1 TITLE PAGE

Protocol Number:	BUP14-CN-101
Title:	An open-label, randomized, single-dose, parallel-group study to investigate the pharmacokinetic profile of single dose Buprenorphine transdermal patch 20 mg applied for 3 days, 40 mg for 3 days and 40 mg for 4 days in Chinese subjects with chronic pain.
EudraCT/IND number:	Not applicable
Sponsor:	Mundipharma (China) Pharmaceutical Co. LTD 18F, Tower D Central International Trade Center, 6A Jianguomen Wai Avenue, Chaoyang District, Beijing, China 100022
Test IMP:	Buprenorphine transdermal patches
Indication:	Not applicable
Phase:	Phase 1
Release Date and version number:	10 Jan 2019, Version 2.0
GCP Statement:	This study is to be performed in full compliance with the protocol, ICH and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by competent authorities.
Confidentiality:	This document is confidential. It contains proprietary information of Mundipharma (China) Pharmaceutical Co., Ltd. Any viewing or disclosure of such information that is not authorised in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

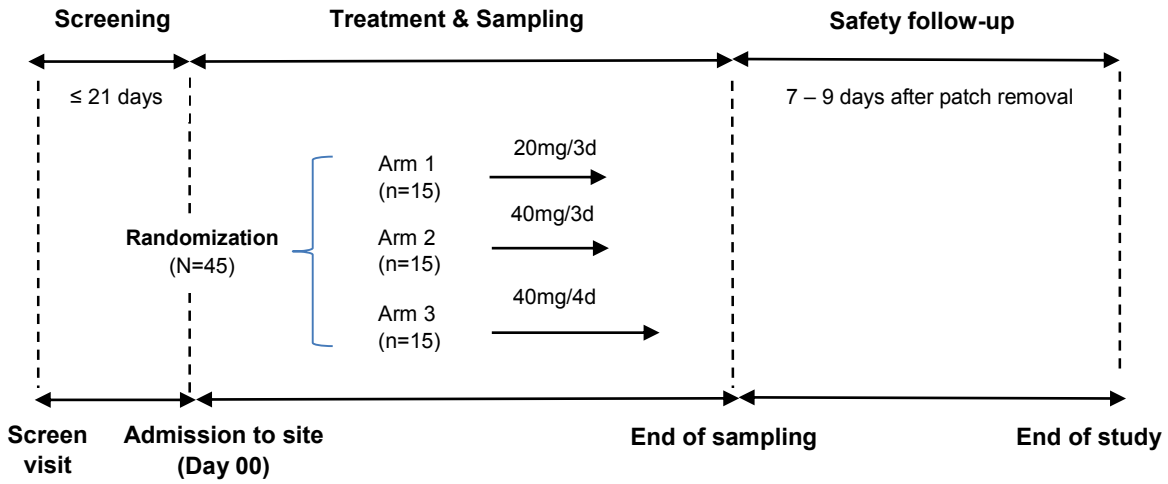
2 VERSION HISTORY

Version number and Date	Reason for update
1.0	Initial version
2.0	Inclusion criteria #1 updated following EC review

3 CLINICAL PROTOCOL SUMMARY

Name of Company: Mundipharma (China) Pharmaceutical Co., Ltd.	
Name of Finished Product: Buprenorphine Transdermal Patch 20 mg and 40 mg	**Name of Active Ingredient:** Buprenorphine
Protocol No.: BUP14-CN-101	**<EudraCT><IND> No.:** N/A
Registration: https://register.clinicaltrials.gov	
Short Title of the Study: A single dose PK study of Buprenorphine Transdermal Patch (20 mg, 40 mg application for 3 days and 40 mg application for 4 days) in Chinese subjects with chronic pain.	
Full Title of the Study: An open-label, randomized, single-dose, parallel-group study to investigate the pharmacokinetic profile of single dose Buprenorphine transdermal patch 20 mg applied for 3 days, 40 mg applied for 3 days and 40 mg applied for 4 days in Chinese subjects with chronic pain.	
Objectives: **Primary** To evaluate the pharmacokinetic (PK) profile of buprenorphine and its primary metabolite, norbuprenorphine of single dose buprenorphine transdermal patch (BUP TDS) 20 mg applied for 3 days, 40 mg for 3 days and 40 mg for 4 days. **Secondary** To evaluate the safety and tolerability following a single application of BUP TDS.	
Sample size and Investigator(s)/Site(s): Total sample size of 45 subjects (15 subjects/arm) will be randomised to receive IMP with the aim to have at least 36 subjects (12 subjects/arm) completing the study and providing valid PK data. The study will be conducted in 1-3 sites in China.	
Summary of Study Design: This is an open-label, randomised, single-dose, 3 arms study design. Subjects will be randomised into one of 3 arms, in a 1:1:1 ratio, wearing BUP TDS 20 mg for 3 days or 40 mg for 3 days or 40 mg for 4 days.	

Study Diagram



20mg/3d = BUP TDS 20 mg application for 3 days
40mg/3d = BUP TDS 40 mg application for 3 days
40mg/4d = BUP TDS 40 mg application for 4 days

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5 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine transaminase (also SGPT)
AST	Aspartate transaminase (also SGOT)
AUC	Area under the plasma concentration-time curve
AUCt	Area under the plasma concentration-time curve calculated from the time of dosing to the last measurable concentration
BP	Blood Pressure
bpm	Beats per minute
BMI	Body Mass Index
BUP	Buprenorphine
CA	Competent Authorities
CS	Clinical Significant
cm	centimeter
Cmax	Maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CYP	Cytochrome
D	Day
DMP	Data Management Plan
DRM	Data Review Meeting
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
g	gram
GGT	Gamma-glutamyl-transferase
GLP	Good Laboratory Practice
H	Laboratory value above the reference range
h	Hour
hrs	hours
HB_sAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus Antibodies
hCG	Human chorionic gonadotropin
HCO_3^-	Bicarbonate
HIVAb	Human immunodeficiency virus antibodies
IB	Investigator Brochure
ICF	Informed Consent Form
I/E	Inclusion/Exclusion
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
kg	Kilogram
L	Laboratory value below the reference range
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LDH	Lactate dehydrogenase

LLN	Lower limit of the laboratory reference (normal) range
LNH	Classification according to whether the Laboratory test result was below (L), within (N), or above (H) the reference range
µg	Micrograms
m	Meter
MAH	Marketing Authorisation Holder
MCPC	Mundipharma (China) Pharmaceutical Co., Ltd
MOA	Monoamine oxidase
mg	Milligram
mL	Millilitre
mmHg	Millimetre mercury
N	Laboratory value within the reference range
NCS	Non Clinical Significant
NIMP	Non-Investigational Medicinal Product/Auxillary Product
NMPA	National Medical Products Administration
NRS	Numeric Rating Scale
PIS	Patient Information Sheet
PK	Pharmacokinetic
PR	Pulse rate
PT	Preferred Term
QA	Quality Assurance
RBC	Red blood cell (count)
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analyses Software
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOPs	Standard Operating Procedures
t1/2Z	Apparent terminal phase half-life
tmax	Time from dosing to the maximum observed concentration
TEAA	Treatment Emergent adverse event
TDS	Transdermal Delivery System
ULN	Upper limit of the laboratory reference (normal) range
USA	United States of America
WBC	White blood cell (count)
WHO	World Health Organisation

6 STUDY CONDUCT AND OVERSIGHT

6.1 Sponsor

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

6.2 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and Contract Research Organisation (CRO), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as described in Section 16 of this protocol.

6.3 Investigators and Study Personnel

The study will be conducted in 1-3 centres in China. The contact details of the Investigator and other contact persons at the Sponsor and CRO will be listed in the study site file.

6.4 Data Management

All data management related tasks will be outsourced to a CRO. The Data Management Plan (DMP) will include a task and responsibility list for all data management tasks.

Clinical data will be captured by using an Electronic Data Capture (EDC) system. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical data. The Monitoring Plan and supporting documents will detail the data entry, source data verification, data validation, and locking procedures to be followed by all relevant study staff. The DMP describes the data flow between the EDC system, external vendors (e.g. lab) and different functional parties involved in the handling of clinical data.

At the end of the study each site will be provided with an archiving media including one PDF per subject with the clinical data and audit trail extracted from the EDC system.

6.5 Monitoring

The study will be monitored by qualified personnel from the CRO. The Monitoring Plan for the study will detail this process. The Investigator will allow monitoring, audit and inspection of the clinical, laboratory, and pharmacy facilities as required, to assure compliance with GCP and Good Laboratory Practice (GLP) as applicable. The EDC system and subject's corresponding original medical records (source documents) are to be fully available for review by the CRO/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 site are subject to inspection by the local competent and local health authorities.

6.6 Medical Monitoring & Safety

The name of the Study Physician along with the telephone and fax numbers of the other contact persons at the Sponsor and CRO are listed in the contact list stored in the study site file. 24-hour medical support will be provided by the CRO; the contact details are supplied in the Investigator Site File.

6.7 Central Review/Central Laboratory/Bioanalytical Laboratory

Local laboratories will be used for sample analysis for safety assessment. A qualified bioanalytical laboratory will be employed to process all study samples to generate bioanalytical data.

7 INTRODUCTION

7.1 Therapeutic Area/Background

Pain is one of the most common symptoms for cancer patients, seriously affecting their quality of life. The incidence of pain is about 25% in newly diagnosed cancer patients and around 60% to 80% in advanced cancer patients, where one third is assessed as severe pain (China Ministry of Health, Cancer pain clinical guidelines, 2011).

Pain is classified on the basis of its duration (i.e. acute and chronic pain) and underlying pathophysiology (i.e. nociceptive, neuropathic, mixed and psychogenic pain). Cancer pain patients commonly experience more than one kind of pain. The highest prevalence of pain (>85%) is related to cancers of pancreas, bone, brain, lung and head and neck.

Current treatment of cancer pain is based on the World Health Organisation's (WHO) concept of an "analgesic ladder" which involves a stepwise approach to the use of analgesic drugs and is essentially a framework of principles rather than a rigid protocol (WHO, 1996). This three-step approach is broadly established and 80 – 90% effective for the treatment of malignant and non-malignant pain.

Opioids are the mainstay of pain management for patients with moderate-to-severe cancer pain and are increasingly used for the treatment of chronic pain that is non-malignant in origin. Buprenorphine containing formulations are considered step III agents in the WHO analgesic ladder for pain.

7.2 Investigational Medicinal Product (IMP)

Buprenorphine is a synthetic opioid analgesic derived from the opium alkaloid thebaine. It is a μ-opioid receptor agonist, while it shows an antagonistic effect on κ-opioid receptors (Cowan *et al*, 1977). The analgesic potency of buprenorphine was found to be 25-50 times higher (on a weight-by-weight basis) than that of morphine (Budd, 2002).

With the indication for alleviation of moderate/severe pain, buprenorphine injection was first launched in the United Kingdom in 1978 and in the United States in 1982. It was mainly used for postoperative pain control, but also used for alleviation of moderate to severe pain in patients with cancer, trigeminal neuralgia, ureteral stones, myocardial infarction, and trauma. Moreover, a

sublingual tablet (Subutex®) was approved as a treatment for opioid dependency at doses of up to 16 mg/day, which was well above the analgesic range. Through international clinical experience for almost 4 decades, the safety and efficacy of buprenorphine for treating various types of moderate and severe pain have been demonstrated (Heel *et al*, 1979; Hoskin & Hanks, 1991; Lewis, 1995; Wolff *et al*, 2012). Pharmacokinetics of buprenorphine was found to be dose-proportional after both sublingual and intravenous administration (Walsh *et al.,* 1994; Budd, 2002). In China, buprenorphine injection and sublingual tablet were approved in 1995 and 1997 respectively, and used for many kinds of pain treatment.

However, the immediate-release formulations administered sublingually showed marked fluctuations of buprenorphine plasma concentration, i.e. high peak and low trough concentration during a dosing interval, which tend to induce inconsistent pain relief at trough or increased adverse events (AEs) at peaks. Oral formulations are not available for buprenorphine as the absolute bioavailability was found to be insufficient to achieve analgesic drug concentrations (Tegeder *et al*. 1999) due to the high first-pass effect.

