Statistical Analysis Plan

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

Product Name: Oxycodone Naloxone Prolonged Release Tablets (OXN PR)

Sponsor: Mundipharma (China) Pharmaceutical Co., Ltd.

Version 1.0: Mar 1, 2017

STATISTICAL ANALYSIS PLAN

Study title:	An open-label, randomized, single-dose, parallel group study to investigate the pharmacokinetics of oxycodone and naloxone from oxycodone/naloxone (OXN) prolonged release (PR) tablet 5/2.5 mg (OXN 5/2.5)and20/10 mg (OXN 20/10) in Chinese patients with moderate to severe chronic non-malignant pain.
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Clinical trial approval number:	2011L01178,2011L01179,2012L02501,2012L02502
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Version/Date:	1.0: Mar 1, 2017

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Table of abbreviations

Abbreviation	Annotation
AE	Adverse events
$AUC_{0\text{-}inf}$	Area under plasma drug concentration-time curve from zero time to infinity
$AUC_{0\text{-}t}$	Area under plasma drug concentration-time curve from zero time to the last measurement
$AUC_{\_\%Extrap}$	Percentage of extrapolated area
BLQ	Below Limit of Quantification
BMI	Body mass index
CFDA	China Food and Drug Administration
C_{max}	Peak plasma concentration
CRF	Case report form
ECG	Electrocardiogram
Lambda_z	Elimination rate constant
LLOQ	Lower Limit of Quantification
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculate
ND	Not detectable
OXN PR	Oxycodone Naloxone Prolonged Release Tablets
PK	Pharmacokinetics
SAE	Serious adverse events
T_{max}	Time to peak plasma concentration
$t_{1/2}$	Elimination half-life

1. Overview

1.1 Study Rationale

Mundipharma Research GmbH & Co. KG and independent affiliates (NPRL and Purdue Pharma L.P) have developed a novel compound prolonged-release analgesic tablet composed of an opioid agonist oxycodone and an opioid antagonist naloxone. Oxycodone is a sustained-release dosage form of opioid analgesics indicated for moderate-severe pain.

Adding naloxone component to the fixed combination can offset opioid-induced constipation by locally blocking the effect of oxycodone on opioid receptors in the intestines. In addition, due to the presence of opioid receptor antagonist naloxone, lower abuse rate is expected with Oxycodone Naloxone Prolonged Release Tablets (OXN PR) than with single-component sustained-release opioids when the tablet is grounded for intravenous or intranasal administration. Opioids are the cornerstone of chronic pain management. It has been shown that opioid sustained-release drugs are effective for pain management; however, the adverse events (AE) have limited the ability to appropriately increase opioid doses to manage the pain. Among patients who receive opioid to manage pain, the induced constipation is a frequently occurring severe adverse event (SAE). Laxatives are the currently recommended treatment, but many patients frequently discontinue opioid therapy because opioid-induced constipation continues to exist with medication. Therefore, it is highly beneficial to minimize the occurrence or reduce the severity of constipation. In the current compound formulation, the high first-pass effect of naloxone is considered to be an advantage: the local action of naloxone in the intestine can improve intestinal function; given the low systemic bioavailability of naloxone, however, the analgesic activity of oxycodone is not inhibited. The results of all clinical studies conducted so far have shown no significant effect on the analgesic efficacy after compound OXN PR formulation is administered, but the patients indeed benefited from relieved constipation and tolerated this product very well.

1.2 Study objectives

The primary objectives of this study are:

- To determine the pharmacokinetic (PK) characteristics of oxycodone, naloxone and its metabolites in Chinese patients (with moderate to severe chronic non-malignant pain).
- To assess, in a single dose investigation, the dose-proportionality of OXN.

1.3 Study design

1.3.1 Study design

This is an open-label, randomized, single-dose and parallel-group study. A total of 24 subjects are expected to be enrolled and randomized at 1:1 ratio into single-dose Oxycodone Naloxone Prolonged Release Tablets (OXN PR) 5/2.5 mg group or OXN PR 20/10 mg group, each group includes 12 subjects who will orally receive OXN PR active drug. If fewer than 12 subjects in each group have completed this study, more subjects will be included.

