be summarised descriptively by treatment and time point. The frequency of clinical laboratory and vital sign results with respect to normal ranges will be presented. Results of clinical laboratory evaluations that lie outside the normal range will be flagged on the listings as high or low.

The frequency of clinically significant ECG results will be presented.

Sample Size Rationale:

The study is designed to have a power of ⩾ 95% to demonstrate a BE (e.g. AUCt and Cmax) of OTR tablet 40 mg, in terms of oxycodone, with OXYCONTIN tablet 40 mg in a fasted state.

The null hypothesis is that the two treatments are not bioequivalent. The alternative hypothesis is that both treatments are bioequivalent. BE between both treatments will be concluded if the 90.00% CI for the ratio lies within 80.00% to 125.00% for both AUCt and Cmax for the oxycodone analyte.

A total of 38 subjects will be randomised to receive study drug (19 subjects per treatment sequence) with the aim that 30 subjects will provide valid PK data (15 subjects per treatment sequence) and PK parameters (Cmax and AUCt). This will provide ≥ 95% power to show BE simultaneously in both parameters, Cmax and AUCt, between test and reference formulation, assuming a true ratio of 1, a within standard deviation (SD) of the period differences of 0.32 on the log scale for AUCt and 0.28 on the log scale for Cmax, both PK parameters are not anti-correlated, and 90% CI for the ratios of the population means within the BE limits of 80.00% and 125.00%. The within SD of the period differences was based on Purdue Pharma BE study OTR1005 in healthy volunteers taking oxycodone[8].

The sample size was estimated using NQuery t-tests *(TOST of equivalence in ratio of means*

for crossover design (natural log scale).

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4. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the plasma concentration-time curve
AUCINF	Area under the plasma concentration-time curve calculated from the time of dosing to infinity
AUCt	Area under the plasma concentration-time curve calculated from the time of dosing to the last measurable concentration
BE	Bioequivalence
BMI	Body Mass Index
bpm	beats per minute
CA	Competent Authorities
CI	Confidence Interval
Clast	the final observed plasma concentration
Cmax	Maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture system
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
H	Laboratory value above the reference range
HB_sAg	Hepatitis B Surface Antigen
hCG	Human chorionic gonadotropin
HCO_3^-	Biocarbonate
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
ITT	The intent to treat
IUD	Intrauterine Device
Kg	Kilogram
L	Laboratory value below the reference range
LambdaZ	Terminal phase rate constant
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LLN	Lower limit of normal

LNH	Classification according to whether the Laboratory test result was below (L), within (N), or above (H) the reference range
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
N	Laboratory value within the reference range
NIMP	Non-Investigational Medicinal Product
NRS	Numeric Rating Scale
OTR	Oxycontin Tamper Resistant
PIS	Patient Information Sheet
PK	Pharmacokinetic
PT	Preferred Term
QA	Quality Assurance
RAS	Random Allocation Schedule
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOPs	Standard Operating Procedures
t1/2Z	Apparent terminal phase half-life
TEAE	Treatment emergent adverse event
tmax	Time from dosing to the maximum observed concentration
ULN	Upper limit of normal
UK	United Kingdom
WBC	White Blood Cell
WHO	World Health Organisation

5. STUDY CONDUCT AND OVERSIGHT

5.1 Sponsor

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

5.2 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating procedures (SOPs) of the Sponsor and Contract Research Organisation (CRO), which are designed to ensure adherence to GCP (ICH and China, GCP means both ICH and China hereinafter.) guidelines as described in Section15 of this protocol.

5.3 Investigators and Study Personnel

The study will be conducted at 1-2 Sites in China.

5.4 Randomisation

Randomisation will be completed using a RAS system by the sponsor in a 1:1 ratio.

5.5 Data Management

Data management will be the responsibility of the Data Management team from CRO. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. The Monitoring Plan and Data Management Plan (DMP) will detail the data entry, cleaning, clarification, and validation procedures to be followed by all relevant study staff. Data will be collected by an electronic data capture (EDC) system.

5.6 Monitoring

The study will be monitored by qualified personnel from CRO. The Monitoring Plan for the study will detail this process. The Investigators will allow monitoring, audit, and inspection of the clinical, laboratory, and pharmacy facilities as required, to assure compliance with GCP. 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 local regulations and GCP. All records at the Sites are subject to inspection by the local CA.

5.7 Medical Monitoring & Safety

The name of the Study Physician and Drug Safety Responsible Person along with the telephone and fax numbers of the other contact persons are listed in the study site file.

5.8 Bioanalytical Laboratory

A central bioanalytical laboratory will be employed to process all bioanalytical data.

6. INTRODUCTION

6.1 Investigational Drug/Background

Oxycodone, the derivative of the opium alkaloid analgesic, is a strong, semi-synthetic opioid analgesic, effective in the relief of mild to severe malignant and non-malignant pain[1-5]. As a mu- and kappa- opioid receptor agonist[3], oxycodone exerts its agonist activity similar to that of morphine and other opioid analgesics.

Oxycodone was launched in the United Kingdom (U.K.) in January 2000 as a prolonged release oral preparation (OXYCONTIN tablets) for the treatment of moderate to severe continuous pain. These OXYCONTIN tablets, manufactured and marketed by Bard Pharmaceuticals Ltd. and Napp Pharmaceuticals Limited respectively, are currently available as 5, 10, 20, 40, and 80 mg strengths.

In China, starting from 2004, the 5, 10, 20, 40, and 80 mg of OXYCONTIN tablets have been marketed. These preparations have since been authorized for the treatment of moderate to severe around-the-clock pain. OXYCONTIN tablets are for 12-hourly administration.

A new formulation, OTR, developed by Purdue Pharma L.P., provides improvements in the tamper resistant characteristics to make the tablet more difficult to manipulate for misuse and abuse. There is an increase in the ability of OTR to resist crushing, breaking, and dissolution using a variety of tools and solvents, which makes misuse more difficult and therefore safer for patients. The physicochemical properties make abuse via injection difficult. When subjected to an aqueous environment, OTR gradually forms a viscous hydrogel, i.e. a gelatinous mass, which resists passage through a needle. Clinical studies also suggest that OTR has physicochemical properties that are expected to reduce abuse via the intranasal route[6].

The goal of this study is to demonstrate that the new formulation, OTR, is bioequivalent to the marketed available OXYCONTIN in 40 mg dosage in a fasted state.

6.2 Design Rationale

OTR tablet 40 mg contains the same amount of active ingredient oxycodone as OXYCONTIN tablet 40 mg, which is market available. The BE of OTR tablet 40 mg to OXYCONTIN tablet 40 mg will be examined.

The investigation is designed as an open-label, single dose, randomized, and cross-over study to determine the PK profile of oxycodone from OTR tablet 40 mg and OXYCONTIN tablet 40 mg in Chinese subjects with chronic pain in a fasted state due to the reasons addressed in the following paragraphs.

First of all, the China regulations for drug registration require that controlled medicine (opioid is categorized to be a controlled medicine) should not be applied in healthy volunteers in clinical studies. In this BE study, subjects with histories of chronic pain are chosen as the target population. Per guideline, in this situation, Sponsor should attempt to enrol subjects whose disease process is expected to be stable for the duration of the study[9].

Inclusion/exclusion criteria are strictly defined to reduce the potential variation of the PK data. The subjects with abnormal liver and kidney functions, which may affect the metabolism of oxycodone, or with recent histories of taking medications which are classified as inducers or inhibitors of CYP3A4 and CYP2D6 will be excluded from the study. The eligible subjects will generate more valid PK data for the study analysis.

Single dose design is chosen per Food and Drug Administration (FDA)/WHO guideline on bioavailability (BA)/BE studies for modified-release products, i.e., "single dose studies are preferred to multiple-dose studies as single-dose studies are considered to provide more sensitive measurements of the release of active pharmaceutical ingredient (API) from the pharmaceutical product into the systemic circulation."