In order to achieve a sustainable analgesic effect, the 3-day buprenorphine transdermal patch (Transtec®) was developed in the 1990s, and firstly approved in Switzerland in June 2000, for the management of moderate to severe cancer pain and severe pain refractory to non-opioid analgesics. As of August 2017, it has been approved in 32 countries worldwide but not yet in China.

The transdermal patch consists of a polymer matrix in which the active substance buprenorphine is dispersed. When applied to the skin, buprenorphine is continuously released from the matrix leading to constant transdermal invasion of the drug into the systemic circulation. The rate-controlled release of buprenorphine from the transdermal patch ensures relatively constant plasma levels which translate into long-term and consistent pain relief with the chance of minimizing the potential for of side effects.

Three dose strengths of Transtec® have been developed containing 20, 30, or 40 mg buprenorphine. The in-vivo release rates were found to be 35 µg/h, 52.5 µg/h, and 70 µg/h over 72 hours (3 days), respectively. Plasma concentrations increased in a linear fashion according to dose.

After the initial application of Transtec®, the minimum clinically effective plasma concentration (100 pg/ml) was reached in about 11 hours for 70 µg/h patch and about 21 hours for 35 µg/h patch, and t_{max} across patch strengths was found to be 60 – 80 hours on average. After removing the patch, a steady decrease of plasma concentrations occurred about 1 hour later. The average terminal half-lives across patch strengths ranged from 20 to 27 hours.

Buprenorphine is metabolized in the liver, primarily to norbuprenorphine glucuronide (Kacinko *et al*, 2009). Cytochrome P450 (CYP) 3A4 is the phase 1 enzyme involved in metabolism of buprenorphine to norbuprenorphine (Kacinko *et al*, 2009).

Biliary excretion is the predominant route of elimination. After intravenous administration of buprenorphine, only 10% to 27% of the administered drug was excreted in urine. The faeces contain mainly unchanged buprenorphine, while urinary excretory products are conjugates of the parent compound and norbuprenorphine (Hand *et al*, 1986; Heel *et al*, 1979).

Clearance of buprenorphine was shown to be relatively independent of the renal system and is not altered in patients with renal impairment (Hand *et al*, 1990). Administration of the buprenorphine transdermal patch was found to be safe in these patients (Filitz *et al*, 2006). Neither buprenorphine nor norbuprenorphine plasma levels were found to be elevated. No

difference in pain relief before and after haemodialysis was observed. No dose adjustment is needed in these patients.

Additional data showed that each patch could provide sustained delivery of buprenorphine for up to 4 days (Likar, 2005), thus enabling the patient to change the patch twice a week, e.g. always on Monday and on Thursday. This is expected to improve the convenience of the usage of buprenorphine patch and positively contribute to the compliance of patients.

In addition to the 3 - 4 day patch, a 7-day patch formulation has been developed by Mundipharma / Purdue (Butrans® or Norspan®) and was first approved in Denmark in 2003. Since then, with the main indication of non-cancer pain, it has been approved in 47 countries up to January 2018. In the USA, 3 doses of buprenorphine (5, 10 and 20 mg with a release rate of 5, 10 and 20 µg/h, respectively) were approved by the FDA in July 2010 for management of moderate to severe chronic pain requiring 24-hour sustained opioid analgesia. The 7-day buprenorphine patch was launched in China in December 31st, 2012 under trade name of Norspan®.

7.3 Study Rationale and Aim

The aim of this study is to evaluate the pharmacokinetic (PK) profile of buprenorphine and its primary metabolite, norbuprenorphine, after a single dose of buprenorphine transdermal patches being applied in Chinese subjects. The safety of buprenorphine transdermal patches will also be evaluated in the study.

This study consists of three treatment arms. Subjects will be randomised in a 1:1:1 ratio to BUP TDS 20 mg for 3 days, or BUP TDS 40 mg for 3 days or BUP TDS 40 mg for 4 days. The doses chosen cover the lowest and highest doses to be used in clinic in the future. These doses have been found to be well tolerated to date. The known and potential risks are those described in the latest version of the Investigator Brochure (IB).

Per Technical Guideline for Pharmacokinetic Studies of Chemical Drug Products (NMPA, 2005), if the drug will be used in clinics consecutively for multiple times, its PK characteristics at steady state with multiple administrations should be identified. This will be completed in a second PK study, BUP18-CN-101.

According to the regulations on narcotic drugs and psychotropic substances (State Council Order No. 442), the clinical trials of narcotic drugs and the first class psychotropic substances are not allowed to be conducted in healthy populations, the participants will therefore be chronic mild pain patients.

7.4 Design Rationale

The study design and data analysis follow the recommendations issued from the “Technical Guideline for Pharmacokinetic Studies of Chemical Drug Products prepared by China National Food and Drug Administration (NMPA, 2005) and from Pharmacopoeia of the P.R.C. (2015).

As the main study criterion is PK parameters which are objective and not subject to bias, an open label study design is therefore acceptable.

The plasma elimination half-life of buprenorphine is about 20-27 hours.

No formal sample size calculation was performed. The planned number of subjects will meet the requirement of the PK study guideline (NMPA, 2005), which recommends 8 to 12 subjects in each treatment arm.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the declaration of Helsinki and the applicable regulatory requirements.

7.5 Benefit Risk Assessment

The safety and tolerability of buprenorphine are well established and generally regarded as favourable. Its safety profile has been described and summarized in a number of publications (Budd, 2002; Budd & Collett, 2003; Walsh *et al*, 1994; Dahan *et al*, 2005). Buprenorphine has been approved for more than 4 decades for intravenous and sublingual use in many countries, including the United States and many European countries.

The controlled-release method of buprenorphine administration via the transdermal matrix patch technology further enhances the safety margins of buprenorphine, without compromising the therapeutic value in the management of chronic pain in Chinese subjects.

Overall the assessment of all currently available published clinical data indicates a positive benefit-risk ratio of 3- or 4-day BUP TDS.

8 STUDY OBJECTIVES

8.1 Primary Objectives

- To evaluate the pharmacokinetic profile of buprenorphine and its primary metabolite, norbuprenorphine of single dose Buprenorphine transdermal patch (BUP TDS) 20 mg applied for 3 days, 40 mg for 3 days and 40 mg for 4 days.

8.2 Secondary Objectives

- To evaluate the safety and tolerability following single application of BUP TDS.

9 STUDY ENDPOINTS

9.1 Primary Endpoint

The primary endpoint will be the PK assessment. Pharmacokinetic parameters of the prototype buprenorphine, and the primary metabolite norbuprenorphine, calculated from plasma concentration-time data following a single application of BUP TDS 20 mg (3 days), 40 mg (3 days) and 40 mg (4 days).

9.2 Safety Endpoints

Subjects will be closely monitored throughout the study for evidence of any AE. Vital signs, including pulse rate, respiration rate, sitting blood pressure and body temperature, will be measured at regular intervals. Furthermore, examinations including physical examination, 12-

lead ECG as well as laboratory parameters, will be performed on the day of the last blood sample taken.

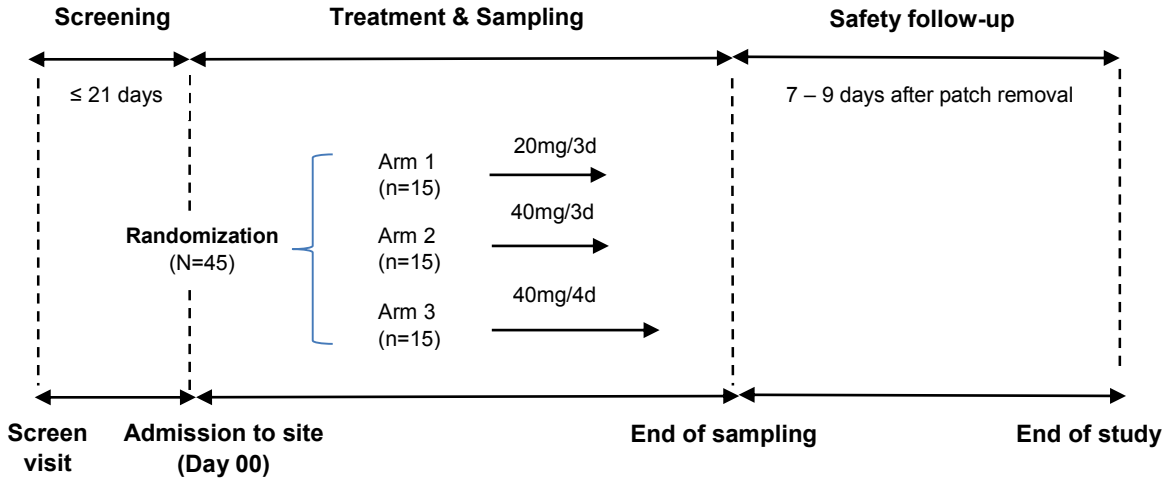
10 STUDY SUMMARY AND GRAPHIC

10.1 Overall Study Design and Plan

This is a randomised open-label, single dose PK study. Subjects will be randomised into one of 3 treatment arms, wearing BUP TDS 20 mg for 3 days or 40 mg for 3 days or 40 mg for 4 days.

10.2 Study Diagram

Figure 1: Study diagram



20mg/3d = BUP TDS 20 mg application for 3 days
40mg/3d = BUP TDS 40 mg application for 3 days
40mg/4d = BUP TDS 40 mg application for 4 days

10.3 Data Monitoring Board

Not applicable in this study.

11 SELECTION OF SUBJECTS

Subjects to be included in the study must comply with the eligibility criteria as detailed in Sections 11.1 and 11.2.

11.1 Inclusion Criteria

Only subjects meeting all of the following inclusion criteria will be considered for study inclusion:

1. Chinese male or female subjects with chronic pain (regardless of the aetiology, cancer-pain excluded), aged 18-55 years (both inclusive).
2. The average pain over the last 24 hours should attain ≤ 3 assessed with Numeric Rating Scales (NRS) refer to section 19.5. The pain condition has been lasting for at least 1 month and stable for 7 days prior to entering into the screening and is expected to be stable during the study duration.
3. Patients on stable permissible non-opioid analgesics, who in the opinion of the investigator are unlikely to require a change in treatment during the study.
4. Karnofsky score of Performance Status ≥ 70.
5. Body mass index (BMI) of 19 to 28 kg/m^2 (both inclusive); and a total body weight ≥50 kg.
6. Normal dietary habits (e.g. not vegetarian nor vegan) and willing to only take the food supplied during the period of hospitalization.
7. Subjects who are able to read, understand and sign written informed consent prior to study participation and are willing to follow the protocol requirements.
8. Female subjects of child bearing potential (less than 1 year post-menopausal) must have a negative urine pregnancy test prior to first dose of study medication, be non-lactating, and willing to use adequate and highly effective methods of birth control throughout the study such as sterilisation, implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner.

   Male subjects (surgical history of bilateral vasectomy excluded) with a partner of child bearing potential must be willing to use adequate and highly effective methods of birth control throughout the study.

11.2 Exclusion Criteria.

Subjects having any of the following criteria, either at screening or at baseline will not be included in the study.

1. Unstable condition of the primary disease of chronic pain, which, in the opinion of the investigator, would complicate the subject's participation in the study (e.g. require initiation of new medication).
2. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies).
3. History of seizures or at risk (i.e. head trauma, epilepsy in family, anamnesis, unclear loss of consciousness).
4. Any history of frequent nausea or emesis regardless of aetiology.
5. Malignancy or a history of malignancy.
6. History of orthostatic hypotension.
7. Subjects who have any medical or surgical conditions that might interfere with transdermal absorption, distribution, metabolism, or excretion of drugs.
8. Positive results for Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibodies (HCV Ab), human immunodeficiency virus antibodies (HIVAb).
9. Urine screening before study is positive for opioids, barbiturates, amphetamines, cocaine metabolites, methadone, benzodiazepines, phencyclidine, methamphetamine, or cannabinoids or alcohol breath test is positive.
10. Subjects who have a current or past (within 5 years) history of substance or alcohol abuse, or subjects who, in the opinion of the investigator or the sub-investigator, have demonstrated addictive or substance abuse behaviors. Alcohol abuse 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).