Subjects will attend a screening visit within 14days of the first (OXN) dosing day (Day 1).

Eligible subjects will then check into the study unit on the day before OXN dosing (Day -2). Subjects will be administered their OXN dose the next 2 morning (Day 1), following an overnight fast.

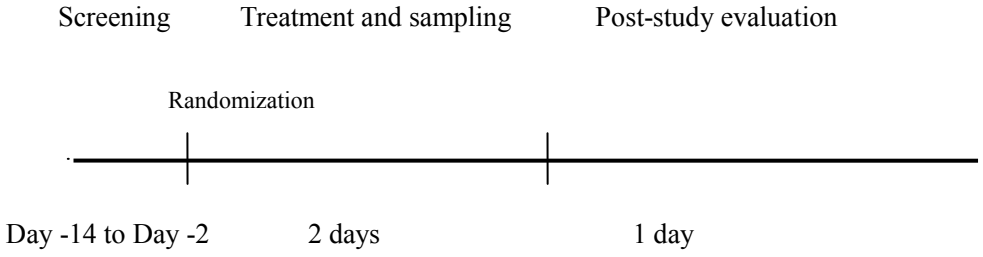
There will be 24 subjects with moderate to severe chronic non-malignant pain enrolled in this single-dose study, to be comprised of males and females aged 18-65 years. Blood samples will be collected in tubes containing the anticoagulant EDTA pre-dose and up to 48 hours after administration of OXN. Subjects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

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

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

Figure 1: Study Diagram

Single-dose administration:



Screening period: Day -14 to Day -2

Treatment and sampling period: 2 days

Group A: **OXN PR** 5/2.5 mg, 1 tablet

Group B: **OXN PR** 20/10 mg, 1 tablet

Post-study evaluation: 1 day

1.3.2 Determination of sample size

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

1.3.3 Blinding

Not applicable.

1.4 Guidelines

This statistical plan will follow the SOP of Clinical Pharmacology Research Center of Peking Union Medical College Hospital and the requirements of China authority.

2. Study subjects

2.1 Subject arrangement

The number and percentage of subjects completed and discontinued from this trial should be included in the statistical analysis report; meanwhile, the information of the subjects discontinued from the trial, including the reason for discontinuation, should be listed.

2.2 Analytical sets

- **Intention-to-treat (ITT) population**

  ITT population consists of all randomized subjects who meet the inclusion and exclusion criteria.

- **Safety set (SS)**

  Safety set is a subset of ITT population and consists of all subjects who receive at least 1 dose and have evaluable safety data.

- **PK analysis set (PKS)**

  PK analysis set is a subset of ITT population and consists of all subjects who receive at least 1 dose and have evaluable PK data. It should also be noted: according to the protocol, subjects who experience vomiting within 12hr after OXN is administered should not be included in the PKS.

  All the above analysis sets will be determined in data review report.

2.3 Protocol deviation

Primary and secondary protocol deviations should be listed in the statistical analysis report. (Note: Major PD will be identified in the data review report.)

2.4 Demographics and baseline analysis

2.4.1 Demographics

Safety set (SS) will be used to summarize and list demographic and baseline variables. Individual demographic and baseline characteristic data should be listed in the statistical analysis report.

Demographic variables such as age, gender, weight, height and ethnicity will be listed by dose group and subject; descriptive statistical analysis will be conducted by dose group. The continuous variables in the table should list the descriptive statistical results, while the categorical variables should list the frequency and percentage.

Medical History should be listed in the statistical analysis report.

2.4.2 Concomitant Medication

The list of Concomitant Medication should include all combined use of drugs in safety sets by drug and drug category.

2.5 Determination of treatment compliance

The beginning date, ending date and time of administration in these subjects will be listed in the statistical analysis report.