As a general rule, cross-over design is applied in the study to decrease the inter-individual variations between the two cohorts. A washout period lasting for at least 7 half-lives of the investigational medicine is needed to eliminate the drug residual from the previous period[7]. The elimination half-life of oxycodone from OTR is 4.5 hours[6], and a 6-day washout period is sufficient to achieve the aim.

Finally, open label design is applied since the plasma concentration of oxycodone is to be objectively tested and analysed and randomization will be applied to reduce selection bias. Naltrexone cover is used to reduce opioid-related AEs and increase tolerance to the study treatment.

6.3 Risk/Benefit Assessment

Opioid misuse and abuse is always the focus of attention from the regulatory authorities and clinical practisers. Compared with OXYCONTIN, OTR provides improvements in the tamper resistant characteristics which make the tablet more difficult to manipulate for misuse and abuse. The available data from clinical studies demonstrated that OTR has physicochemical properties that are expected to make abuse difficult and therefore reduce abuse.

Subjects will get study treatment with close monitoring by the Investigators in a medical surveillance environment. Naltrexone cover will be applied in the study to reduce opioid-related AEs since naltrexone can block the effect of oxycodone effectively as an opioid antagonist. Common side effects, such as nausea and emesis, will be targeted by ondansetron. Also, in case of flare ups of pain during the study, rescue drugs paracetamol or ibuprofen can be used at the discretion of the Investigators.

7. STUDY OBJECTIVES

7.1 Aim of the study

This open-label, single dose, randomised, cross-over study aims to determine the fasted-state PK of oxycodone from OTR tablet 40 mg and OXYCONTIN tablet 40 mg in Chinese subjects with chronic pain.

7.2 Primary Objectives

To confirm the BE of OTR tablet 40 mg and OXYCONTIN tablet 40 mg in a fasted state.

7.3 Secondary Objectives

To assess the safety of OTR tablet 40 mg and OXYCONTIN tablet 40 mg, when given to Chinese subjects with chronic pain in a fasted state.

8. STUDY SUMMARY AND GRAPHIC

8.1 Overall Study Design and Plan

Protocol ONF16-CN-102 is an open-label, single dose, randomised, cross-over study to determine the fasted-state PK of oxycodone from OTR tablet 40 mg and OXYCONTIN tablet 40 mg in Chinese subjects with chronic pain.

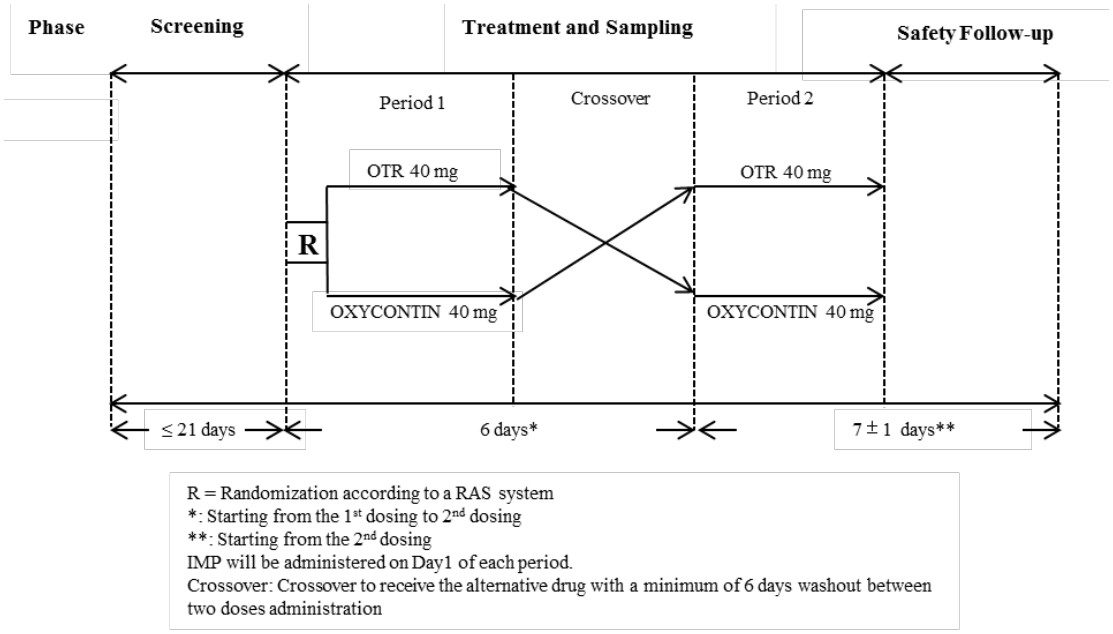
The study consists of a Screening Phase, a Treatment and Sampling Phase, and a Safety Follow-up Phase. The Screening Phase aims to check the eligibility of all subjects and will be completed within 21 days. The Treatment and Sampling Phase includes Period 1 and Period 2. Eligible subjects will report to the Sites one day before Period 1 for the reconfirmation of I/E criteria and will be randomized following a RAS system for the single-dose administration of either test or reference treatment. The randomized subjects will be administered with a single dose of the study drug on Day 1 of each Period at a fasted state. In Period 2, subjects will cross over to receive the single-dose administration of alternative study drug following a minimum 6-day washout between the 2 doses administration. Naltrexone tablets 50 mg will be administered at 13 hours, 1 hour before and at 11, 23 hours after each dosing with the study drug respectively to reduce opioid-related AEs. Blood samples for PK analysis will be collected per each study drug dosing until 32 hours after as described in Table 1and Table 2. Subjects will remain in the study unit for 72 hours after each study drug administration and will be contacted by phone calls for a safety follow-up on 7±1 days after the last study drug dosing in the case of completion or early discontinuation from the study.

Subjects will be fasted (only water is permitted) from at least 10 hours prior to and at least 4 hours after each dosing. Subjects will also have restricted fluid for one hour preceding and one hour after each dosing.

AEs and concomitant medication will be recorded throughout the study. Vital signs will be periodically monitored as described in Table 1 and Table 2.

8.2 Study diagram

Fig.1 study diagram



8.3 Efficacy Parameters

Not investigated.

8.4 PK Measurements

8.4.1 Drug Concentration Measurements

Blood samples for determining oxycodone plasma concentration will be collected within 5 minutes pre dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 28, and 32 hours post each study drug administration. For each sample, 4 mL blood sample will be drawn from a forearm vein into a tube containing K_2EDTA anticoagulant. The total volume of blood to be collected from each subject will be approximately 152 mL. If subjects experience vomiting within 12 hours after dosing of the study treatment, no further PK blood sampling will be undertaken for the rest of the study period. After procurement, samples should be kept in a cool environment, preferably in a container of ice water, until processing. Samples must be centrifuged within 30 minutes of collection. Following centrifugation (1500 g, 4℃, 15 minutes), the plasma will be equally transferred, via pipettes, into two labelled polypropylene tubes, and stored at -20℃ within one hour of collection.

Plasma concentration of oxycodone will be quantified by Liquid Chromatography - Tandem Mass Spectrometry (LC-MS/MS) methodology using a previously validated assay.

8.4.2 PK Parameters:

AUCt, AUCINF, LambdaZ, t1/2Z, Cmax, and tmax for oxycodone will be calculated.

AUCt will be calculated using the linear trapezoidal method. Where possible, LambdaZ will be estimated using those points determined to be in the terminal log-linear phase. And t1/2Z will be determined from the ratio of ln 2 to LambdaZ. The areas under the plasma concentration-time curve between the last measured point and infinity will be calculated from the ratio of Clast to LambdaZ. This will be added to the AUCt to yield AUCINF.

Cmax and tmax will be obtained directly from the reported data.

PK parameters will be determined using actual sampling times. All PK calculations will be conducted using the Phoenix WinNonlin, Version 6.2 or later.

9. SELECTION OF SUBJECTS

9.1 Number of Subjects

A total of 38 subjects with histories of chronic pain will be randomized to receive the study drug to achieve 30 subjects (15 subjects per treatment sequence) to complete the study with valid PK data.