11. Consumption of alcoholic beverages within 48 hours before patch application, and / or refusal to abstain from alcohol throughout the study until at least 48 hours after patch removal.
12. Use of tobacco- or nicotine-containing products in excess of the equivalent of 5 cigarettes per day.
13. Use of 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 first patch administration.
14. Subjects who are currently taking tricyclic antidepressants or have used tricyclic antidepressants within 4 weeks prior to the first patch administration.
15. Subjects taking monoamine oxidase (MAO) inhibiters within the past 14 days prior to the first patch administration
16. Subjects taking any opioid drug within the past 14 days prior to the first patch administration.
17. Use of prescription or nonprescription drugs, vitamins and dietary supplements within 7 days prior to the first patch administration. As an exception, acetaminophen could have been used at doses of ≤1 g/day.
18. Subjects who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days prior to the screening visit. Concurrent enrolment in another clinical trial is not permitted unless the sole purpose of the other trial is for collection of long-term follow-up/survival data.
19. Donated 400 mL or more of blood or blood products within 3 months prior to the start of the study.
20. Screening sitting blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.
21. 12-lead ECG demonstrating QTc>450 msec or a QRS interval >120 msec at Screening. If QTc exceeds 450 msec, or QRS interval exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS interval values should be used to determine the subject's eligibility.
22. Subjects who have history of hypersensitivity to opioid analgesic formulations.
23. Subjects who have history of hypersensitivity to naltrexone.
24. Subjects who have history of hypersensitivity to transdermal delivery system or patch adhesives.
25. Subjects with any potential dermatological disorder at a patch application site, e.g. previous and/or current unhealed extensive dermal damage in the area where the patch will be applied (e.g. dermatitis, burns, tattoos, scarring of the skin)
26. Subjects who could not discontinue therapy that involved direct heat sources (e.g. heat lamps, electric blankets, heating pads or heated water beds) for the duration of the study
27. Subjects with hairy areas who could not, or would not, cut the hair at the patch site for proper placement of the patch
28. Special diets such as caffeine or xanthine-containing foods and beverages (including pitaya fruit, mango, grapefruit, coffee, tea, cola, chocolate, grapefruit juice, etc.) should be taken within 48 hours before patch application or during the study.
29. Subjects who have difficulty swallowing tablets.
30. Subjects who cannot tolerate venipuncture, or subjects who have difficulty in collecting blood, or subjects who have a history of fainting at the sight of blood or needles.

31. Unwilling or suspected of not being able to comply with the study protocol.

12 ASSESSMENTS AND PROCEDURES

12.1 Summary of procedures (specific data collection)

Data will be collected for each assessment/procedure as indicated in Tables 1.1, 1.2, 1.3 and 1.4.

Adverse Events (AEs)

AE data is obtained by the Investigator through observation of the subject (including examinations and investigations), from any information volunteered by the subject and through active questioning. Throughout the study, after informed consent has been signed, subjects will be asked about AEs and will be reminded to immediately report AEs experienced to medical staff.

Occurrence, frequency, nature and severity of AEs will be recorded. This includes observations or abnormalities in physical examination, vital signs, laboratory or other investigations reported as AEs. Any treatment for AEs will also be recorded.

For further details regarding AEs including definitions and reporting procedures refer to section 14.

Physical examination
Physical examination includes inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, vascular system, extremities, musculo-skeletal system and nervous system. The skin check should include a dermatological assessment of the application site. Abdominal ultrasound scan can be performed to understand the medical history per investigator's judgement.

Please note:
A new appearance of an abnormal finding or worsening of a concomitant disease that is considered clinically significant and occurs after signature of informed consent have to be documented as AE. If the abnormal lab result is considered as clinical significance, the investigator should judge the start time of this situation, if it is considered as happening before the signature of informed consent, this case should be recorded as medical history, if it is considered as happening after the signature of informed consent, this case should be recorded as AE.

Pharmacokinetic samples:

Blood samples for determining the plasma concentration of buprenorphine and norbuprenorphine will be collected as the following schedule:

- 3-day application (20 mg/3d & 40 mg/3d): Pre-dose (0), 12, 24, 48, 72 (pre-removal), 73, 74, 76, 84, 96, 120, 144 and 168 hours post administration of patch, 13 blood samples in total.
- 4-day application (40 mg/4d): Pre-dose (0), 12, 24, 48, 72, 96 (pre-removal), 97, 98, 100, 108, 120, 132, 144, 168 and 192 hours post administration of patch, 15 blood samples in total.

For each sample, about 6 mL blood sample will be drawn from a Upper limb vein into a tube containing K_2EDTA anticoagulant, 0.5-1 mL of blood discarded before blood collection. Soft reversal of blood vessels 6-8 times to make blood samples and anticoagulants fully mixed The total volume of blood to be collected from each subject will be approximately 85 mL (3-day application) and 98 mL (4-day application). After procurement, samples should be kept in a cool environment, preferably in a container of ice water, until processing. Samples must be centrifuged within 60 minutes of collection. Following centrifugation (2000 g, 2-8℃ , 10 minutes), the plasma will be equally transferred, via pipettes, into two labelled polypropylene tubes, and stored at ≤ -60℃ within two hours of collection. All details will be provided in lab manual.

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

Vital signs:
Vital signs and body weight are measured with the following methods/ units:

- **Supine blood pressure** is measured in mmHg according to the Riva Rocci method while the subject has been resting in sitting position for at least 5 minutes. The same arm should be used as possible for blood pressure measurements throughout the study. The size of the cuff has to be chosen appropriately in relation to the subject's arm circumference.
- **Respiration rate** is measured in breaths per minute when subjects have been resting in supine position for at least 5 minutes. The measurement involves counting the number of breaths for one minute by counting how many times the chest rises is suggested.
- **Pulse rate** is measured in beats per minute either electronically or by palpation for 1 minute, while the subject is supine and has been resting for at least 5 minutes.
- **Body temperature** is measured in ℃ from forehead. If another region is used for body temperature measurement, this must be indicated in the eCRF.
- **Weight** should be measured with shoes and coat taken off and pockets emptied of heavy objects (e.g. keys, coins).
- **Height** is measured once at screening visit for the purpose of calculation of body mass index (BMI). Shoes have to be taken off during the measurement.

ECG
A standard 12-lead ECG will be performed at the time points specified in section 12.2. The ECG recordings are to be reviewed by the Investigator, under consultation with a specialist, if necessary. Results must be summarized in the source data and classified as 'normal' or 'abnormal'. Abnormal ECGs must be classified as 'clinically significant' or 'not clinically significant'. For consistency, the same physician should read all ECGs from one subject. Original printouts are to be retained in the source notes.

Abnormal, clinically significant findings occurring after signature of informed consent have to be reported as AE (unless already pre-existing at baseline).

Laboratory samples and tests

The local laboratory will perform tests to qualify subjects for entry into the study. Laboratory certification will be included in the clinical study report for this protocol. Appendix 19.4.2 presents the clinical laboratory tests to be performed.

Values out of the normal range do not automatically lead to a discontinuation of the subject from the study. The decision to discontinue a subject from the study due to values out of the lower and higher limit of normal should be based on the medical judgement of the Investigator.

Blood and urine samples for laboratory safety assessment will be taken at the time points specified in Section 12.2.

Subjects should be fasting, i.e. instructed accordingly by the site not to eat or drink anything but water for 12 hours before the blood and urine samples collected. Date and time of sampling will be documented. Sample handling at the site, shipment and assessment methods will be described in the Laboratory Manual.

All laboratory results have to be evaluated in the eCRF and or laboratory report form provided to the Investigator according to the following pattern:

a) Within reference range (normal range)
b) Outside reference range but not clinically relevant (e.g. due to already known conditions, due to sampling conditions, marginal deviation only, due to underlying diseases in the study population)
c) Outside reference range and clinically relevant

The following items should be considered for the evaluation of the laboratory reports:

- Laboratory values occurring (by date of blood sampling) after signature of informed consent, which are outside the reference range and assessed as a clinically relevant change versus pre-treatment values (as determined by Investigator), have to be controlled and documented as an AE.
- 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).
- An abnormal laboratory value that is a sign of an AE (e.g. infection) that has already been reported, has to be documented but the respective abnormal laboratory value does not constitute a separate AE.
- Abnormalities in laboratory values which result in a change in Investigational Medicinal Product (IMP) schedule of administration (change in dose, delay in administration, IMP discontinuation or other medical or treatment intervention e.g. anaemia requiring transfusions or hyperglycaemia requiring potassium supplement) have to be reported as an AE.

Wherever reasonable the Investigator should use the clinical term rather than the laboratory term (e.g. anemia vs. low hemoglobin value).

Assessment of patch adhesion

The status of IMP application will be confirmed. The result of these inspections should be recorded in the source documentation and eCRFs in accordance with the following criteria:

1. Not detached at all
2. The edge is partially detached
3. Patch detached reaches 1/4 but less than 1/3
4. Patch detached reaches 1/3 but less than 1/2
5. Patch detached reaches 1/2 or more
6. Trial drug patch is completely detached (or missing)

In cases where an IMP became loose or detached from the skin, the patch will be secured by the attachment of tape. Any occurrence of a patch becoming loose and requiring taping will be documented in the eCRF with start dates and times recorded.

Dermatological examination of IMP application site

The dermatological response at patch site after removal should be assessed by investigators using the skin status scale (see Appendix 19.6). The assessment will be rated where possible by the same observer each time. Only a skin reaction assessment score ≥ 2 on the scale should be recorded as an AE.

12.2 Schedule Overview

Schedule of visits and procedures for the 3-day application and 4-day application respectively. All procedures will be collected in the source documents.

Table 1.1: Investigation schedule for 3-day application

Phase	Screening	3-day application									Safety follow-up (telephone contact)[11]
Day	**D-21 to D-1**	**D00**	**D01**	**D02**	**D03**	**D04**	**D05**	**D06**	**D07**	**D08**	**7-9 days after patch removal (D4)**
Informed Consent	X										
Average pain over last 24 hours on 0-10 score NRS	X	X									
Karnofsky score	X										
Medical / surgical history[1]	X										
Drug, Alcohol, Tobacco History	X										
Inclusion/Exclusion criteria	X	X									
Demography	X										
Dermatological assessment of application site	X										
Height	X										
Weight	X									X	
BMI	X										
HIV Ab, HBsAg, HCV Ab, Syphilis Antibody	X										
Alcohol Breath Test	X	X									
Urine Drug Test	X	X									
Pregnancy Test[2]	X	X								X	
Clinical Laboratory Test (Chemistry, Hematology, Urinalysis)	X									X	
Physical Examination	X	X								X	
12-Lead ECG	X	X								X	
Vital Signs[3] (body temperature, respiration rate, PR and BP)	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant treatment		X (recorded continuously throughout the study)									
Adverse Event		X (monitored continuously throughout the study)									
Non-Pharmacological Therapies		X (monitored continuously throughout the study)									

Phase	Screening	3-day application									Safety follow-up (telephone contact)[11]
Day	D-21 to D-1	D00	D01	D02	D03	D04	D05	D06	D07	D08	7-9 days after patch removal (D4)
Admission to site		X[4]									
Randomization		X									
Naltrexone Dosing[5]		X	X	X	X	X					
Study Patch Administration			X								
Study Patch Removal[6]						X					
Assessment of patch adhesion[7]			X	X	X	X					
Dermatological examination of IMP application site[8]						X	X	X			
Blood sampling[9]			X	X	X	X	X	X	X	X	
End of blood collection visit										X	
End of the study[10]											X

[1.] Abdominal ultrasound scan might be performed to understand the medical history per investigator's judgement.

[2.] Pregnancy test will be performed for females of childbearing potential and less than one year post-menopausal. Serum pregnancy test at screening. Urine pregnancy test at admission to site and discharge from site (or early termination).

[3.] Timing for vital signs:

- At screening
- At Day 00: 13 hours prior to IMP application, within 30 min prior to naltrexone taken.
- From Day 01 to Day 04: twice a day, within 30 min prior to each dosing of naltrexone.
- From Day 05 to Day 08: once in the morning, within 30 min prior to PK blood sampling.

[4.] Admission to site at latest in the afternoon (before dinner), at least 15 hours before the patch administration of D01.

[5.] On Day 00, naltrexone 50 mg will be orally taken only in the evening, 13 hours (±5 min) prior to the patch administration of D01; From D ay 01 to Day 04, naltrexone 50 mg will be orally taken every 12 hours, in the morning and in the evening, at the fixed time in each morning or evening, with a time window of ± 5 min based on scheduled time. The intake in the morning of Day 01 should be 1 hour (±5 min) prior to IMP administration. Naltrexone to be taken after meal.