3. Pharmacokinetic evaluation

3.1 Analytical data

PK evaluation will be based on the data of all subjects in PKS.

3.2 Pharmacokinetic evaluation

3.2.1 Calculation of PK parameter

If there is no protocol deviation (e.g. failure to take study drug) that may affect PK endpoint variables (e.g. AUC, Cmax) during this trial, the subject will be included in PKS.

Non-compartmental analysis method (Linear Up Log Down) of Phoenix WinNonlin 6.3

(Pharsight Corp., Mountain View, CA, USA) software will be used not only to calculate PK parameters of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone), and naloxone and its metabolites (6β-naloxol, naloxone-3-glucuronate and 6β-naloxol-3-glucuronate) but also to conduct descriptive statistical analysis, including the following parameters:

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

Descriptive statistical analysis of the PK parameters of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone), and naloxone and its metabolites (6β-naloxol,

naloxone-3-glucuronate and 6β-naloxol-3-glucuronate) are conducted by dose group. The descriptive statistics include mean, standard deviation, coefficient of variation, minimum and maximum.

The mean concentration-time curve (Mean±SD) for oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone), naloxone and its metabolites (6β-naloxol, naloxone-3-glucuronate and 6β-naloxol-3-glucuronate) are plotted by dose group.

3.2.2 Evaluation of dose-proportionality

The linear mixed effect model (treatment as fixed factor, subject as random effect) will be used for exploratory evaluation of the dose-proportionality of for oxycodone, naloxone and metabolites ($AUC_{0\text{-}48h}$, AUC0-inf and C_{max}).

Evaluation objectives

The objective of drug dose-proportionality assessment is to determine whether there is a proportional relationship between the dose and exposure level of study drug, which is usually evaluated by measuring the relationship between concentration-related PK parameters (e.g. $AUC_{0\text{-}48hr}$, AUC0-inf and C_{max}) and doses.

Method for the evaluation of drug dose-proportionality

Power Model

Power Model [1,2] is used to find the point estimate and 90% confidence interval (CI) for the degree of drug dose-proportionality deviation between the lowest dose and the highest dose during this trial; then, the acceptable range after correction by the dose range (see texts below for correction method) is used to determine whether the drug demonstrates linearity within this dose range. If 90% CI for β falls within (θ_L, θ_U), the drug dose linearly can be established within this dose range; if 90% CI for β completely falls outside (θ_L, θ_U), the drug dose linearly cannot be established within this dose range; if 90% CI for β partially falls within (θ_L, θ_U), the drug dose linearly cannot be fully established within this dose range, but 90% CI for deviation of the drug dose linearly falls within (β_L, β_U).

Correction method of the acceptance range: γ=maximum dose/minimum dose; $\theta_L = \exp((\beta_L - 1) * \ln\gamma)$; $\theta_U = \exp((\beta_U - 1) * \ln\gamma)$; β_L is the lower limit of CI for β; β_U is the upper of CI for β. The β estimate and its CI are obtained with the mixed model after logarithmic conversion of PK parameters. The β estimate, θ_L and θ_U should be all listed in statistical analysis report.

3.3.3 Data handling conventions

3.3.3.1 Basic principles of PK data handling

The handling of PK concentration data and the calculation of PK parameters in this trial should comply with following basic principles:

1) When calculating PK parameters of data obtained at drug concentration below the lower limit of quantitation (BLQ), the value should be replaced with zero if occurring before T_{max} and the value should be replaced with ND if the BLQ occurs after T_{max};

2) After T_{max}, if measurable concentration appears after two consecutive NDs, it should be replaced with ND if there is no measurement error;

3) When descriptive statistics for concentration at each time point are calculated, all data below LLOQ are not brought into the calculation;

4) When descriptive statistics for concentration at each time point are calculated, if more than 1/3 of the individual data is not brought into the calculation, the descriptive statistics at that time point will not be calculated and are represented with NC;

5) When the descriptive statistics of concentrations at each time point are calculated, if a subject vomits within 12 hours after the administration, then this subject will not be included in the statistical analysis of PK, but the plasma drug concentration at the corresponding time point will be provided in the listing;

6) If the extrapolated area of AUC is greater than 20% of AUC_{0-inf}, $AUC_{0-t}/AUC_{0-inf}<0.8$, then the AUC_{0-inf} will neither be included nor be brought into any statistical analysis of AUC_{0-inf};

7) The calculation of all PK parameters employs the actual time and measured concentration.