9.2 Inclusion Criteria

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

1. Chinese male or female subjects with histories of chronic pain regardless of the aetiology, aged 18-55 years both inclusive
2. The average pain over the last 24 hours should be scored < 4 assessed with NRS, when not receiving analgesics. And the condition has been kept stable at least in the past 7 days prior to entering into the screening and is expected to be stable during the study duration
3. Body weight ≥45 kg and a BMI ≥18 and ≤28 kg/m^2
4. Karnofsky score of Performance Status ≥70
5. Willing to take all the food supplied while the subject is in the study unit
6. Be able to read, understand, and sign written ICF prior to study participation and be willing to follow the protocol requirements
7. Willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, some IUD, sexual abstinence, or vasectomised partner.
8. Female subjects, including those up to less than one year post-menopausal, must have a negative serum pregnancy test and be non-lactating.

9.3 Exclusion Criteria:

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

1. Subjects who are currently taking opioids or have used opioids in the past 14 days prior to receiving the study drug
2. Have hypersensitivity history to any opioids or related compounds or any contraindications as detailed in the OXYCONTIN and OTR tablet Summary of Product Characteristics
3. Histories of or any current conditions that might interfere with drug absorption, distribution, metabolism, or excretion
4. Subjects who are likely to have paralytic ileus or acute abdomen or to require an operation on abdominal region
5. Subjects with biliary tract diseases, pancreatitis, prostatic hypertrophy, or corticoadrenal insufficiency

6. Subjects with respiratory depression, corpulmonale, or chronic bronchial asthma
7. Any history of seizures or symptomatic head trauma
8. Subjects with abnormal liver function (values exceeding the ULN for ALT, AST, or total bilirubin during the Screening Phase) or abnormal renal function (values exceeding the ULN for serum creatinine during the Screening Phase). Note: if the values of ALT, AST or total bilirubin are between 1 to 1.2 times of ULN and confirmed not clinically significant by the Investigators, the subject may be recruited after getting the approval from Sponsor.
9. Any other significant illness other than the primary disease of chronic pain during the 4 weeks preceding the entry into this study
10. Subjects who are unable to stop taking monoamine oxidase inhibitor during this trial period or time lapses less than 2 weeks since drug withdrawal prior to the study drug administration
11. Subjects who are currently taking tricyclic antidepressants or have used tricyclic antidepressants within 4 weeks prior to the study drug administration
12. Subjects who have used any medicinal product which inhibits CYP3A4 (e.g. troleandomycin, ketoconazole, gestodene, etc.) or induces CYP3A4 (e.g. glucocorticoids, barbiturates, rifampicin, etc.) within 4 weeks prior to the study drug administration
13. Subjects who have used any medicinal product which inhibits CYP2D6 (e.g. fluoxetine, quinidine, ritonavir, etc.) or induces CYP2D6 (e.g. dexamethasone, rifampicin, glutethimide, etc.) within 4 weeks prior to the study drug administration
14. Histories of smoking (being a smoker or an occasional smoker) within 45 days prior to the study drug administration and refusal to abstain from smoking during the study. According to WHO, a smoker is defined as having smoked at least 1 cigarette per day continuously for more than 6 months and an occasional smoker is defined as having smoked for more than 4 times per week and less than 1 cigarette per day continuously for more than 6 months
15. Subjects with histories of alcoholism or drug abuse. Alcoholism is defined as regular alcohol consumption exceeding 14 drinks/week (1 drink = 150 mL of wine or 360 mL of beer or 45 mL of hard liquor)
16. Consumption of alcoholic beverages within 48 hours before study drug administration, and refusal to abstain from alcohol for at least 48 hours after study drug administration
17. Refusal to abstain from food for 10 hours preceding and 4 hours following administration of the study drug and to abstain from caffeine or xanthine entirely during each confinement
18. Positive HBsAg, anti-HCV, anti-HIV, or syphilis antibody test result
19. Urine screening before study is positive for opioids, barbiturates, amphetamines, cocaine metabolites, methadone, benzodiazepines, phencyclidine, methamphetamine, or cannabinoids or alcohol breath test is positive
20. Any history of frequent nausea or emesis regardless of aetiology
21. Blood or blood products donated within 30 days prior to administration of the study drugs or anytime during the study, except as required by this protocol
22. Subjects who participated in a clinical research study within 30 days of study entry

10. ASSESSMENTS AND PROCEDURES

10.1 Schedule Overview

Table 1 and Table 2 present the detailed procedures to be carried out at each study visit.

Table 1 Schedule of Visits and Procedures

Phase	**Pre-treatment**	**Treatment and Sampling**												
Visit Name and Number	**Screening (V1)**	**Period 1 and Washout (V2)**						**Period 2 (V3)[1]**						**Safety Follow-up[2] (V4)**
Day	≤20	-1	1			2	4	-1[3]	1[3]			2[3]	4[3]	7±1[2]
Hours	NA	-13	-1	0	11	23	72	-13	-1	0	11	23	72	
Report to Study Site	x	x[4]						x						
Informed Consent	x													
Demography	x													
NRS Score	x													
Inc. /Exc. Criteria	x	x[5]												
Medical History	x													
Vital Signs[6] and BMI	x	x	x	See Table 2 for VS testing			x	x	x	See Table 2 for VS testing			x	
Physical Examination	x	x					x	x					x	
ECG	x												x	
Haematology, Blood Chemistry, Urinalysis	x												x	
HBsAg, anti-HCV, anti-HIV, Syphilis Antibody	x													
Urine Drug Screen and Alcohol Test	x	x						x						
β-HCG Test (Female only)[7]	x[8]	x[9]						x[9]					x[9]	
Study Restriction Check		x						x						
Naltrexone Dosing[10]		x	x		x	x		x	x		x	x		
Randomization		x												
Study Drug Dosing[11]				x						x				
PK Blood Sampling		See Table 2 for Blood Sampling Schedule												
Concomitant Medication and Non-pharmacological Therapies	x	Concomitant medication will be recorded continuously.												x
AE	x	AE will be monitored continuously.												x
Discharge from Site[12]							x						x	

1. A minimum washout period of 6 days starting between the 1st study drug dosing and the 2nd.
2. Safety Follow-up visit will be 7±1 days after the last dose of study drug in the case of completion/discontinuation from the study.
3. Referring to the day in Period 1.
4. Eligible subjects will report the Sites 24 hours before the 1st study drug dosing for each period.
5. Inclusion/exclusion criteria will be verified to note any changes.

6. Vital signs include pulse rate, respiration rate, supine blood pressure, and axillary temperature. Axillary temperature will be measured only at screening, 13, 1 hours before each study drug dosing and 24, 72 hours after each study drug dosing. Vital signs will be tested within 10 minutes before naltrexone dosing. The BMI will be measured only at screening.
7. Including women up to less than one year post-menopause. Women with more than one year post-menopause, hysterectomy, and sterilization will not be applied.
8. A blood β-HCG test will be tested.
9. A urine β-HCG test will be performed.
10. Naltrexone tablets 50 mg will be administered at 13, 1 hours before and 11, 23 hours after each dosing respectively (dosing is defined as 0 hours).
11. OTR tablet 40 mg or OXYCONTIN tablet 40 mg administered orally with 200 mL water in a fasted state on the morning of Day 1 in each period.
12. The subjects will not be discharged from the Sites till 72 hours after the study drug administration in each period.

Table 2: PK Blood Sampling Schedule

PK Blood Sampling																			
Visit Name & Number	**Period 1 (V2) and Period 2 (V3)**																		
Day	1																2		
Hours Post-dose	Pre-dose	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	6	8	10	12	16	24	28	32
4 mL blood sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs			x		x				x				x		x		x		x

Notes: Time window for the blood sampling and vital sign:

- Pre-dose blood sampling will be drawn within 5 minutes before the dosing of the study drug.
- For all other blood sampling except the pre-dose sampling: blood sample collection will be within ± 2 minutes of scheduled time for within the first 5 hours after study drug dosing and within ± 5 minutes thereafter. Every effort should be made to ensure accurate sampling time and deviations should be minimal.
- Vital sign will be tested within 10 minutes before the corresponding blood sampling time.