6. Patches will be removed 72 hours (±2min) after administration. Blood sampling should occur in the last 2 minutes of dosing i.e. within 2 minutes prior to the patch being removed

[7.] Assessment of patch adhesion will be performed twice a day in the morning and in the evening (every 12±1 hours). The first evaluation on Day 01 will be conducted immediately after the first patch applied on Day 01. On Day 04, the evaluation will be done once just before the patch removed.

[8.] Dermatological examination of IMP application site will be conducted within 0.5 hour after IMP removal and in the morning of D05 and D06. In case that the result of the examination conducted at D05 is judged "No evidence of irritation", the examination scheduled for D06 will not be conducted. In case AE was reported for the skin reaction and not recovered at D06, more examinations may be needed for the AE follow-up.

[9.] Blood sampling timing: Pre-dose (0), 12, 24, 48, 72 (pre-removal), 73, 74, 76, 84, 96, 120, 144 and 168 hours post administration of patch. Time window: within 30 minutes prior to the patch administration for pre-dose (0); ±2 minutes for 12-48 hours and 73-76 hours; within 2 minutes prior to the patch being remuved for 72 hours; ±1 hour for 84 -168 hours. In case of IMP being removed ahead of schedule, blood sampling for drug concentration measurement will not be conducted following removal.

[10.] Safety follow-up completion or early termination.

[11] Safety follow-up visit can be performed as a telephone visit.

Table 1.2: Investigation schedule for 4-day application

Phase	Screening	4-day application										Safety follow-up (telephone contact)[11]
Day	**D-21 to D-1**	**D00**	**D01**	**D02**	**D03**	**D04**	**D05**	**D06**	**D07**	**D08**	**D09**	**7-9 days after patch removal (D5)**
Informed Consent	X											
Average pain over last 24 hours on 0-10 score NRS	X	X										
Karnofsky score	X											
Medical / surgical history[1]	X											
Drug, Alcohol, Tobacco History	X											
Inclusion/Exclusion criteria	X	X										
Demography	X											
Dermatological assessment of application site	X											
Height	X											
Weight	X										X	
BMI	X											
HIV Ab, HBsAg, HCV Ab, Syphilis Antibody	X											
Alcohol Breath Test	X	X										
Urine Drug Test	X	X										
Pregnancy Test[2]	X	X									X	
Clinical Laboratory Test (Chemistry, Hematology, Urinalysis)	X										X	
Physical Examination	X	X									X	
12-Lead ECG	X	X									X	
Vital Signs[3] (Body Temperature, respiration rate, PR and BP)	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant treatment		X (recorded continuously throughout the study)										
Adverse Event		X (monitored continuously throughout the study)										
Non-Pharmacological Therapies		X (monitored continuously throughout the study)										
Admission to site		X[4]										
Randomization		X										
Naltrexone Dosing[5]		X	X	X	X	X	X					
Study Patch Administration			X									
Study Patch Removal[6]							X					
Assessment of patch adhesion[7]			X	X	X	X	X					

Phase	Screening	4-day application										Safety follow-up (telephone contact)[11]
Day	**D-21 to D-1**	**D00**	**D01**	**D02**	**D03**	**D04**	**D05**	**D06**	**D07**	**D08**	**D09**	**7-9 days after patch removal (D5)**
Dermatological examination of IMP application site[8]							X	X	X			
Blood sampling[9]			X	X	X	X	X	X	X	X	X	
End of blood collection visit											X	
End of the study[10]												X

[1.] Abdominal ultrasound scan might be performed to understand the medical history per investigator's judgement.
[2.] Pregnancy test will be performed for females of childbearing potential and less than one year post-menopausal. Serum pregnancy test at screening. Urine pregnancy test at admission to site and discharge from site (or early termination).
[3.] Timing for vital signs:
- At screening
- At Day 00: 13 hours prior to IMP application, within 30 min prior to naltrexone taken.
- From Day 01 to Day 05: twice a day, within 30 min prior to each dosing of naltrexone.
- From Day 06 to Day 09: once in the morning, 30 minutes prior to PK blood sampling.

[4.] Admission to site at latest in the afternoon (before dinner), at least 15 hours before the patch administration of D01.
[5.] On Day 00, naltrexone 50 mg will be orally taken only in the evening, 13 hours (± 5 min) prior to the patch administration of D01; From Day 01 to Day 05, naltrexone 50 mg will be orally taken every 12 hours, in the morning and in the evening, at the fixed time for every morning or evening, with a time window of ± 5 min based on scheduled time. The intake in the morning of Day 01 should be 1 hour (± 5 min) prior to IMP administration. Naltrexone to be taken after meal. [6.] Patches will be removed 96 hours (± 2 min) after administration. Blood sampling should occur in the last 2 minutes of dosing i.e. within 2 minutes prior to the patch being removed.
[7.] Assessment of patch adhesion will be performed twice a day in the morning and in the evening (every 12±1 hours). The first evaluation on Day 01 will be conducted immediately after the patch applied on Day 01. On Day 05, the evaluation will be done once just before the patch removed.
[8.] Dermatological examination of IMP application site will be conducted within 0.5 hour after IMP removal and in the morning of D06 and D07. In case that the result of the examination conducted at D06 is judged "No evidence of irritation", the examination scheduled for D07 will not be conducted. In case AE was reported for the skin reaction and not recovered at D07, more examinations may be needed for the AE follow-up.
[9.] Blood sampling timing: Pre-dose (0), 12, 24, 48, 72, 96 (pre-removal), 97, 98, 100, 108, 120, 132, 144, 168 and 192 hours post administration of patch, Time window: within 30 minutes prior to the patch administration for pre-dose (0); ±2 minutes for 12-72 hours and 97-100 hours; within 2 minutes prior to the patch being remuved for 96 hours; ±1 hour for 108 -192 hours., blood sampling for drug concentration measurement will not be conducted following removal.
[10.] Safety follow-up completion or early termination.
[11] Safety follow-up visit can be performed as a telephone visit.

Tables 1.3 and 1.4 present the schedule of PK blood sampling for 3-day application arm and 4-day application respectively.

Table 1.3 PK Blood Sampling Schedule for 3-day application

	3-day application												
Day	**Day 01**		**Day 02**	**Day 03**	**Day 04**					**Day 05**	**Day 06**	**Day 07**	**Day 08**
Time after administration (h)[1]	Pre-dose[2]	12	24	48	72 (pre-removal)	73	74	144	84	96	120	144	168
6 mL Blood Sample	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Blood samples collected after IMP administration should be performed strictly according to scheduled nominal time. Time window: ±2 minutes for 12-48 hours and 73-76 hours; within 2 minutes prior to the patch being removed for 72 hours; ±1 hour for 84 -168 hours..
[2] Pre-dose: within 30 minutes before the IMP administration (patch administration is defined as 0 hour).

Table 1.4 PK Blood Sampling Schedule for 4-day application

	4-day application														
Day	**Day 01**		**Day 02**	**Day 03**	**Day 04**	**Day 05**					**Day 06**		**Day 07**	**Day 08**	**Day 09**
Time after administration (h)[1]	Pre-dose[2]	12	24	48	72	96 (pre-removal)	97	98	100	108	120	132	144	168	192
6mL Blood Sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Blood samples collected after IMP administration should be performed strictly according to scheduled nominal time. Time window: ±2 minutes for 12-72 hours and 97-100 hours; within 2 minutes prior to the patch being removed for 96 hours; ±1 hour for 108 -192 hours.
[2] Pre-dose: within 30 minutes before the IMP administration (patch administration is defined as 0 hour).

12.3 Screening Period

No study procedure will be completed until the subject has given written informed consent.

The Screening Period (up to 21-days before the first study check in at Day 00) aims to evaluate if subjects are eligible for the study according to inclusion/exclusion (I/E) criteria. The reasons for screening failures will be documented. subjects will perform the following procedures in the Screening Period:

- The ICF (subjects will sign an ICF prior to executing all other activities)
- Demography
- Dermatological assessment to check for potential dermatological disorder at the patch application site
- Medical / surgical history collection
- Abdominal ultrasound if deemed necessary by the investigator
- Details of Alcohol/Tobacco/Sensitivity/blood donation history
- Physical examination
- Karnofsky score
- Vital signs: pulse rate, respiration rate, sitting blood pressure and body temperature will be examined. It will be repeated if any vital sign falls outside the normal range and is considered potentially clinically significant.
- Weight, height and BMI
- Average pain over last 24-hours on 0-10 score NRS - see section 19.5.
- 12-Lead ECG
- Haematology, blood chemistry (fasted), 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 breath test
- Blood β-HCG test for female subjects up to less than one-year post-menopause
- AEs collection after the ICF acquisition
- Collection of prior and 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. 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 eCRF and reported according to Section 13.3.

12.4 Re-Screening Instructions

Subjects who do not meet the criteria for study entry can be re-screened if there is an indication that the reason for exclusion has changed. Any screening measurements that fall outside of the 21-day window must be repeated and subjects must meet the study entry criteria during these

assessments. A new subject screening number will be assigned each time a subject is re-screened and the subject must be re-consented. Any subject re-screening judged by investigator should be informed and agreed by sponsor.

12.5 Randomisation

Randomisation will be completed once all inclusion and exclusion criteria are verified. Refer to Section 13.5 for further details on the treatment assignment.

12.6 Treatment and Sampling Period

Refer to section 12.8 for the food restrictions during the study.

12.6.1 Check-in Visit (Day 00)

The check-in visit (Day 00) aims to further confirm eligibility to continue in the study. At Day 00 if the subjects meet all I/E criteria, they will be randomized into one of the 3 treatment arms. Subjects will complete all the following examinations:

- Subjects will report to the study unit on the day at least 15 hours before the scheduled study drug dosing.
- Physical examination
- Average pain over last 24-hours on 0-10 score NRS - see section 19.5.
- Alcohol breath test and urine drug screen; the results must be negative before IMP application in each period
- Urine β-HCG test for female subjects before menopause and less than one year after menopause and the results must be negative prior to IMP application.
- Subjects will be asked 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 and strenuous exercise within 48 hours before the scheduled study drug dosing. I/E criteria will be verified again to notice any changes
- 12-Lead ECG
- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be executed within 30 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
- AE collection
- Concomitant medications and non-pharmacological therapies
- Inclusion/Exclusion criteria list will be checked when all the results of examinations are available.

12.6.2 Three-day application period

12.6.2.1 Day 01

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained every 12 hours, within 30 min prior to the dosing of naltrexone.

- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, the first dosing at 1 hour (± 5 minutes) before the IMP application and the second at 11 hours (± 5 minutes) after IMP application.
- Pre-dose PK sampling: a blood sample (6 mL) drawn within 30 minutes before the IMP application.
- Based on the randomization schedule, either 20 mg or 40 mg BUP TDS will be applied respectively (see section 13 for details of IMP application).
- Observe patch adhesion status immediately after patch applied and 12 hours (±1 hour) later and assess whether additional taping is required.
- Post-dose PK sampling: a blood sample (6 mL) will be drawn at 12 hours after patch application. Blood sample collection will be performed ± 2 minutes of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.2.2 Day 02 and Day 03

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained within 30 min prior to the dosing of naltrexone.
- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, with a time window of ±5 min based on scheduled time.
- A blood sample (6 mL) will be drawn at:
  - Day 02: 24-hours after patch application
  - Day 03: 48-hours after patch application

  Blood sample collection will be performed ± 2 minutes of scheduled time post dose. Every effort should be made to ensure accurate sampling time and protocol deviations should be kept to a minimum.
- Observe patch adhesion status twice a day (every 12 hours ± 1 hours) and assess whether additional taping is required.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.2.3 Day 04

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained within 30 min prior to each dosing of naltrexone.
- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, with a time window of ±5 min based on scheduled time.
- Observe patch adhesion status once, just before patch removal.
- BUP TDS will be removed.
- BUP patch will be removed 72 hours (±2 minutes) after being applied.
- Prior to IMP removal PK sampling: PK blood sampling to occur in the last 2 minutes of dosing i.e. within 2 minutes before the patch is removed, a blood sample (6 mL) will be drawn.