8) All individual plasma drug concentration retains 3 significant digits, while the descriptive statistical results (mean and standard deviation) retain 2 digits after the decimal point; individual PK parameters and their descriptive results retain 2 significant digits.

9)Handling of missing data:

When missing data is determined, the test results corresponding to this point will not be brought into the calculation of relevant statistics.

3.3.3.2 Statistical method for PK analysis

Descriptive statistics of PK parameters include the number of cases (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV), minimum (Min), median and maximum (Max). The descriptive statistics of PK parameters (mean, standard deviation, coefficient of variation, minimum, median and maximum) will be provided by the listing of test drugs. All statistical analysis will employ SAS® 9.3.

4. Safety assessment

All statistical analysis will employ SAS® 9.3.

4.1 Analytical data

Safety analysis will be based on the data of all subjects in safety set (SS).

4.2 Exposure data

The date, time and dose of drugs given to the subjects should be listed in the statistical analysis report.

4.3 Adverse events

All AE-related information will be provided in the listings of statistical analysis report (including: SAE or not, severity, whether concomitant treatment is given, AE outcome and relationship with study treatment); each AE will be encoded with MedDRA (preferred term (PT), organ system classification (SOC)). The number of AE with different severity and the relationship with study treatment will be summarized by dose group; the incidence and percentage of AE will be summarized and analyzed with preferred term (PT) and organ system classification (SOC) by different dose groups. (AE occurring in all periods is given in the listing, but only TEAE (Treatment Emergent Adverse Events) will be statistically analyzed.)

Double histograms of PK exposure (AUC, C_{max}) and AE incidence will be plotted by dose group for naloxone and oxycodone, respectively.

4.3.1 Serious adverse events

Individual SAE data should be listed in the statistical analysis report.

4.4 Evaluation of laboratory tests

For safety set, laboratory examination results of the subjects at the scheduled evaluation point will be summarized by different dose group; meanwhile, the relative changes from the baseline will be summarized by evaluation point. The table for reference (normal) ranges of laboratory parameters will be listed for subjects in each dose group.

The laboratory test results will be classified and summarized by LNH according to lower than (L), equal to (N) or higher than (H) reference range of laboratory parameters.

4.5 Vital signs

All vital sign data will be presented by listing of dose groups and subjects, in which the outliers will be marked. Descriptive statistics and listing of various vital signs and their changes from the baseline after administration will be provided by dose group. For abnormal data, frequency and percentage will be calculated by treatment and abnormality.

4.6 Physical examination

Individual data of physical examination should be listed in statistical analysis report, in which the outliers will be marked. For abnormal data of physical examination, the frequency and percentage will be calculated by treatment and normality.

4.7 ECG evaluation

All ECG data will be listed by dose groups and subjects, while the outliers will be marked. Descriptive statistics of the changes in examination values of ECG parameters relative to baseline after administration will be provided by dose group. For abnormal ECG data, the frequency and percentage will be calculated by dose group and clinical significance.

4.8 Evaluation of pain scores

The pain scores will be summarized at the scheduled evaluation points by different dose groups.

5. Quality control

Statistical analysis and PK analysis should be carried out under the guidance of statisticians and PK experts, and reviewed by relevant quality control personnel.