10.2 Screening Phase (V1)

The Screening Phase (up to 20 days before the study treatment at Day -1) aims to evaluate if the subjects are eligible for the study according to inclusion/exclusion criteria. The reasons for screening failures will be documented. Subjects will perform the following procedures in the Screening Phase:

- The ICF (subjects will sign an ICF prior to executing all other activities.)
- Demography
- Medical history collection
- Physical examination
- Vital signs and BMI: pulse rate, respiration rate, supine blood pressure, and axillary temperature will be examined. Height and weight will be only performed at Screening Phase. It will be repeated if any vital sign falls outside the normal range and is considered potentially clinically significant.
- NRS score (‹ 4)
- ECG
- Haematology, blood chemistry, and urinalysis
- Serology testing (HBsAg, anti-HIV, anti-HCV, and syphilis antibody)
- Urine drug screen (opioids, barbiturates, amphetamines, cocaine metabolites, methadone, benzodiazepines, phencyclidine, methamphetamine, or cannabinoids) and alcohol test
- Blood β-HCG test for female subjects up to less than one year post-menopause
- AEs collection after the ICF acquisition
- Collection of concomitant medication and non-pharmacological therapies
- Inclusion/Exclusion criteria list will be checked when all the results of examinations are available.

Subjects who do not meet the inclusion/exclusion criteria are not permitted to attend the study. Eligible subjects also need to be instructed not to take alcohol 48 hours prior to the study drug dosing. Throughout the study, subjects will be reminded to immediately report AEs experienced to the medical staff. These will be recorded in the AE section of EDC and reported according to Section 13.2.

10.3 Treatment and Sampling Phase (V2 and V3)

Treatment and Sampling Phase includes Period 1 and Period 2. Eligible subjects will report to the Sites at Day -1 of each study period and remain to the unit till 72 hours after each study drug dosing. Subjects will take either a test (OTR tablet 40 mg) or a

reference treatment (OXYCONTIN tablet 40 mg) in accordance with a RAS system in Period 1. After that, subjects will cross over to take the alternative study treatment in Period 2 following a washout period of 6 minimum days between the 2 doses administrations. Naltrexone cover with a total of 4 occasions will be administered at each study period. And 4 mL of blood sample will be drawn for PK analysis from pre-dose to 32 hours post study drug dosing for each study period as described below.

10.3.1 Period 1 (V2)

10.3.1.1 Day -1

- Subjects will report to the study unit on the day 24 hours before the scheduled study drug dosing.
- Physical examination
- Subjects will be asked how they have been felt since their last visit, whether they have collected spontaneous AEs, whether they have taken any prescribed or over the-counter medications, or any vitamins or mineral supplements or herbal products since their last visit, and whether they have abstained from alcohol during the previous 2 days.
- Urine drug screen for opioids related drugs and alcohol test will be checked the second time and the results must be negative before subjects taking the first dose of naltrexone.
- Urine β-HCG test with female subjects before menopause and less than one year after menopause prior to taking the first dose of naltrexone
- Inclusion/exclusion criteria will be verified the second time to notice any changes compared to the first time.
- Vital signs (including axillary temperature) will be executed within 10 minutes before taking naltrexone.
- At 13 hours (±5 minutes) before the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- Subjects will be randomized into either OTR or OXYCONTIN group following a RAS system and randomization numbers will be assigned.
- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.1.2 Day 1

- Vital signs (including axillary temperature) will be executed within 10 minutes before taking naltrexone.

- At 1 hour (±2 minutes) before the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- A blood sample (4 mL) drawn at 5 minutes before the study drug administration.
- Based on the randomization schedule, either a tablet of OTR 40 mg or OXYCONTIN 40 mg will be administered with 200 mL water in a standing position.
- A blood sample (4 mL) will be drawn at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours post study drug administration. Blood sample collection will be within ± 2 minutes of scheduled time for within the first 5 hours after study drug dosing and within ± 5 minutes thereafter. For all the blood sampling, every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Vital signs (excluding axillary temperature) will be executed at 1, 2, 4, 8, and 12 hours after study drug administration and will be performed within 10 minutes before the corresponding blood sampling time.
- At 11 hours (±5 minutes) after the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.1.3 Day 2

- At 23 hours (±5 minutes) after the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- Vital signs will be executed at 24 (including axillary temperature) and 32 hours (excluding axillary temperature) after study drug administration and will be performed within 10 minutes before the corresponding blood sampling time.
- A blood sample (4 mL) will be drawn for PK analysis at 24, 28, and 32 hours post study drug administration. Blood sample collection will be within ± 5 minutes of the scheduled time.
- AEs collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.1.4 Day 4

- Physical examination examined at 72 hours after study drug dosing
- Vital signs (including axillary temperature) will be executed at 72 hours (± 10 minutes) after study drug administration.

- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine
- Subject will be discharged from the unit around 72 hours post study drug dosing. Before their discharge, Subjects need to be instructed that they must abstain from alcohol during the previous 2 days (within 48 hours) before the scheduled study drug dosing in the Period 2. And any vitamins or mineral supplements or herbal products will be prohibited until the end of the study.

10.3.2 Period 2 (V3)

10.3.2.1 Day -1, Period 2

- Subjects will report to the study unit on the day 24 hours before the last scheduled study drug dosing.
- Physical examination
- Subjects will be asked how they have been felt since their last visit, whether they have collected spontaneous AEs, whether they have taken any prescribed or over the-counter medications, or any vitamins or mineral supplements or herbal products since their last visit, and whether they have abstained from alcohol during the previous 2 days (within 48 hours before the scheduled study drug dosing).
- Urine drug screen for opioids related drugs and alcohol test will be checked again and the results must be negative before subjects taking naltrexone at Period 2.
- Urine β-HCG test with female subjects before menopause and less than one year after menopause prior to taking the first dose of naltrexone at Period 2
- Vital signs (including axillary temperature) will be executed within 10 minutes before taking naltrexone.
- At 13 hours (±5 minutes) before the last study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.2.2 Day 1, Period 2

- Vital signs (including axillary temperature) will be executed within 10 minutes before taking naltrexone

- At 1 hour (±5 minutes) before the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- A blood sample (4 mL) drawn at 5 minutes before the study drug administration.
- Following the sequence of study treatment in Period 1, subjects will cross over to take an alternative study treatment of either OTR 40 mg or OXYCONTIN 40 mg with 200 mL water in a standing position.
- A blood sample (4 mL) will be drawn at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours post the study drug administration. Blood sample collection will be within ± 2 minutes of scheduled time for within the first 5 hours after study drug dosing and within ± 5 minutes thereafter.
- Vital signs (excluding axillary temperature) will be executed at 1, 2, 4, 8, and 12 hours after study drug administration and will be performed within 10 minutes before the corresponding blood sampling time.
- At 11 hours (±5 minutes) after the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.2.3 Day 2, Period 2

- At 23 hours (±5 minutes) after the study drug dosing, 50 mg of naltrexone tablet will be administered with 150 mL water in a standing position.
- Vital signs will be executed at 24 (including axillary temperature) and 32 hours (excluding axillary temperature) after the study drug administration and will be performed within 10 minutes before the corresponding blood sampling time.
- A blood sample (4 mL) will be drawn at 24, 28, and 32 hours (± 5 minutes) post the study drug administration.
- AEs collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine

10.3.2.4 Day 4, Period 2

- Physical examination
- Vital signs (including axillary temperature) will be executed at 72 hours (± 10 minutes) after last study drug administration.
- ECG will be examined at 72 hours after study drug dosing.
- Haematology, blood chemistry, and urinalysis

- Urine β-HCG test with female subjects before menopause and less than one year after menopause before subjects are discharged from the unit
- AE collection
- Collection of concomitant medication and non-pharmacological therapies including rescue medicine
- Subject will be discharged from the unit around 72 hours post study drug dosing. Before the discharge, Subjects need to be instructed to report AEs experienced to Sites until the telephone visit.