- A blood sample (6 mL) will be drawn at 73, 74, 76 and 84 hours after administration of patch with a time window of ± 2 minutes for 73-76 hours and ±1 hour for 84 hours . Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Dermatological examination of patch application site will be conducted within 0.5 hour after patch removal using a 0 – 7 skin status scale – refer to section 19.6.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.2.4 Day 05 and Day 07

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained in the morning within 30 minutes prior to PK blood sampling.
- A blood sample (6 mL) will be drawn at:
  - Day 05: 96 hours after patch application
  - Day 06: 120 hours after patch application.
  - Day 07: 144 hours after patch application.

  Blood sample collection will be performed ± 1 hour of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Dermatological examination of patch application site will be conducted in the morning of D05 and D06 using a 0 – 7 dermal response score (section 19.6). In case that the result of the examination conducted at D05 is judged "No evidence of irritation", the examination scheduled for D06 will not be conducted. In case AE was reported for the skin reaction and not recovered at D06, more examinations may be needed for the AE follow-up.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.2.5 Day 08

- A blood sample (6 mL) will be drawn at 168 hours after patch application. Blood sample collection will be performed ± 1 hour of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.
- The following procedures will only be conducted for 3-day application on Day 08 of the third period, or early termination:
  - Physical examination and weight
  - Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature), within 30 minutes prior to the PK sampling.
  - 12-Lead ECG
  - Urine β-HCG test for female subjects before menopause and less than one year after menopause
  - Haematology, blood chemistry (fasted), and urinalysis

Following completion of the above procedures, the subject will complete the blood collection visit.

12.6.3 Four-day application

12.6.3.1 Day 01

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained within 30 min prior to each dosing of naltrexone.
- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, the first dosing at 1 hour (± 5 minutes) before the IMP application and the second at 11 hours (± 5 minutes) after IMP application.
- Pre-dose PK sampling: a blood sample (6 mL) drawn within 30 minutes before the IMP application.
- Based on the randomization schedule, 40 mg BUP TDS will be applied (see section 13 for details of IMP application).
- Observe patch adhesion status immediately after patch applied and 12 hours (±1 hour) later, and assess whether additional taping is required.
- Post-dose PK sampling: a blood sample (6 mL) will be drawn at 12 hours after patch application. Blood sample collection will be performed ± 2 minutes of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.3.2 Day 02, Day 03 and Day 04

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained within 30 min prior to each dosing of naltrexone.
- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, with a time window of ±5 min based on scheduled time.
- A blood sample (6 mL) will be drawn at:
  - Day 02: 24 hours after patch application
  - Day 03: 48 hours after patch application
  - Day 04: 72 hours after patch application

  Blood sample collection will be performed strictly according to scheduled nominal time and within ± 2 minutes of scheduled time post dose; every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Observe patch adhesion status twice a day (every 12 hours ±1 hour) and assess whether additional taping is required.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.3.3 Day 05

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained within 30 min prior to each dosing of naltrexone.
- 50 mg of naltrexone tablet will be administered twice a day (every 12 hours) with 150 mL water in a standing position, with a time window of ±5 min based on scheduled time.
- Observe patch adhesion status once, just before patch removal.
- BUP patch will be removed 96 hours (±2 minutes) after being applied.
- Prior to IMP removal PK sampling: PK blood sampling to occur in the last 2 minutes of dosing i.e. within 2 minutes before the patch is removed, a blood sample (6 mL) will be drawn.
- A blood sample (6 mL) will be drawn at 97, 98, 100 and 108 hours after administration of patch, with a time window of ± 2 minutes for 97-100 hours and ±1 hour for 108 hours. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Dermatological examination of patch application site will be conducted within 0.5 hour after patch removal using a 0 – 7 skin status scale – refer to section 19.6.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.3.4 Day 06 and Day 08

- Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature) will be obtained in the morning within 30 minutes prior to PK blood sampling.
- A blood sample (6 mL) will be drawn at:
  - Day 06: 120 and 132 hours after patch application
  - Day 07: 144 hours after patch application.
  - Day 08: 168 hours after patch application.

  Blood sample collection will be performed ± 1 hour of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- Dermatological examination of patch application site will be conducted in the morning of D06 and D07 using a 0 – 7 dermal response score (refer to section 19.6). In case that the result of the examination conducted at D06 is judged "No evidence of irritation", the examination scheduled for D07 will not be conducted. In case AE was reprted for the skin reaction and not recovered at D07, more examinations may be needed for the AE follow-up.
- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.6.3.5 Day 09

- A blood sample (6 mL) will be drawn at 192 hours after patch application. Blood sample collection will be performed ± 1 hour of scheduled time post dose. Every effort should be made to ensure accurate sampling time and deviations should be kept to a minimum.
- AE collection.

- Collection of concomitant medication and non-pharmacological therapies.
- The following procedures will only be conducted for 4-day application on Day 08 of the third period, or early termination:
  - Physical examination and weight
  - Vital signs (pulse rate, respiration rate, sitting blood pressure and body temperature), within 30 minutes prior to the PK sampling.
  - 12-Lead ECG
  - Urine β-HCG test for female subjects before menopause and less than one year after menopause
  - Haematology, blood chemistry (fasted), and urinalysis.

Following completion of the above procedures, the subject will complete the blood collection visit.

12.7 End of study

The end of study for each subject is defined as the day of the safety follow-up visit. The end of the study is defined as last subject last follow-up visit.

12.7.1 Early Discontinuation/Withdrawal/Loss to Follow-up

The Investigator or subjects themselves may stop study treatment at any time for safety or personal reasons. Whenever possible, the subjects will be instructed to complete the end-of-study procedures (listed in Table 1.1 and Table 1.2) and the Investigators or a designee will give phone contacts to the discontinued subjects to complete the safety follow-up as described in Section 12.8. A subject removed from the study for any reason may not be replaced. i.e. the same randomisation number will not be reused.

12.7.2 Safety follow-up (telephone contact)

Subjects who complete treatment or discontinue from treatment will be followed up 7 – 9 days after the last BUP TDS removal will be telephoned by site staff.

The following evaluations will be performed over the telephone:

- AE collection.
- Collection of concomitant medication and non-pharmacological therapies.

12.7.3 Withdrawal Criteria

The participation of an individual subject may be terminated prematurely for reasons such as:

1. Withdrawal of written informed consent
2. Adverse Events during administration of the IMP
3. Evidence of exclusion criteria

Any other condition which in the opinion of the Investigator no longer permits a safe participation in the study.

12.8 Study Restrictions

12.8.1 Food and Beverages

Menus will be standardised while subjects are resident in the study unit. However, the menus for each day will not be identical. Subjects must consume only the food given to them while in the unit.

A standardised breakfast, lunch, dinner and an evening snack will be provided to subjects at the same time in each treatment period during hospitalisation.

On the days of admitting to hospital, a standard dinner and a snack will be served, and on the day of discharging from hospital, an optional breakfast will be provided.

There will be free access to drinking water throughout the day, except for 1 hour after each dosing of Naltrexone and 30 minutes before vital sign measurements. Naltrexone to be taken after meal.

12.8.2 Alcohol, Caffeine, Smoking and other Restrictions

Subjects must comply with alcohol restrictions per exclusion criteria 11 and smoking restrictions per exclusion criteria 12 (section 11.2) during the study. Grapefruit (and its juices), caffeine- and xanthine-containing food or beverages will not be permitted while subjects are in the study unit. Intense physical activity will also be prohibited during the study.

13 STUDY TREATMENTS AND CONCOMITANT THERAPIES

13.1 Study Treatments (IMPs and NIMPs)

The definitions of IMPs and NIMPs (auxiliary products) are described in Appendix Section 19.22.

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

The buprenorphine transdermal patches (Transtec®) are manufactured by LTS Lohmann Therapie-Systeme AG, Germany, and the marketing authorization holder (MAH) is Grünenthal GmbH, Germany.

The buprenorphine transdermal patches are rectangular or square, beige-coloured system consisting of a protective liner and functional layers.

Store at 15-25 ℃.

Table 2: Test IMP Identity

Test IMP	Effective area	Buprenorphine load	Buprenorphine release rate	Mode of Administration
Buprenorphine transdermal patch 20 mg	25 cm^2	20 mg	35 µg/h	Transdermal
Buprenorphine transdermal patch 40 mg	50 cm^2	40 mg	70 µg/h	Transdermal

13.1.2 Reference IMP, Dose and Mode of Administration

Not applicable.

13.1.3 Non-Investigational Medicinal Product (NIMP / Auxillary product), Dose and Mode of Administration

The NIMP is defined in Section 19.22. NIMPs will be supplied by the Sponsor.

Table 3: NIMP Identity

NIMP	Dosage Form	Unit Strength	Active Ingredients	Dosing frequency	Mode of Administration
Naltrexone hydrochloride	Tablet	50 mg	Naltrexone	Twice daily	Oral

Naltrexone hydrochloride is manufactured by Aesica Queenborough Limited and the MAH is Bristol-Myers Squibb Pharmaceuticals Limited.

13.2 Study Treatments to be supplied

The Sponsor will package the study treatments. IMPs will be supplied in labelled containers by the Sponsor. The Product Release Certificate(s) for the IMP will be included in the clinical study report for this protocol. The study treatment will be supplied in packs labelled to meet the national requirements and will include a unique pack identifying number, including generic name, strengths, storage requirements etc.

13.3 Dosing Schedule

Table 1.1 and Table 1.2 present the schedule of visits and procedures for the 3-day application and 4-day application respectively. All procedures will be collected in the source documents. Procedures should be completed in the order presented.

The BUP TDS will be administrated in the morning for each subject.

One patch (20 mg or 40 mg) will be applied in the morning of Day 01:

- For the 3-day application (20 mg or 40 mg): the patch will be removed in the morning of Day 04, 72 hours after administration.
- For the 4-day application (40 mg): the patch will be removed in the morning of Day 05, 96 hours after administration.

Naltrexone cover:

The study patch will be applied under the cover of naltrexone to reduce opioid related side-effects.

Naltrexone 50 mg will be taken orally every 12 hours, from the evening of Day 00 (13 hours prior to IMP application), until the evening of the patch removal. Naltrexone should be taken at the

fixed time in each morning or evening, with a time window of ± 5 min based on scheduled time.

- For 3-day application: the last dose will be taken in the evening of Day 04, for a total of 9 dosing's.
- For 4-day application: the last dose will be taken in the evening of Day 05, for a total of 11 dosing's.

13.4 Method of Administration

Do not use the patch on any skin with larger scars, but on skin with less or no hair. If this is not possible, you should use scissors to cut off the hair, but don't use a razor to shave off the hair. In the morning of the test day, the skin should be cleaned with water first. Soap, alcohol, oil, lotion or scrubbing equipment should not be used. The skin must be dry before using the patch.The patch should be applied immediately after removal from the sachet to non-irritated, clean and intact skin.

- Cut open foil pouch (use scissors carefully avoiding damaging the BTDS), tear pouch open, remove the BTDS from foil pouch. The pouch containing the patch should only be opened immediately prior to application. Do not discard the opened pouch.
- Remove larger half of the BTDS liner and grasp smaller half (taking care not to touch the central part of the adhesive which may contain buprenorphine).
- Apply BTDS to skin, remove smaller half of the backing. Do not discard the liner. If the person applying the BTDS inadvertently touches the adhesive part behind the protective liner, they should wash the affected area with water (some soaps, lotions, alcohol or other solvents may facilitate buprenorphine transfer through the skin).
- Press down on BTDS with the palm of your hand for 30 seconds, making sure contact is complete, especially round the edges (do not rub).
- It is important that the BTDS patch application sites on the back do not overlap.
- Place the opened pouch and liner into a separate, clean plastic bag, sealed and labelled for storage of the used BTDS.
- After removal of each BTDS patch, it will be placed on the original release liner with care taken to ensure it is returned to the correct side of the liner (side with a dull, matte like appearance).
- If at any time the edges of the patch begin to peel off, the edges should be taped down with suitable skin tape e.g. Tegaderm. Any occurrence of a patch becoming loose or detached will be documented in the eCRF with start dates and times recorded. If a patch has detached completely it should be re-applied to the same site using suitable skin tape.