6. List of Tables

6.1 List of Tables

6.2 List of figures

	their metabolites
Figure 2.2	Individual plasma drug concentration-time semi-logarithmic curve for oxycodone, naloxone and their metabolites

6.3 Table of listings

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Listing12.5:5	Listing of individual pain scores results

7. References

[1] Drug Information Journal, Vol.29, pp. 1039-1048, 1995. Assessment of Dose Proportionality: Report from the Statisticians in the Pharmaceutical Industry/ Pharmacokinetics UK Joint Working Party.

[2] Brian P. Smith, Francois R. Vandenhende, Karl A. DeSante, Nagy A. Farid, Pamela A. Welch, John T. Callaghan and S. Thomas Forgue. Confidence Interval Criteria for Assessment of Dose Proportionality; Pharmaceutical Research, Vol. 17, No. 10, 2000

8. Examples of tables

Tables

Table 10.1:1 Study completion status

	TreatmentA *(N*= xx*)* *n (%)*	TreatmentB *(N*= xx*)* *n (%)*
Subjects without taking study drug	xxx	xxx
Subjects receiving study drug	xxx	xxx
Study completion status	xxx(xx,x)	xxx(xx,x)
Withdraw from the trial		
Reason A	xxx(xx,x)	xxx(xx,x)
Reason B	xxx(xx,x)	xxx(xx,x)
Reason C	xxx(xx,x)	xxx(xx,x)

N: Number of subjects in each group

n: Number of subjects with effective data

%: N-based percentage

Table 10.2.1 Demographics results

	TreatmentA *(N*= xx*)*	TreatmentB *(N*= xx*)*
Age(years)		
Mean(SD)	xx.x(xx.xx)	xx.x(xx.xx)
Median(CV)	xx(xx.xx)	xx(xx.xx)
(Min, Max)	(xx,xx)	(xx,xx)
Height(cm)		
Mean(SD)	xx.xx(xx.xx)	xx.xx(xx.xx)

	TreatmentA *(N= xx)*	TreatmentB *(N= xx)*
Median(CV)	xx.xx(xx.xx)	xx.xx(xx.xx)
(Min, Max)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Weight(kg)		
Mean(SD)	xx.xx(xx.xx)	xx.xx(xx.xx)
Median(CV)	xx.xx(xx.xx)	xx.xx(xx.xx)
(Min, Max)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
BMI(kg/m^2)		
Mean(SD)	xx.xx(xx.xx)	xx.xx(xx.xx)
Median(CV)	xx.xx(xx.xx)	xx.xx(xx.xx)
(Min, Max)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Gender		
Male	xx(xx.xx%)	xx.xx(xx.xx)
Female	xx(xx.xx%)	xx.xx(xx.xx)

Table 11.3 Descriptive statistical results of plasma concentrations of oxycodone, naloxone and their metabolites

			Subject														
			101	102	103	104	105	106	107	108	109	110	111	112	N	Mean	SD
Treatment	Analyte	Nominal_Time (hr)	conc (ng/mL)														
Treatment A	OXN PR	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12	0.00	0.00
		0.5	49.6	78.6	2.19	18.3	231	10.2	149	0.601	36.5	13.4	111	110	12	67.5	71.2
		1.0	108	147	64.6	246	217	71.2	261	40.8	125	237	180	189	12	157	75.7
		1.5	147	151	132	178	189	98.8	154	107	187	175	147	176	12	153	29.7
		2.0	125	126	140	175	160	119	124	138	193	133	136	141	12	142	22.5
		3.0	129	98.7	106	129	118	114	114	84.9	141	165	120	128	12	121	20.5
		4.0	130	82.5	87.2	106	106	126	106	109	121	139	89.3	106	12	109	17.6
		…															

Table 11.4.1.2:1 Descriptive statistical analysis results (summary) of the PK parameters of oxycodone, naloxone and their metabolites

Analyte	Parameters	Units	Treatment A
OXN PR	AUC0_48hr	hr*mg/L	xx(xx)
	AUC_%Extrap_pred	%	xx (xx)
	AUC0-inf		xx (xx)