10.4 Safety Follow-up (V4)

- The safety follow-up phase will be 7 ±1 days post last study drug dosing, the Investigators or a designee will call subjects to collect AEs and concomitant medication after being discharged from the unit, and every effort will be given to complete the safety follow-up.
- During this period, subject may contact Investigators for any AE occurred after being discharged from the unit.
- Subjects will complete the study.

10.5 Early Discontinuation/Withdrawal/Loss to Follow-up

The Investigators(s) or subjects themselves may stop study treatment at any time for safety or personal reasons. Subjects will continue to finish the 4 occasions of naltrexone dosing if he or she already takes the study treatment when withdrawing from the study from the consideration of safety purpose. Whenever possible, the subjects will be instructed to remain at the unit to complete the above treatment and safety monitoring. Otherwise, subjects will be instructed the timing, dosage, and administration method of taking naltrexone.

Whenever possible, the Investigators or a designee will give phone contacts to the withdrawal/discontinued subjects to complete the safety follow-up as described in 10.4.

10.6 Study Restrictions

10.6.1 Food and Beverages

Menus will be standardised while subjects are resident in the study unit. The menus should be kept the same for each study period. However, the menus for each day will

not be identical. Subjects must consume only the food given to them while in the unit. All the meals provided by the Sites will be low fat (<30% fat). Food and water will be restricted as follows:

- Day -1 (Period 1 and 2)-Subjects will be given a lunch and dinner following check-in to the study unit. Subjects will fast (only water is permitted) for at least 10 hours prior to each dosing. There will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurements.
- Day 1 (Period 1 and 2)-Subjects will fast (only water is permitted) for at least 4 hours after each dosing. No fluid will be allowed from one hour prior to and one hour after each dosing. A lunch, dinner, and evening snack will be provided at 4, 10, and 14 hours after the dosing of study drug. From 1 hour after dosing there will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurement.
- Day 2-3 (Period 1 and 2)-A breakfast, lunch, dinner, and evening snack will be provided from the Sites. There will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurements.
- Days 4 (Period 1 and 2)-A breakfast will be provided from the Sites. There will be free access to drinking water throughout the day, except within 30 minutes before vital sign measurements.

10.6.2 Alcohol, Caffeine, and Smoking Restrictions

Subjects must abstain from alcohol during the study period. Grapefruit juice, caffeine- and 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. Acute exercise will also be prohibited during the study period.

11. Study treatments and concomitant therapies

11.1 Treatment administration

11.1.1 Definitions

The IMP is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. IMP for this study consists of the test treatment (OTR tablet 40 mg) and the reference treatment (OXYCONTIN tablet 40 mg).

The non-IMP (NIMP) is defined as any medicinal products intended for research and development trials, which does not fall within the definition of an IMP. NIMP for this study is composed of naltrexone and other medications as the followings.

The other medications used for this study include ondansetron, paracetamol, and ibuprofen. They will be used per Investigators' discretion. These medicines will be supplied by Sites directly, and reimbursement will be provided by Sponsor.

11.1.2 Test IMPs, Dose, and Mode of Administration

Table 3 Investigational Drug

Investigational Drug	Dosage Form	Unit Strength	Trade Name	Active Ingredients	Mode of Administration
Oxycodone Hydrochloride Controlled-release Tablets	Tablet	40 mg	OTR	Oxycodone hydrochloride	Oral

The OTR tablet 40 mg is manufactured by Purdue Pharma L.P., U.S.

Table 4 Reference Investigational Drug

Reference Drug	Dosage Form	Unit Strength	Trade Name	Active Ingredients	Mode of Administration
Oxycodone Hydrochloride Prolonged-release Tablets	Tablet	40 mg	OXYCONTIN	Oxycodone hydrochloride	Oral

The OXYCONTIN tablet 40 mg is manufactured by Bard Pharmaceutical Ltd., U.K.

11.1.3 NIMP, Dose, and Mode of Administration

Table 5 NIMP

NIMP	Dosage Form	Unit Strength	Trade Name	Active Ingredients	Mode of Administration
Naltrexone hydrochloride	Tablet	5 mg	NuoXinSheng®	Naltrexone	Oral

Naltrexone hydrochloride is manufactured by Wellso Pharmaceutical Co., Ltd.

11.1.4 Other Medications, Dose, and Mode of Administration

Ondansetron will be permitted for the treatment of nausea or vomiting based on the clinical judgement by the Investigators. Paracetamol or Ibuprofen will be used as

rescue medicine for subjects who need the analgesic for pain relief. The maximum allowed daily doses of paracetamol and ibuprofen are 2.0 and 1.2 g respectively.

11.2 Identity of Investigational Products and Study Treatments Supply

OTR 40 mg Tablets are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other. OTR should be stored at 25°C (77° F) and excursions are permitted between 15° to 30°C (59°-86°F). Tablets should be dispensed in a tight and light-resistant container. OTR Tablets are supplied as 2 tablets per blister.

OXYCONTIN Tablets are yellow, round, convex tablets marked OC on one side and 40 on the other. OXYCONTIN Tablets cannot be stored above 25°C. OXYCONTIN Tablets are supplied as 2 tablets per blister.

Nuoxinsheng (naltrexone) is a white or off-white tablet. 5 mg tablets are contained in plastic bottles with 100 tablets per bottle. Nuoxinsheng (naltrexone) should be tightly sealed and kept away from light.

The Sponsor will supply IMPs and NIMP. The Product Release Certificates for the IMPs will be included in the clinical study report for this protocol. The study products will be supplied in packs labelled to meet the national requirements and will include a unique pack identifying number, including generic name, strengths, storage requirements etc.

11.3 Dosing Schedule

Table 1 presents details of the dosing schedule for each subject in the study.

11.4 Dose Modification

IMP is a single dose application and will not be modified. Naltrexone application consists of a total of 4 occasions. Any change due to intolerance will be judged by the Investigators in consultation with the Sponsor and will be recorded in EDC.

11.5 Method of Administration

For oxycodone dosing, subjects will be dosed in a standing position. Subjects will swallow a sip of water immediately before dosing. Subjects will then swallow their

dose, whole, with the remainder of the water (total volume of water 200 mL). The oral cavity will be checked by study site personnel to ensure that the dose is swallowed.

For naltrexone dosing, subjects will be dosed in a standing position. Subjects will swallow a sip of water immediately before dosing. Subjects will then swallow their dose, whole, with the remainder of the water. The naltrexone dosing (10 tablets for 50 mg) will be given with 150 mL water. The oral cavity will be checked by study site personnel to ensure that the dose is swallowed.

11.6 Treatment Assignment

Randomisation will be performed using a RAS system that automates the random assignment of treatment groups to randomisation numbers. The randomisation scheme will be reviewed by the Data Management and Statistics Department and locked after approval.

11.7 Blinding

Not applicable.

11.8 Treatment Compliance/Drug Accountability

The Investigators and study staff will be responsible for the accountability and management of all clinical supplies (dispensing, inventory, record keeping, return, etc.) following Sponsor instructions and adhere to GCP guidelines.

Under no circumstances will the Investigators allow the study medication 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 and dispensing of study medication to the subject must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study medication dispensing/return reconciliation log, (c) study medication accountability log, and (d) all shipping service receipts. All forms will be provided by the Sponsor. Any comparable forms that the Sites wish 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, or CA. 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/Sponsor designated warehouse must be sealed with tamper-evident

seals and shipped back to the Sponsor/warehouse following all China regulatory and shipment laws.

11.9 Concomitant Therapies (Permitted and Prohibited)

Administration of medications (including vitamins, herbal and/or mineral supplements, CYP3A4 inhibitors and inducers, and CYP2D6 inhibitors and inducers) other than the study drug will be prohibited from the start to the completion of the study, with the exceptions of Vitamin D, calcium supplements, and any drug therapy for AEs developed during study.