During the period with IMP application, attention should be paid to ensure that no rubbing or warming (e.g. sauna, infrared-radiation) occurs at the site of application. Regarding washing, showering will be only permitted. Soap or any other cleansing agents should not be used to the application site. Cosmetics, lotions or creams should not be applied to the application site.

For this study the IMP should be applied to right upper chest.

BUP patch removal will be conducted by pinching the edge of the patch and gradually peeling away from the skin.

13.5 Treatment Assignment

Randomisation will be performed by the Sponsor using a validated system that automates the random assignment of treatment to randomisation numbers. The randomisation scheme will be reviewed by the Sponsor's Data Management and Statistics Department and locked after approval. The randomisation scheme and identification for each subject will be included in the Clinical Study report.

Subjects will be randomised to which IMP they receive at Visit 2.

- Treatment A: BUP TDS 20 mg applied for 3 days
- Treatment B: BUP TDS 40 mg applied for 3 days
- Treatment C: BUP TDS 40 mg applied for 4 days

13.6 Blinding

Not applicable, this is an open-label study.

13.7 Treatment Compliance/IMP Accountability

The Investigator and study staff will be responsible for the IMP accountability and will record maintenance of all clinical supplies, and rescue medication (dispensing, inventory, and returns) following Sponsor instructions and will adhere to GCP guidelines as well as applicable country specific regulations.

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

13.8 Concomitant Therapies – Permitted

All medications are not allowed during the study, but the medication considered necessary for the subject's welfare may be administered under the supervision of the Investigator.

For subjects who receive IMP, concomitant medications and therapies, including over-the-counter medications and non-pharmacological treatments such as physiotherapy, that are ongoing as of the date of informed consent will be recorded in the respective section of the EDC and must be approved by the Sponsor. The forms for Concomitant Therapy and non-pharmacological therapies and procedures will be maintained and updated throughout the subject's participation in the study for any new therapies of changes to existing therapies. The use of such concomitant medications should be approved in advance by the Sponsor, when possible. The Investigator will record the AE for which the concomitant medication was administered on the eCRF.

Acetaminophen up to 2.0 g/day 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.

The study site must hold a supply of naloxone for injection as emergency rescue medication. This will be supplied by the investigator site.

The use of other concomitant medications during this trial is discouraged, unless necessary to treat adverse events. The use of other concomitant medications should be approved by the Sponsor in advance, when possible.

13.9 Concomitant Therapies - Prohibited

Monoamine oxidase inhibitors cannot be used during this trial and must be withheld for at least two weeks prior to IMP administration.

Tricyclic antidepressants cannot be administered during the trial or have been used within 4 weeks prior to the first IMP administration.

Use of any medicinal product which inhibits CYP3A4 (e.g. troleandomycin, ketoconazole, gestodene, etc) or induces CYP3A4 (e.g. glucocorticoids, barbiturates, rifampicin,etc) are prohibited from the start of the study (admission to site) to end of the study. If the patient needs to receive these drug therapies for any adverse events, the patient should withdraw from the study

13.10 Shipping, Handling, Storage, and Destruction/Return

IMP and NIMP will be supplied to the Principal Investigator or the delegated staff by the Sponsor, either directly or via a local warehouse contracted by the Sponsor. Specific Good Distribution Practice requirements for the shipment will be assessed by the Sponsor and requirements for handling and monitoring of temperature sensitive products will be communicated to the Investigator within the Investigator instructions. Once the shipment has been opened, the products must be stored according to the conditions specified on the labels and must be kept in an appropriate secure area (e.g. locked cabinet/pharmacy). Specific laws relating to the handling and storage of narcotics/chemotherapeutics must be followed, and this will be the responsibility of the Investigator or designee such as pharmacist.

Investigational site personnel must maintain an accurate and timely record of the receipt of all clinical supplies, dispensing of IMP/NIMP to the subject, collection of unused supplies returned by the subject and subsequent return of unused or expired IMP/NIMP to the Sponsor. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) IMP/NIMP dispensing/return reconciliation log, (c) IMP/NIMP accountability log, and (d) all shipping service receipts. All forms will be provided by the Sponsor. Any comparable forms that the site wishes to use must be approved by the Sponsor. A copy of these records must be given to the Sponsor at the end of the study.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or Competent Authority (CA).

All used and unused IMP/NIMPs, including empty containers, are to be returned to the Sponsor or Sponsor designated warehouse at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site. The investigational site personnel must not destroy any IMP/NIMP labels or any partly used or unused IMP/NIMP supply until directed by the Sponsor or designee following accountability

checks. Upon completion of IMP/NIMP accountability and reconciliation procedures by investigational site personnel and monitoring procedures by Sponsor personnel, IMP/NIMP 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 China regulatory and shipment laws, including but not limited to Good Clinical Practice Guideline, Regulation on the Control of Narcotic Drugs and Psychotropic Drugs and Management Measures of Mailing Narcotic Drugs and Psychotropic Drugs.

14 SAFETY ASSESSMENTS

Safety assessments will be recorded from the point at which the Informed Consent is signed. Please refer to Sections 9 and 12 for actual safety variables and endpoints.

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 regulations and are documented in a separate Safety Management Plan (SMP).

14.1 Safety Definitions and Requirements

14.1.1 Adverse Event (AE)

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

An AE can be:

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

14.1.2 Serious Adverse Event (SAE)

A SAE is any AE that:

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

- is a medically important event or reaction.

14.1.3 Special Situations

Special situations may occur that may or may not be associated with AEs. Such situations, whether or not associated with an AE, are documented on dedicated forms. Any AE that occurred in association with such a special situation has to be entered on the eCRF form. For these situations special reporting provisions apply. Special situations have to be reported within 24 hrs by the Investigator to the Sponsor.

For this study special situations comprises:

- Pregnancy
- Drug exposure via parent
- Medication errors (including overdose)
- Abuse/misuse of the IMP
- Drug Diversion - Defined as IMP that is sold or given to other persons either deliberately or accidentally. This may include accidental misdirection of study supply into mainstream hospital supplies. Adverse events in persons other than the subject after drug diversion will be processed in the Sponsor's drug safety database.

14.1.4 Pregnancy

Pregnant women are excluded from the study, and female study subjects of child-bearing potential undergo pregnancy testing at screening and regularly during the study (see section 12.2 (Flowchart of study)). If pregnancy is suspected in a study subject during treatment with the IMP, the IMP must be immediately withheld until the result of a confirmatory test is available. If confirmed, the subject must be withdrawn from the study.

Although not an AE per se, pregnancy in a female study subject or the partner of a male study subject must be reported via the paper pregnancy form if it occurs during the period of observation of the study. The CRO will contact the Investigator to confirm significant pregnancy information i.e. AEs during pregnancy, the pregnancy outcome, and any events to 3-months post-partum.

The Investigator must contact the Sponsor immediately in such a situation.

The following forms have to be used:

Pregnancy in female study subject	Patient Pregnancy Notification Form
Pregnancy in partner of male study subject	Partner Pregnancy Notification Form

If an SAE or AE occurs in relation to the pregnancy, it has to be recorded in the eCRF according to Section 14.2 and 14.3. For follow up information, see Section 14.4.

The Investigator must make all reasonable efforts to follow up the pregnancy until its end and will report all outcomes associated with the pregnancy to the Sponsor. In the situation of

pregnancy of the female partner of a male study subject, consent for the release of medical data should be obtained from the female partner to allow collection of information on the outcome of the pregnancy.

14.2 Period of Observation

The period of observation for each subject for collection of AEs extends from the time the subject signs the informed consent form until the subjects last study visit (telephone call), which is scheduled at least 7 to 9 days after removal of IMP.

Abnormal, clinically relevant findings or observations made prior to signature of informed consent are to be recorded as medical history/ concomitant disease but not as AEs.

If an adverse drug reaction (ADR) occurs in a subject after the period of observation, i.e. after the last study visit, usual spontaneous reporting should occur to the relevant marketing authorization holder (MAH).

All laboratory results and other clinical observations such as ECGs, vital signs, etc. from scheduled and unscheduled tests, taken from Consent through to the subject's last scheduled visit (i.e. follow up visit) are included in the eCRF.

If a lab test or clinical observation isn't scheduled until after the follow up visit then the Investigator will determine CS (and therefore AE) or not clinically significant (NCS) for the initial laboratory result or clinical observation. The repeat lab test or observation result is then only captured in the source documents.

Additional follow up laboratory tests or clinical observations if required after the follow up date would be through routine clinical practice and local laboratory services if applicable and not through the central laboratory services.

The same follow up period is applied for each subject (i.e. to their follow up visit/telephone call and not until database lock).

14.3 Reporting of Adverse Events

See also Figure 2, Appendix Section 19.1.

All AEs that occur **during the period of observation** defined for the study (see section 14.2) have to be fully recorded in the eCRF according to the provisions in this section of the study protocol and eCRF completion guidelines, as well as in the subject's source data. This applies also to AEs in subjects who signed the informed consent but never received IMP/NIMP.

For the recording/reporting of adverse events the following shall be considered:

- **Diagnosis vs. Signs/ Symptoms**
    - The diagnosis rather than individual signs and symptoms, should be provided wherever possible and appropriate.
        - if there is not enough information to provide a diagnosis, individual signs and symptoms are to be recorded.
        - If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the unusual symptoms have to be reported separately.

- For SAEs the Investigator should provide any other supporting information that is required for the assessment of the events, specifically in the free text narrative description of the case.

- **Onset date, end date**
  - If an AE started during the study but did not end before the final follow-up visit, the Investigator must make a reasonable effort to establish the outcome and the end date. If this is not possible, e.g. because the AE is still ongoing, or the subject is lost to follow-up, there will be no end date for the AE.
  - For all AEs that resolve, resolve with sequelae, or have a fatal outcome, an end date must be provided.
  - If an AE stops and restarts later. If the investigators consider that this event belongs to the same event as the previous AE, that is, the recurrence of the previous event, and the previous AE did not achieve a true recovery, they can be recorded as an AE. If nor, all occurrences have to be recorded separately.

- **Intensity/Severity**

  Refers to the extent to which an AE affects the subject's daily activities. This is not the same as seriousness, which is based on set criteria and/or subject/event outcome. Severity will be categorized according to the following criteria:

Table 4: Adverse Event Severity

Mild	The AE does not interfere with the subject's routine activities.
Moderate	The AE interferes with the subject's daily routine, but usual routine activities can still be carried out.
Severe	The AE results in inability to perform routine activities.

- **Seriousness**
  For definition of seriousness criteria refer to Section 14.1.2. All seriousness criteria that apply have to be recorded.
- **Action Taken with the IMP**
  The action taken with the IMP as a result of the AE has to be documented.
- **Treatment for the AE**
  Any treatment for an AE, whether pharmacological or other (e.g. surgical) treatment, has to be recorded in the eCRF.
- **Outcome**
  The outcome recorded should be reflective of the outcome at the time of reporting the AE. The following categories should be used:
  - **Not recovered/Not Resolved**
    - Indicates that the event is ongoing and there has been no recovery.
  - **Recovering/Resolving**
    - Indicates that the event is in the process of recovery but has not yet fully resolved.

- **Recovered/Resolved**
  - Indicates that the event has fully resolved.
- **Recovered/Resolved with sequelae**
  - Indicates that there is a residual, possibly permanent consequence of the event (e.g. residual hemiparesis subsequent to stroke).
- **Fatal**
  - Indicates that the subject died due to the event. The outcome "fatal" applies only to the event(s) that were the cause(s) of death. For other adverse events that were ongoing at the time of death, the outcome must be recorded as "not recovered" and not "fatal".
- **Unknown**
  - Indicates that the outcome of the AE cannot be determined despite the best efforts of the Investigator. This may be due to the subject being 'Lost to Follow-up' and therefore the Safety Follow-Up visit could not be performed.

- **Causal Relationship of AE**

  The causal relationship refers to the presence or absence of a reasonable possibility of a causal relationship between the IMP and the adverse event. The following assessments should be used:

  - **Reasonable Possibility**: there are facts (evidence) or arguments to suggest a causal relationship between the IMP and the AE.

    This could be based on but not limited the information below:

    - Temporal relationship to IMP exposure
    - Event is known to be associated with the IMP drug class.
    - Event improved on discontinuation or dose reduction of IMP
    - Event reoccurred on Re-challenge of IMP
    - Biological plausibility
    - Other: a free text field to include any other text

  - **No Reasonable Possibility**: there are no facts (evidence) or arguments to suggest a causal relationship between the IMP and the AE.