Cmax	ng/mL	xx (xx)
Tmax	hr	xx (xx, xx)
Lambada_z	1/hr	xx (xx)
$T_{1/2}$	hr	xx (xx)
…		

Tmax: Median(Min,Max); Other PK parameters Mean (SD)

Table 11.4.1.2:2 Descriptive statistical analysis results (including individual data) of the PK parameters of oxycodone, naloxone and their metabolites

Analyte	**Treatment**	**statistics**	**Lambada_z (1/hr)**	**T1/2 (hr)**	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC0-inf (hr*ng/mL)**	**%AUCextrap (%)**	**AUC0_48hr (hr*mg/L)**
OXN PR	**Treatment A**	**N**	**	**	**	**	**	**	**
		Mean	**	**	**	**	**	**	**
		SD	**	**	**	**	**	**	**
		Min	**	**	**	**	**	**	**
		Median	**	**	**	**	**	**	**
		Max	**	**	**	**	**	**	**
		CV%	**	**	**	**	**	**	**
…									

Table 11.4.1.2:3 Dose proportionality assessment results

Analyte	*Item*	*Confidence Level*	*Point Estimate*	*Confidence Interval*	*Criterion*
OXN PR	AUC0-48h	0.1	xx	(xx, xx)	(0.800,1.250)
	AUC0-inf	0.1	xx	(xx, xx)	(0.800,1.250)
	Cmax	0.1	xx	(xx, xx)	(0.800,1.250)
	…				

Table 12.2.3 Summary on adverse events

Parameter	Treatment A N， N(%)	Treatment B N， N(%)	Total N， N(%)
All AE			
Study drug-related AE*			
Severe AE**			
Study drug-related severe AE			
Serious adverse events (SAE)			
Study drug-related SAE			
AE leading to study termination			
AE given combined treatment			
AE given other treatment			
AE leading to reduced dose of study drug			

*: Positively related, probably related and possibly related are regarded to be correlated with the study drug

**: The severity of AE is SAE

N，N(%)：Nbr of AE, Nbr of Subject(incidence)

Table 12.2.3:1 Table for severity of adverse events and treatment-related frequency

Treatment	*AE Severity*	*Definitely related*	*Probably related*	*Possibly related*	*Possibly unrelated*	*Definitely unrelated*	*Total*
TreatmentA （N=12）n (%)	Mild	**(**)	**(**)	**(**)	**(**)	**(**)	
	Moderate	**(**)	**(**)	**(**)	**(**)	**(**)	
	Severe	**(**)	**(**)	**(**)	**(**)	**(**)	
	。。。						

N: Number of subjects in each group

n: Number of subjects with effective data

%: N-based percentage

Table 12.2.3:2 Table for incidence of adverse events (by SOC and PT)

System organ classification GT	*Standard name of AE PT*	*Treatment A (N=12)*	*Treatment B (N=12)*
Infection and infectious diseases	*Total*	**(**)	**(**)
	Upper respiratory tract infection	**(**)	**(**)
Various types of examinations	*Total*	**(**)	**(**)
	Elevated alanine aminotransferase	**(**)	**(**)
	Elevated blood myoglobin	**(**)	**(**)
	Elevated creatine phosphokinase	**(**)	**(**)
Various types of nervous system diseases	*Total*	**(**)	**(**)
	Head discomfort	**(**)	**(**)
Skin and subcutaneous tissue diseases	*Total*	**(**)	**(**)
	Dermatitis	**(**)	**(**)
	Rash	**(**)	**(**)

System organ classification GT	*Standard name of AE PT*	*Treatment A (N=12)*	*Treatment B (N=12)*
Systemic disease and various administration site reactions	*Total*	**(**)	**(**)
	Fatigue	**(**)	**(**)
	Local reaction	**(**)	**(**)
	Drowsiness	**(**)	**(**)
Kidneys and urinary system diseases	*Total*	**(**)	**(**)
	Frequent micturition	**(**)	**(**)
Gastrointestinal diseases	*Total*	**(**)	**(**)
	Constipation	**(**)	**(**)
	Abdominal pain	**(**)	**(**)
	Diarrhea	**(**)	**(**)
	Oral ulcer	**(**)	**(**)
Blood and lymphatic system diseases	*Total*	**(**)	**(**)
	Neutropenia	**(**)	**(**)
Eye diseases	*Total*	**(**)	**(**)
	Conjunctival hyperemia	**(**)	**(**)