For subjects who receive study drug, any concomitant medications and therapies that are ongoing as of the date of informed consent will be recorded on the Concomitant Therapy section of EDC and must be approved by the Sponsor. The Investigators will record all concomitant medications, including over-the-counter medications, on the Concomitant Therapy section of EDC. The use of such concomitant medications should be approved in advance by the Sponsor, when possible. The Investigators will record the AE for which the concomitant medication was administered on the AE section of EDC.

Paracetamol or ibuprofen will be used as rescue medicine for subjects who need the analgesic for pain relief. Nausea and vomiting may be treated with Ondansetron as deemed appropriate.

Monoamine oxidase inhibitors cannot be used during this trial period or time lapses less than 2 weeks since drug withdrawal prior to the study drug administration. Tricyclic antidepressants cannot be administered during the trial or have been used within 4 weeks prior to the study drug administration. CYP3A4 and CYP2D6 inhibitors and inducers cannot be applied within 4 weeks prior to the study drug administration. Other concomitant treatments should be agreed upon in advance by the Sponsor, where possible.

11.10 Shipping, Handling, Storage, and Destruction/Return

IMPs and NIMP (naltrexone) will be supplied to the Principal Investigators or the delegated staff by the Sponsor directly. The other medications including ondansetron, paracetamol, or ibuprofen will be supplied by the Sites. Drug supplies must be kept in an appropriate secure area (e.g. locked cabinet/pharmacy) and stored according to the conditions specified on the drug labels. Specific laws relating to the handling and

storage of narcotics must be followed, and this will be the responsibility of the Investigators.

The investigational site personnel must not destroy any study treatment labels or any partly used or unused study treatment supply until directed by the Sponsor or designee following accountability checks. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by Sponsor personnel, study treatment that is to be returned to the Sponsor or Sponsor designated warehouse must be sealed with tamper-evident seals and shipped back to the Sponsor or Sponsor designated warehouse following all China local regulatory and shipment laws.

11.11 Retention of IMP Samples

The samples of IMP must be retained for two years after the drug is approved for marketing[7].

12. Reference Values

12.1 Physical/Vital Sign Assessments

Vital signs (pulse rate, respiration rate, supine blood pressure, and axillary temperature) and weight measurements will be obtained at the visits designated on Table 1 and Table 2. Blood pressure and pulse rate will be measured after the subject has been supine for 3 minutes.

Normal ranges for vital signs are shown in Appendix 18.2.1 Table 6.

Each clinically notable vital sign abnormality has to be recorded on the AE section of the EDC. Table 7 in Appendix 18.2.1 describes parameters for clinically notable vital signs. Additionally, if the change in vital signs qualifies as an SAE it has to be reported to the Sponsor using the SAE data form (Section 13).

12.2 Laboratory Assessments

Local Site laboratories will perform tests to qualify subjects for entry into the study. Table 1 shows the time points when clinical laboratory tests will be performed. Table 8 in Appendix 18.2.2 presents the clinical laboratory tests to be performed.

A laboratory abnormality may qualify as an AE or SAE as described in Section 13.1. Additionally, if the abnormality qualifies as an SAE it must be reported to the Sponsor using the SAE data form (Section 13). Table 9 in Appendix 18.2.2 presents the criteria, i.e. upper limit, lower limit criteria for each laboratory parameter, which will be used to identify subjects with markedly abnormal laboratory values.

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

13. SAFETY ASSESSMENTS

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

- Monitoring and recording all AEs and SAEs, observed or volunteered, regardless of suspected causal relationship to the IMP. This includes reactions, interactions, accidents, illnesses, misuse, and abuse.
- Please refer to Table 1 section 10 for schedule visit arrangement including AE collection.

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

13.1 AEs and SAEs

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

An AE can be:

- Any unfavourable and unintended sign (including reactions from overdose, abuse, or 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 IMPs
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline
- Other medical events regardless of their relationship to the IMPs, such as accidents, falls, and any injuries resulting from them.

An 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 IMPs)
- is a medically important event or reaction.

Assessment of medically important events:

The Investigators **must** check the list of Important Medical Events (supplied in the Investigators Site File) to determine whether criteria for an SAE is met. Additionally, any event not on this list, but that the Investigators determine 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 Investigators 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/Screening number

- SAE

- IMPs

- Serious Criteria

- Investigators' name and contact details

- Causality assessment.

A succinct medical summary narrative should be provided 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 Investigators Site File.

The medical safety of the subject is of paramount importance when discussing study continuation. Not all SAEs will require the subject to be discontinued from the study.

13.2 Reporting of AEs

Reporting period – Events will be recorded from the point at which the ICF is signed until 7±1 days after last oxycodone dose in the case of completion/discontinuation from the study. This includes new AEs that are reported within 7±1 days after last oxycodone dosing after the subject's completion/discontinuation visit. Any AE that is still ongoing 7±1 days after the last oxycodone dose will have an outcome of 'ongoing' in the EDC, however the Investigators 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 AEs if they are known to have started or are suspected to have started after the subject has signed the ICF. 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 ICF and the date/time of the physical examination.

If the Investigators become aware of an SAE after the completion of the study, which may have been caused by IMPs or NIMP used in the study, they should report it to the Sponsor by phone, fax, or e-mail.

Screen failures - For subjects who are screen failures, AEs that occurred from the date of consent to the date of screen failure will be recorded on the AE section of EDC.

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

SAEs- All SAEs will be collected on the AE section of EDC and flagged as serious. A separate paper SAE Data Form is supplied for immediate reporting.

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 (e.g. fever, elevated white blood cell (WBC), cough, abnormal chest x-ray, etc. can all be reported as "pneumonia.").

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

13.3 Causality/Expectedness Assessment

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

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

The Investigators will be asked if a **reasonable possibility of a causal relationship** to the IMPs 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.

If an AE is related to a non-investigational medicinal product, e.g. concomitant therapy only, and not an interaction or effect of the IMP, or to a study procedure, the causality assessment will be "No" (no reasonable possibility of a causal relationship to IMP). The suspected drug or procedure should be indicated in the narrative in such cases.

Assessment of Expectedness - The expectedness of an AE is determined by the Sponsor in the reference safety information. The reference safety document used for assessing expectedness of AEs in this study is: the current Investigator's Brochure (IB) for OTR and OXYCONTIN. The reference safety information is included in the safety section of the IB.

13.4 Severity Assessment

The Investigators (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 AE will not necessarily be an SAE.

Any medication necessary for the treatment of an AE must be recorded on the Concomitant Therapy Section of the EDC.

13.5 Pregnancy

Pregnancy occurring in a male subject's female partner or in a female subject during a clinical study must be reported to the Sponsor using the Pregnancy Notification Form. The Sponsor will contact the Investigators to confirm significant pregnancy information, i.e. AEs during pregnancy, the pregnancy outcome, and any events to 3 months post-partum.

13.6 Laboratory Abnormalities

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

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

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 Phase 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 documented in the source notes (e.g. normal fluctuation of the disease).

13.7 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 Investigators as **clinically significant**
- And/or meets the clinically notable abnormal criteria (see Table 7 in section 18).

13.8 ECG TEAE

A simultaneous 12-lead resting ECG will be obtained at V1 and V3 will be performed during study only if clinically indicated. For consistency, the same physician should read all ECGs from one subject whenever possible. Abnormal test findings as judged by the Investigators as clinically significant should be recorded as AEs.

13.9 Other Safety Considerations/Risk Management

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

- Overdose - This must always be reported, and may additionally (but not always) meet the criteria for an AE/SAE.
- Drug Abuse - Defined as intentional excessive and persistent or sporadic use of a medicinal product which is accompanied by harmful physical or psychological effects. Drug abuse is always a medically important event and subject to immediate SAE reporting.
- Drug Diversion - Defined as study treatment that is sold or given to other persons either deliberately or accidentally. This may include accidental misdirection of study supply into mainstream hospital supplies. AEs in persons other than the subject after drug diversion will be processed in the Sponsor's drug safety database.

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

14. STATISTICAL ANALYSES

14.1 Statistical Methodology and Analytical Plans

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

14.2 Statistical Considerations

All data will be listed by treatment groups.