    This could be based on but not limited to the information below:

    - Event attributed to concomitant medication (if this is ticked further details of the concomitant medication are to be provided in the free text field)
    - Event attributed to the existing disease/ condition (if this is ticked further details of the disease/condition are to be provided in the free text field)
    - Event attributed to NIMP
    - No reasonably temporal relationship associated with IMP administration
    - Event is expected in target disease and/or population
    - Due to the negative De-challenge and/or Re-challenge criteria
    - Other: a free text field.

The Investigator must provide a causal relationship with the IMP for each recorded AE, using medical judgement and taking into account the above, in addition to the subject's medical history and nature of the AE.

SAE causality to NIMP

If in the study a non-investigational medicinal product (NIMP) is used, e.g. as background or rescue medication, the Investigator will be asked for causality assessment with the NIMP as well. Please use the relevant fields in the eCRF and on the SAE form for this purpose.

NOTE: If upon receipt of further information, the Investigator considers the causality assessment to be different to their initial assessment, this should be reported immediately.

Assessment of Expectedness

The expectedness of an AE is determined by the Sponsor based on the reference safety information (RSI).

IMP:

The reference safety document used for assessing expectedness of AEs in this study is: the current IB for BUP TDS. The MAH is Grünenthal GmbH, Germany. The reference safety information is included in section 6 of IB. This document will be found in the Investigator Site File.

NIMP (Naltrexone):

The reference safety document used for assessing expectedness of AEs against the NIMP in the SmPC. The MAH is Bristol-Myers Squibb Pharmaceuticals Limited. The reference safety information is included on the Summary of Product Characteristics (SmPC) and will be found in the Investigator Site File.

14.4 Follow Up of Adverse Events

Adverse events should be followed up to determine the outcome. The cut off for information collection in the eCRF for AEs and SAEs including any follow up lab information is according to Section 14.2. Any AE that is still ongoing at this visit will have an outcome of 'Recovering/Resolving' or 'Not Recovered/Not Resolved' in the eCRF. After that all information still needs to be collected in the source and for SAEs the information needs to be forwarded to the Sponsor.

- All efforts to collect follow-up information must be documented in the subject's source data as soon as it is received.
- All AEs must be followed up by the Investigator until:
    - the AE is resolved or resolved with sequelae and all other queries related to the AE have been clarified, or
    - the end of the period of observation (= last study visit), or
    - the Investigator considers it medically justifiable to stop further follow-up
- If the subject had an AE with fatal outcome, an autopsy report should be provided if possible.

- If SAEs are ongoing at the time of the subject's last study visit, an additional safety follow-up visit should be scheduled for those subjects. This visit will be documented in the source notes and not in the eCRF.
    - The Investigator should set the interval to the additional safety follow-up visit according to his/ her medical judgement. If the EDC system is closed, information from this visit should be forwarded to the Sponsor using the paper SAE form.
- The Investigator should respond to any queries raised by the Sponsor in relation to adverse events, including provision of supporting documentation within the requested timeline.
    - In case of fatal or life-threatening SAEs the Sponsor may request urgent clarification within one business day.

Subjects who were treated with IMP but did not complete the study as per protocol, should receive all the examinations and investigations scheduled for the last study visit. The Investigator should make all efforts to contact subjects lost to follow-up and document the attempts in the subject's source data.

14.5 Reporting By Investigator to Sponsor

When SAE is found, doctors should be contacted in time for rescue. Investigators should fill in the paper SAE report form and record it in eCRF within 24 hours of being informed of SAE, and inform the principal investigator, sponsor and EC, provincial and National medical products administration.

Whenever follow-up information becomes available to a previously reported SAE, this has to be reported by the Investigator immediately but no later than 24 hours after becoming aware of the follow-up information by use of an SAE form via fax or e-mail.

In addition to the AE page, the following eCRF pages have to be updated or completed at the same time as necessary:

- subject demographics
- medical history
- concomitant medication
- study completion/termination (in case of an AE leading to withdrawal)

For questions regarding SAEs or to notify the Sponsor of an SAE in the event of technical failure of the e-mail or fax system, the Investigator should contact the Sponsor or CRO by phone.

All AEs that result in a subject's withdrawal from the study have to be recorded in the eCRF as soon as possible after the investigational site becoming aware of the event.

All Special situations have to be reported as soon as possible (ideally within 24 hours) to the Sponsor using the relevant forms provided to the Investigator site.

15 STATISTICAL ANALYSES

Statistical analyses will be performed by the Sponsor or a designated CRO. All statistical analyses will be performed using Statistical Analyses Software (SAS) and/or other statistical software as required, details will be provided in the SAP.

15.1 General Considerations

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

In general, baseline is defined as last value prior to first dose of IMP of each period.

All details of statistical methods and analyses will be documented in the Statistical Analysis Plan (SAP).

15.2 Analysis Populations

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

Randomised Population

The randomised population is defined as all randomised subjects.

Safety Population

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

Pharmacokinetic Population

The pharmacokinetic population is defined as all subjects who received IMP and have at least one pharmacokinetic concentration measurement. This will be the primary PK analysis population.

15.3 Protocol Deviations

The investigators should comply with all the requirements in the proposal approved by the sponsor, the regulatory authority (if necessary) and the EC, and must strictly implement them. Any intentional or unintentional deviation or violation of the protocol or GCP can be classified as protocol deviation.

This study does not allow deviations from the protocol unless the immediate danger elinination of participants is needed.

If a protocol deviation occurs, the investigator must notify the sponsor or the designated personnel of the sponsor. Any deviation must be recorded in the deviation report form. The time of discovery, the time and process of the event, the cause and the corresponding treatment measures should be recorded in detail. The investigator shall sign the deviation and notify the EC and sponsor. At the end of the study, it is submitted to the statistical analysis party. When serious deviation of the protocol occurs, the evaluation should be made and the sponsor may terminate the study in advance if necessary.

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 leading to exclusion of subjects or data points from the PK analysis 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.

15.4 Sample Size and Power Considerations

The study is descriptive and no formal sample size calculation has been performed for this study.

The China National Drug Administration (NMPA) recommended to investigate at least 8-12 Chinese subjects per treatment arm. Therefore, 15 subjects per arm will be randomised to receive IMP with the aim to have at least 12 subjects/arm completing the study and providing valid PK data.

15.5 Interim Analysis

Not applicable.

15.6 Efficacy Analysis

Not applicable.

15.7 Safety Analyses

Safety data that will be summarised includes exposure, AEs, clinical laboratory assessments, vital signs and ECGs. All safety analyses will be based on the safety population and will be summarised by dose group unless otherwise stated.

15.7.1 Treatment Exposure and Compliance

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 dose group as continuous data.

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

15.7.2 Adverse Events

Adverse events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and Preferred Term (PT) for each AE.

A treatment emergent AE (TEAE) is defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP. This will also include AEs with an onset date up to and including 7 – 9 days after the removal of last IMP. In addition, this will include AEs with an onset date more than 7 – 9 days after the removal of last IMP considered as related to IMP by the Investigator.

Only treatment-emergent AEs will be summarised.

The number and percentage of subjects reporting at least one AE will be summarised by PT nested within SOC for each of the following AE types:

- Any AE
- Any related AE
- Any severe AE
- Any related severe AE
- Any SAE
- Any related SAE
- Any SAE leading to death
- Any AE leading to discontinuation
- Any AE requiring additional therapy

Moreover, the number and percentage of subjects with any AE will be summarised by

- Worst severity (i.e. mild, moderate, and severe) by PT nested within SOC
- Relationship to IMP (i.e. related and not related) by PT nested within SOC.

15.7.3 Laboratory Values

Clinical laboratory data to be summarised includes haematology, blood chemistry, and urinalysis. The clinical laboratory parameters to be assessed are listed in Table 5 and the scheduled time-points for assessment are tabulated in Section 12.

Clinical laboratory parameters at each time-point and change from baseline to each post-baseline time-point will be summarised using descriptive summary statistics for each parameter by dose group and graphical illustrations.

Clinical laboratory values for each parameter will be assigned an LNH classification according to whether the value is lower (L), within (N) or higher (H) than the reference range for that parameter. The values will be summarised using shift tables from baseline to end of study with respect to reference range values (low, normal, high) for each parameter by dose group.

15.7.4 Vital Signs

Vital sign parameters to be summarised include pulse rate, respiration rate, systolic blood pressure, diastolic blood pressure and body temperature. The scheduled time-points for assessment are presented in Section 12.

Vital sign parameters at each time-point, and change from baseline to each post-baseline time-point will be summarised using descriptive summary statistics for each parameter by dose group and graphical illustrations.

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

15.7.5 ECG

The scheduled time-points for ECG assessment are presented in Section 12.

ECGs will be judged by the Investigator as clinically significant (yes/no). The number and percentage of subjects with clinically significant ECG findings will be summarised by dose group for each time-point.

15.8 Pharmacokinetic Measurements and Analyses

15.8.1 Drug Concentration Measurements

Blood samples for PK assessments will be drawn at the time points described in section 12.2 and analysed for plasma concentrations of the analytes (buprenorphine and norbuprenorphine).

Plasma concentration data will be listed by analyte, dose group (i.e. 3 dose groups: 20 mg 3-day, 40 mg 3-day and 40 mg 4-day).

Plasma concentration data for each analyte will be summarised descriptively by dose group, dose administration (i.e. single dose) and nominal time-point. Individual and mean plasma concentrations for each analyte will also be plotted over time by dose group and administration (if applicable). All plasma concentration summaries will be provided for the PK population. Handling of values below the level of quantification for these summaries will be described in the SAP.

15.8.2 Pharmacokinetic Analyses

The main analysis population for all PK analyses will be the PK population. Further, only valid PK parameters will be used for analysis. To have a valid PK parameter, the subject must not receive incorrect study treatment, or have an incomplete plasma profile that cannot detail the PK concentration parameters or have a pre-dose concentration >5% C_{max}.

All summaries and statistical analyses will be done for the PK population.

All statistical analyses are exploratory and not for formal hypothesis testing.

The following PK parameters will be summarized descriptively for analytes buprenorphine and norbuprenorphine:

- C_{max}: Maximum observed plasma concentration
- T_{max}: Time corresponding to C_{max}
- AUC_{0-t}: Area under the concentration-time curve from zero (time of drug administration) to time of last quantifiable observed concentration
- AUC_{0-inf}: Area Under the concentration-time Curve from zero (time of drug administration) to infinity
- λz (where possible): First order rate constant of the terminal phase calculated
- $t_{1/2z}$ (where possible): Terminal elimination half-life

16 ETHICS & REGULATORY

16.1 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and CRO, which are designed to ensure adherence to 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. The relevant version of the Declaration of Helsinki will be available in the Investigator Site File.
2. ICH E6 Guideline for GCP and subsequent notes for guidance (CPMP/ICH/135/95) European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).
3. European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.
4. GCP Directive 2005/28/EC.

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

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

16.2 Ethical and Regulatory Review

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

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

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

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

16.3 Subject Information and Consent

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

As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the subject information sheet (PIS) and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

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

16.4 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 and applicable regulation in China. This will apply to all study data in whatever format it is collected and recorded.

Any scan data, imaging, ECGs etc., collected for the trial will be retained in the subject's notes held with the Investigator.

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

16.5 Quality Assurance & Inspection Requirements

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

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

The clinical trial wards are equipped with necessary medical equipment, rescue drugs and emergency measures to regularly verify and calibrate the instruments and equipment. All participants in the trial were trained by GCP and follow the protocol, GCP and related SOP to ensure the quality of clinical trials. For this reason, clinical trial institution has carried out the following quality control of the trial process:

Before the start of the clinical trial, confirm that the clinical trial project starts after obtaining the approval of the EC, confirm the complete documentation of the preparation stage such as archiving materials and research materials, confirm that the rescue drugs and equipment in the rescue room are complete and within the validity period, confirm that all investigators accept the training of the protocol. Investigators and relevant personnel review and complete protocol, ICF, study data records and CRF forms.

In the course of the trial, the investigators should strictly follow the requirements of the protocol and the relevant SOPs of the institutions, and record in a true, timely, complete and standardized manner. Quality control personnel should control the trial process and the corresponding original records.

After the trial, the institution arranges the corresponding project documents, and after checking by the quality control personnel, the documents are filed and saved. If problems are found, investigators should be promptly notified to correct them and follow up the corrections. Confirm that all the original data are complete and filed in time. Finally, the investigators and relevant personnel review and complete the summary report.

17 STUDY MANAGEMENT RECORDS & PUBLICATION

17.1 Protocol Amendments

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

Any change to the protocol requires a written substantial or non-substantial protocol amendment. Substantial protocol amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require approval by NMPA and the applicable ECs. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Clinical Leader/Study Physician/Medical Monitor must be notified within 1 business day and the EC for the site must be informed in accordance with the policy of the EC approving the study, local regulations and policies. Changes affecting only administrative aspects of the study do not require substantial protocol amendments or EC approval, but the EC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the EC detailing such changes.

17.2 Record Maintenance and Retention

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 are to be collected in the source documents throughout the study.
- EDC/eCRF entries should be made as close to the visit of the subject as possible.

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

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

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

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

17.3 Adherence to the Protocol

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

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

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

Subjects who have not signed an IRB/EC approved ICF cannot enter in to the study.

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

17.4 Discontinuation of Study

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

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

17.5 Retention of Tissue Samples

Blood samples will be retained per local China regulations.

17.6 Registration and Publication of Study Summary and Results

The Sponsor will determine the identity of the Co-ordinating Investigator for the study who will review and sign off the Clinical Study Report. This decision will be based on involvement in the study including, but not limited to, study design, subject recruitment and interpretation of study data.

Clinical trials will be registered in public databases and summary results released / disseminated via publically available clinical trials databases according to the Sponsor's standard operating procedures (SOPs) and local requirements. If such studies and trials do require public registration and/or reporting, this will be undertaken according to local requirements.

The Sponsor registers clinical trials and posts the summary results as follows:

- *https://register.clinicaltrials.gov*

Following the end of the clinical trial, the summary results should be made publically available according to accepted timelines and requirements, usually within 12 months of study completion.

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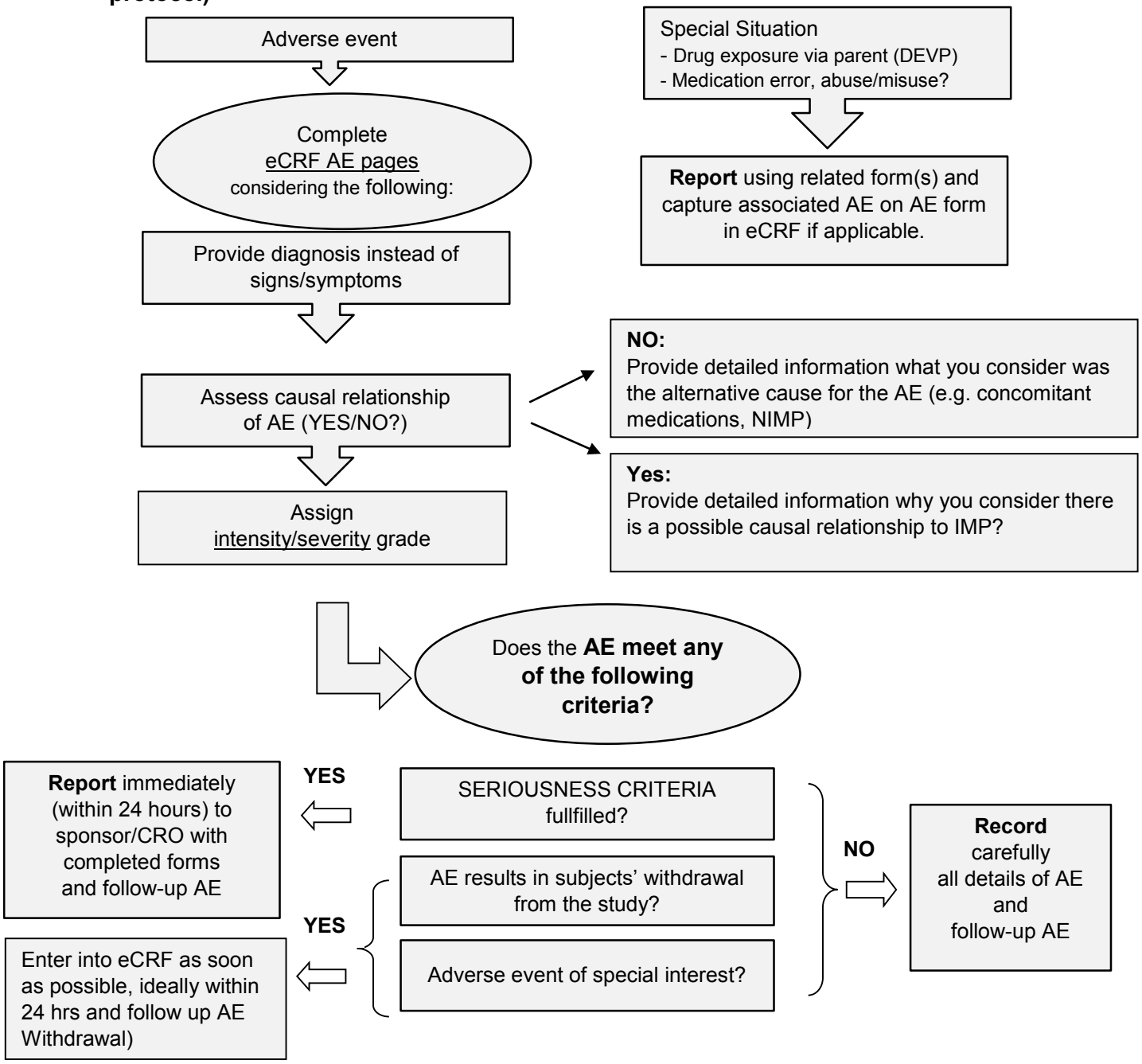
19 APPENDICES

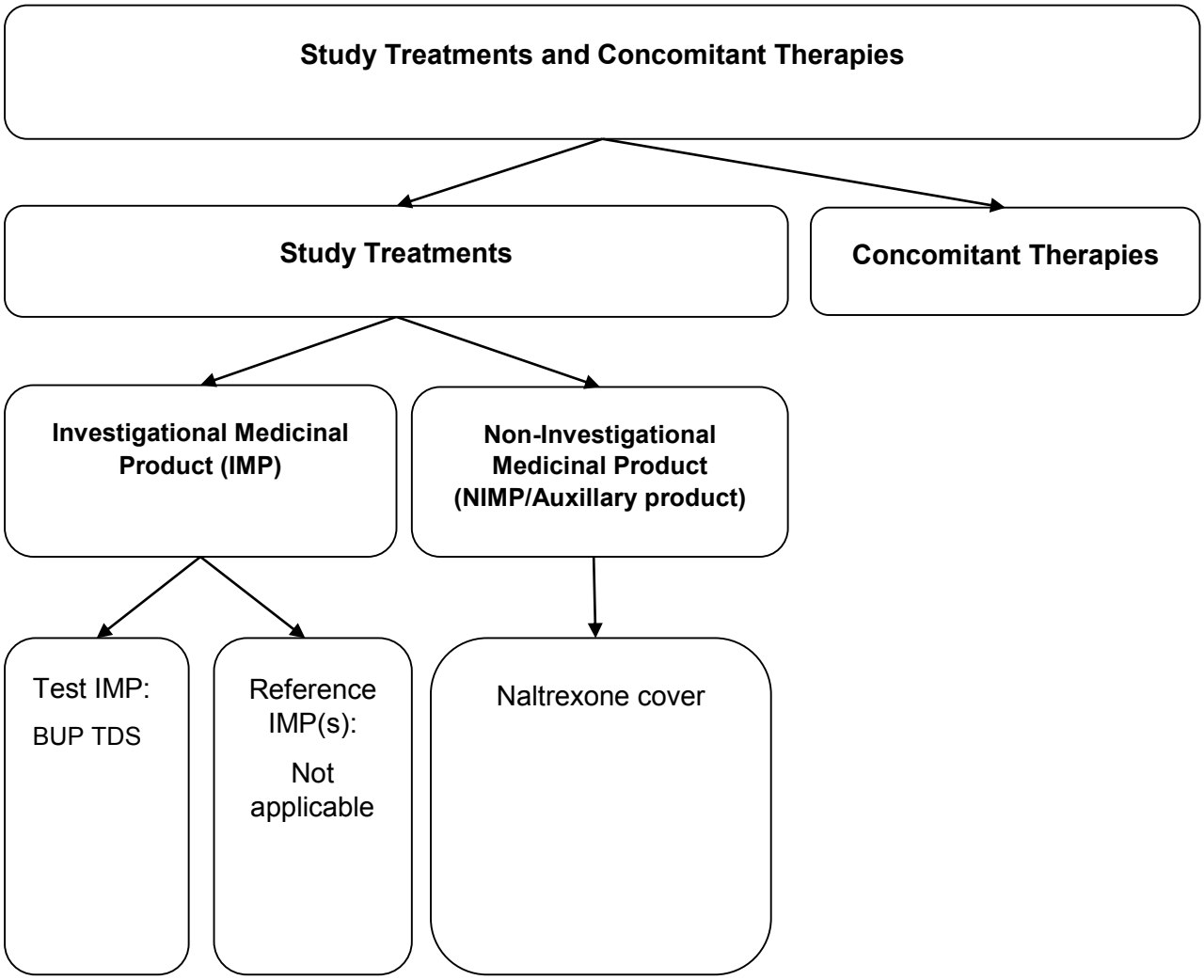
19.1 Adverse Event Reporting Process

Figure 2: Flow diagram for AE reporting (to be considered alongside Section 14 of the protocol)



19.2 Classification of Treatments

Figure 3: Overview of classification of treatments



The **Investigational Medicinal Product (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.

The term **test IMP** is used to indicate only the experimental product under study or development. Note: This term is more specific than “investigational medicinal product” which includes comparators and placebos.

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.

NIMPs include:

- Rescue medication (for ineffective treatment, anticipated adverse reactions, or anticipated emergency situations): e.g. analgesic rescue medication or laxative in opioid studies, naltrexone.
- Challenge agents, e.g. skin prick tests
- Medicinal products used to assess end-points in the clinical trial, e.g. any diagnostic agents used to assess the disease under study
- Concomitant medicinal products systematically prescribed to the study subjects, e.g. cancer treatment in an opioid trial with cancer patients who all get the same cancer treatment according to the protocol
- Background treatment, standard care that all patients receive in addition to the IMP and for the same indication, e.g. standard chemotherapy in addition to a new oncological product to be tested.

19.3 Sample Processing and Shipment

19.3.1 Pharmacokinetic Sample Handling and Shipping

Samples and Sample Log Forms will be shipped by the Investigator to the bioanalytical laboratory. Analysis will be performed by means of LC-MS/MS methodology. 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.

19.3.2 Sample Procurement and Processing

Blood samples, about 6 mL each, will be drawn into tubes containing K2EDTA anticoagulant. After procurement, samples should be kept in a container of ice water, until processing. Samples must be centrifuged within 60 minutes of collection. Following centrifugation (2000 g, 2-8 ℃, 1 0 minutes) the plasma will be transferred via pipette into two labelled polypropylene tubes and stored at least ≤ -60℃ within two hours of collection.

19.3.3 Sample Shipment

Samples will be shipped in accordance with the standard procedures provided by the Bioanalysis Laboratory.

19.4 Clinical Laboratory Tests

Table 5 presents the clinical laboratory tests to be performed.

Table 5: Clinical Laboratory Tests

Category	Parameters
Haematology	RBC, haemoglobin, haematocrit, platelets, and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	sodium, potassium, chloride, bicarbonate (HCO_3^-)
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin
Renal function parameters	blood urea, 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

19.5 Pain Intensity Scale

Numeric Rating Scale (NRS)

Rate your average pain: circle ONE number that best describes your **AVERAGE pain over the last 24 hours**.

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

19.6 Dermal response scale

Score	Dermal Response at patch site
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal oedema or minimal papular response
3	Erythema and papules
4	Definite oedema
5	Erythema, oedema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond the application site

19.7 Karnofsky score

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