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

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

14.3 Analysis Populations

Enrolled Population
The enrolled population is defined as all subjects who signed ICF.

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

Safety Population
The safety population is defined as all randomised subjects who received at least one dose of IMP.

PK Population
The PK population is defined as all subjects who receive IMP and have at least one PK concentration measurement.

14.4 Protocol Deviations

The following major protocol deviations may exclude a subject from the PK analysis:

1) Failure to comply with the inclusion/exclusion criteria

2) Received incorrect study treatment

3) Received study prohibited concomitant drugs

4) Failure to collect data for the primary endpoint as detailed in the protocol.

Further details will be documented in the SAP. Additional factors excluding subjects from analysis populations may be included in the SAP for the study.

Major protocol deviations will be agreed at the Data Review Meeting (DRM) prior to database lock.

14.5 Sample Size and Power Considerations

The study is designed to have a power of ≥ 95% to demonstrate BE (AUCt and Cmax) of OTR tablet 40 mg, in terms of oxycodone, with OXYCONTIN tablet 40 mg in a fasted state.

The null hypothesis is that the two treatments are not bioequivalent. The alternative hypothesis is that both treatments are bioequivalent. BE between both treatments will be concluded if the 90% CI for the ratio lies within 80.00% to 125.00% for both AUCt and Cmax for the oxycodone analyte.

A total of 38 subjects will be randomised to receive study drug (19 subjects per treatment sequence) with the aim that 30 subjects will provide valid PK data (15 subjects per treatment sequence) and PK parameters (Cmax and AUCt). This will provide ≥ 95% power to show BE simultaneously in both parameters, Cmax and AUCt, between test and reference formulations, assuming a true ratio of 1, a within SD of the period differences of 0.32 on the log scale for AUCt and 0.28 on the log scale for Cmax, both PK parameters are not anti-correlated, and 90% CI for the ratios of the population means within the BE limits of 80.00% and 125.00%. The within SD of the period differences was based on Purdue Pharma BE study OTR1005 in healthy volunteers taking oxycodone[8].

The sample size was estimated using NQuery t-tests (TOST of equivalence in ratio of means for cross-over design (natural log scale).

14.6 Primary Outcome/Efficacy Variable(s)

Not applicable.

14.7 Secondary Outcome/Efficacy Variable(s)

Not applicable.

14.8 Exploratory Efficacy Variables

Not applicable.

14.9 Subject Disposition

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

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

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

14.10 Demographic/Baseline Analyses

Demographic and baseline variables will be summarised by treatment groups and overall for subjects in the safety population.

Age, weight, height, and BMI will be summarised as continuous data. Gender and ethnicity will be summarised as categorical data.

Current medical conditions will be summarised by SOC and PT.

14.11 IMP Analyses

IMP will be summarised as treatment exposure.

Treatment exposure will be defined and calculated as the dose of IMP taken by subjects. Treatment exposure will be summarised by treatment group as continuous data.

Treatment exposure will be summarised by treatment group and overall for subjects in the safety population.

14.12 Concomitant Medications Analyses

Concomitant medications will be assigned an 11-digit code using the WHO Drug Dictionary Enhanced (WHO-DDE) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification.

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

14.13 Safety Analyses

All safety summaries will be based on the safety population.

AEs will be classified into standardised terminology from the verbatim description (Investigators term) according to MedDRA Coding Dictionary to give an SOC and PT for each event.

An overall summary of AEs will be provided by treatment groups. The number and percentage of subjects reporting AEs will be summarised by the PT nested within the SOC. In addition the number of reported AEs will be summarised.

TEAE will be summarised. A TEAE will be defined as any AE with an onset date on or after IMP dosing if the AE was absent before IMP dosing, or worsened after IMP dosing. TEAEs/SAEs collected from dosing of IMP till the last visit will be summarized. AEs with an onset data before IMP dosing will be listed.

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

The most frequent TEAEs will be summarised for the treatment period. These will also be presented graphically using a dot plot and a caterpillar plot within which the

percentage of subjects reporting each of the most common TEAEs will be presented alongside the odds ratio (and associated 95% CI) for comparing the incidence of AEs.

Clinical laboratory parameters and vital signs will be summarised descriptively. The frequency of vital sign results with respect to normal ranges will be presented. The frequency of clinically significant ECG results will be presented.

14.14 Analysis of TEAEs

14.14.1 Laboratory Values

Clinical laboratory data to be summarised includes haematology, blood chemistry, and urinalysis. Clinical laboratory results recorded at V1 and V3 and change from baseline to V3 will be summarised as continuous data for each parameter. Each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Results will be summarised using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, and higher than).

Clinical laboratory values after IMP dosing will be evaluated for markedly abnormal values. The number and percentage of subjects reporting markedly abnormal values will be summarised for each parameter by treatment groups. Each subject can be counted once in the parameter high and the parameter low categories, as applicable. Scatter plots will be produced for each laboratory parameter comparing baseline and end of study values. In addition, clinically laboratory parameters will be plotted over time using a box and whisker plot.

14.14.2 Vital Signs

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

Vital sign results recorded at each visit and change from baseline to each test will be summarised as continuous data for each parameter. Table 7 of Section 18.2.1 lists the abnormal ranges applied for this study.

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

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

Scatter plots will be produced for each vital sign parameter comparing baseline and end of study values. In addition, vital signs will be plotted over time using a box and whisker plot.

14.14.3 ECG

ECG results will be recorded at V1 and V3. Clinically significant ECG findings as determined by the Investigators will be reported.

14.15 Other Special Tests

None planned. All analyses, including any further analyses not yet described in this study protocol, will be pre-specified and described in the SAP.

14.16 PK Measurements and Analyses

PK Analyses:

Plasma concentration data and PK parameters will be listed for subjects in the enrolled population.

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

PK parameters (AUCt, AUCINF, Cmax, tmax, LambdaZ, and t1/2Z) for analyte oxycodone will be summarised descriptively by treatment for subjects in the PK population.

The comparison will be OTR tablet 40 mg in fasted state (test) vs. OXYCONTIN tablet 40 mg in fasted state (reference).

Primary Analysis:

The primary analysis will be for PK parameters AUCt and Cmax and for analyte oxycodone. ANOVA with fixed effect terms for treatment, period, sequence, and subject within sequence for ratio of means (using log scale) will be used to compare the test and the reference treatments. BE of test and reference will be confirmed for a PK parameter of analyte oxycodone if the 90% CI for the ratio (test/reference) falls completely within the BE acceptance range of 80.00% to 125.00%. BE of test and reference will be confirmed in all if it can be confirmed with AUCt and Cmax.

Secondary Analysis:

The primary analysis will be repeated for the PK parameter AUCINF and for analyte oxycodone.

The statistical analyses will exclude PK parameters for which any of the following criteria apply: vomiting within 12 hours after dosing, incorrect dosing, incomplete plasma profile which cannot adequately detail the parameter, pre-dose concentration > 5% of Cmax, $R^2 < 0.85$.The validity of PK data will be discussed further and evaluated during the data review meeting at the end of the study. In accordance with BE guidelines, only subjects that provide valid PK data for both the test and reference treatments will be included in the statistical analysis.

Further details will be specified in the SAP.

15. ETHICS& Regulatory

15.1 Declaration of Ethical Conduct

This study will be conducted in accordance with the SOPs of the Sponsor and CRO, which are designed to ensure adherence to GCP guidelines as required by the following:

1. Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
2. GCP and relevant regulations.

This study will be conducted in accordance with the regulation of narcotic drugs and psychotropic drugs in China.

The Investigators agree, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of GCP to which

the protocol conforms as well as all governing local regulations and principles for medical research.

15.2 Ethical and Regulatory Review

The protocol, any protocol amendments, the patient information sheet (PIS), ICF and any study related information or documents issued to subjects for recruitment, data recording, etc., will be reviewed and approved along with other required documents by the study site's local Ethics Committee (EC) before subjects are screened for entry. The ECs should be constituted and functioning in accordance with ICH E6, Section 3.2, and any local regulations.

A signed letter of positive opinion regarding the study from the EC Chairman must be sent to the Investigators who will provide the Sponsor with a copy prior to study start and the release of any study treatment to the Site by the Sponsor (ICH E6). The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the EC of any reportable AEs per ICH guidelines and local EC standards of practice. SAEs should be reported to the EC in accordance with local regulatory requirements.

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

The end of the study will be the date of the last scheduled study visit for the last subject in the study. The Sponsor will always also provide the EC/CA with a summary of the study's outcome.

15.3 Subject Information and Consent

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

As part of administering the informed consent document, the Investigators must explain to all subjects and/or their legally authorised 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 may withdraw from the study at any time and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating physician. The subject should understand the PIS and ICF before signing and dating the ICF. The Investigators or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed ICF and written information.

The original signed ICF for each subject will be verified by the Clinical Research Associates (CRAs) from designated CRO and kept in the study centre investigational site files. This applies for any additional ICFs signed (e.g. for re-consent).

15.4 Data Protection and Human Tissue Sampling

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

Any ECGs etc. collected for the trial will be retained in the patient's notes held with the Investigators.

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

15.5 Quality Assurance & Inspection Requirements

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

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

16. Study management Records & Publication

16.1 Protocol Amendments

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

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

16.2 Record Maintenance and Retention

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained in all study related and source documentation:

- All entries are to be typed or printed using a ballpoint pen.
- There are to be no erasures, write-overs, and 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 initialled 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 Investigators (Principal Investigators or Sub Investigators) must sign and date the CRF.
- Changes to any study document that has been previously signed by the Investigators must be initialled and dated by the Investigators after the change is made. Changes made to CRFs issued by the Sponsor must likewise be traced and signed by the Investigators.

Neither a subject's name nor initials are to appear on documents transmitted to the Sponsor in order to maintain confidentiality.

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

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

The circumstances of completion or termination of the study notwithstanding, the Investigators have the responsibility to retain all study documents, including but not limited to the protocol, copies of CRF, IB, regulatory agency registration documents, ICFs, and EC correspondence.

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

It is requested that at the completion of the required retention period, or should the Investigators retire or relocate, the Investigators contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records. Records retained will be stored independently of the Sponsor, and the Sponsor will not be permitted direct access to this data.

16.3 Adherence to the Protocol

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

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

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

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

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

16.4 Discontinuation of Study

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

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

16.5 Retention of Tissue Samples

The blood samples will be kept for 2 years after the marketing approval per clinical trial approval of the product.

16.6 Registration and Publication of Study Summary and 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 nominees and subject to the protection of the Sponsor's confidential information. The Sponsor has the ultimate control over any decision to publish. 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 of 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 analysed subjects; therefore Investigators participating in multicentre 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.

17. REFERENCE LIST

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Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991 Jul; 46(4): M139-44.

18. APPENDICES

18.1 Sample Processing and Shipment

18.1.1 PK Sample Handling and Shipping

Samples and Sample Log Forms will be shipped by the Investigators to the Bioanalytical central laboratory. Analysis will be performed by means of LC-MS/MS. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report for this protocol.

18.1.2 Sample Procurement and Processing

For each sample, 4 mL of blood sample will be collected at the defined time points. The total volume of blood to be collected from each patient for PK analysis will be approximately 152 mL. Blood samples, 4 mL each, will be drawn into tubes containing K_2EDTA anticoagulant. After procurement, samples should be kept in a cool environment, preferably in a container of ice water, until processing. Samples must be centrifuged within 30 minutes of collection. Following centrifugation (1500 g, 4℃, 15 minutes), the plasma will be transferred equally into two labelled polypropylene tubes via pipettes, and stored at -20℃within one hour of collection.

18.1.3 Sample Shipment

Samples will be shipped in accordance with the standard shipping procedures provided by a central lab.

18.2 REFERENCE VALUES

18.2.1 Physical/Vital Sign Assessments

Normal ranges for vital signs are shown in Table 6 below.

Table 6 Normal Ranges for Vital Signs

	Adult Subjects (≥ 18 yrs)
Systolic blood pressure	*90-140 mmHg*
Diastolic blood pressure	*60-90 mmHg*
Pulse rate	*60-100 bpm*
Respiration rate	*12-20 breaths per minute*
axillary Temperature	*36.0 - 37.5°C*

Table 7 describes parameters for clinically notable vital signs.

Table 7 Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

Vital Sign Parameter	Value	Change From Baseline[a]
Systolic blood pressure	≥155 mmHg	Increase of ≥20 mmHg
	<80 mmHg	Decrease of ≥20 mmHg
Diastolic blood pressure	≥95 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	>24 breaths/minute	-
	<8 breaths/minute	-
Axillary temperature	>38°C	
	<36°C	
[a]Both value and change from baseline criteria must be met to qualify as a clinically notable vital sign abnormality.		

18.2.2 Laboratory Assessments

Table 8 presents the clinical laboratory tests to be performed.

Table 8 Clinical Laboratory Tests

Category	Parameters
Haematology	Red blood cell (RBC), haemoglobin, haematocrit, platelets, and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	sodium, potassium, chloride, biocarbonate (HCO_3^-)
Liver function tests	alkaline phosphatase, AST, ALT, gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin
Renal function parameters	blood urea nitrogen, creatinine
Other	glucose, calcium, albumin, cholesterol, triglycerides, phosphorus (inorganic phosphate), lactate dehydrogenase (LDH), total protein, globulin, uric acid
Urinalysis	pH, protein, glucose, ketone, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity

Table 9 presents the criteria (i.e. upper limit, lower limit criteria for each laboratory parameter) that will be used to identify subjects with markedly abnormal laboratory values.

Table 9 Laboratory Ranges Used to Identify Markedly Abnormal Laboratory Values

	Units	
Laboratory Parameter	**Lower Limit**	**Upper Limit**
Haematology		
Haemoglobin	Male <11 g/dL (110 g/L)	Male >17.5 g/dL (175 g/L)
	Female <10 g/dL (100 g/L)	Female >16.5 g/dL (165 g/L)
Platelets	$<70.0 \times 10^9$/L	$>400.0 \times 10^9$/L
Leukocytes	$<3.5 \times 10^9$/L	$>10.5 \times 10^9$/L
Lymphocytes	$<1.2 \times 10^9$/L	$>4.5 \times 10^9$/L
Neutrophils	$<2.0 \times 10^9$/L	$>7.0 \times 10^9$/L
Clinical Chemistry		
Electrolytes		
Na^+	<130 mmol/L	>150 mmol/L
K^+	<3.2 mmol/L	>5.7 mmol/L
HCO_3^-	≤27.3 mmol/L	>21.4 mmol/L
Liver Function Tests		
Alkaline phosphatase	——	>3 × ULN
AST	——	>3 × ULN
ALT	——	>3 × ULN
GGT (gamma glutamyl transpeptidase, GGTP)	——	>3 × ULN
Total bilirubin	——	>1.5 × ULN
Renal Function Tests		
Creatinine	——	>1.5 × ULN
Other Chemistry		
Calcium	<2.0 mmol/L	>3.0 mmol/L
Phosphorous (inorganic phosphate)	<0.8 mmol/L	—
Glucose	<3.2 mmol/L	>7.0 mmol/L
Uric acid	Male < 180 µmol/L	Male >440 µmol/L
	Female < 120 µmol/L	Female >320 µmol/L
Cholesterol	<2.3 mmol/L	>6.0 mmol/L
Triglycerides	<0.3 mmol/L	>2.5 mmol/L
Albumin	<3.2 g/dL	>5.5 g/dL

LLN: Lower limit of the laboratory reference (normal) range

ULN: Upper limit of the laboratory reference (normal) range

18.3 Numeric Rating Scale

On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable, how would you rate your pain over the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain Worst Pain Imaginable

Pain will be categorized as none (0), mild (1-4), moderate (5-7), and severe (8-10)[10].

18.4 Karnofsky Score of Performance Status

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

The Karnofsky score of performance is categorized as addressed in the table[11].