Table 12.2.3:3 Table for frequency analysis of serious adverse events

Treatment	*SAE related to study drug(%)*	*SAE(%)*
**	**	**

* Absence of SAE

Table 12.4.1:1 Descriptive statistical analysis results for haematology

Treatment	*Item*	*Unit*	*ExpDelta|(min)*	*N*	*Mean*	*SD*	*CV(%)*	*Min*	*Median*	*Max*
Treatment A	Item1	U/L	TimePoint1	**	**	**	**	**	**	**
			TimePoint2	**	**	**	**	**	**	**
			…	**	**	**	**	**	**	**
	Item2	U/L	TimePoint1	**	**	**	**	**	**	**

Treatment	*Item*	*Unit*	*ExpDelta|(min)*	*N*	*Mean*	*SD*	*CV(%)*	*Min*	*Median*	*Max*
			TimePoint2	**	**	**	**	**	**	**
			…	**	**	**	**	**	**	**
	Item3	g/L	TimePoint1	**	**	**	**	**	**	**
			TimePoint2	**	**	**	**	**	**	**
			…	**	**	**	**	**	**	**
	Item4	mmol/L	TimePoint1	**	**	**	**	**	**	**
	…		TimePoint2	**	**	**	**	**	**	**
			…	**	**	**	**	**	**	**
			…							

Screening:TimePoint**—TimePoint**;Baseline:TimePoint**—TimePoint**;Treatment:TimePoint**—TimePoint**;

Similar tables are as follows

Table 12.4.1:2 Descriptive statistical analysis results for changes of haematology relative to the baseline

Table 12.4.1:4 Descriptive statistical analysis results for blood chemistry

Table 12.4.1:5 Descriptive statistical analysis results for changes of haematology relative to the baseline

Table 12.5.1:1 Descriptive statistical analysis results for vital signs

Table 12.5.1:2 Descriptive statistical analysis results for changes of vital signs relative to the baseline

Table 12.5.1:3 Descriptive statistical analysis results for 12-lead ECG

Table 12.5.1:4 Descriptive statistical analysis results for changes of 12-lead ECG relative to the baseline

Table 12.4.1:3 Table for frequency of haematology results

Treatment	*Item*	*ExpDelta (min)*	*Normal n(%)*	*Abnormal, without clinical significance n(%)*	*Abnormal, with clinical significance n(%)*
Treatment A	Item 1	TimePoint 1	**(**)	**(**)	**(**)
		TimePoint 2	**(**)	**(**)	**(**)
		…	**(**)	**(**)	**(**)
	Item 2	TimePoint 1	**(**)	**(**)	**(**)
		TimePoint 2	**(**)	**(**)	**(**)
		…	**(**)	**(**)	**(**)

Treatment	*Item*	*ExpDelta (min)*	*Normal n(%)*	*Abnormal, without clinical significance n(%)*	*Abnormal, with clinical significance n(%)*
	Item 3	TimePoint 1	**(**)	**(**)	**(**)
		TimePoint 2	**(**)	**(**)	**(**)
		…	**(**)	**(**)	**(**)
	Item 4	TimePoint 1	**(**)	**(**)	**(**)
	…	TimePoint 2	**(**)	**(**)	**(**)
		…	**(**)	**(**)	**(**)
				…	

Screening:TimePoint**—TimePoint**;Baseline:TimePoint**—TimePoint**;Treatment:TimePoint**—TimePoint**;

Similar tables are as follows

Table 12.4.1:6 Table for frequency of blood chemistry results

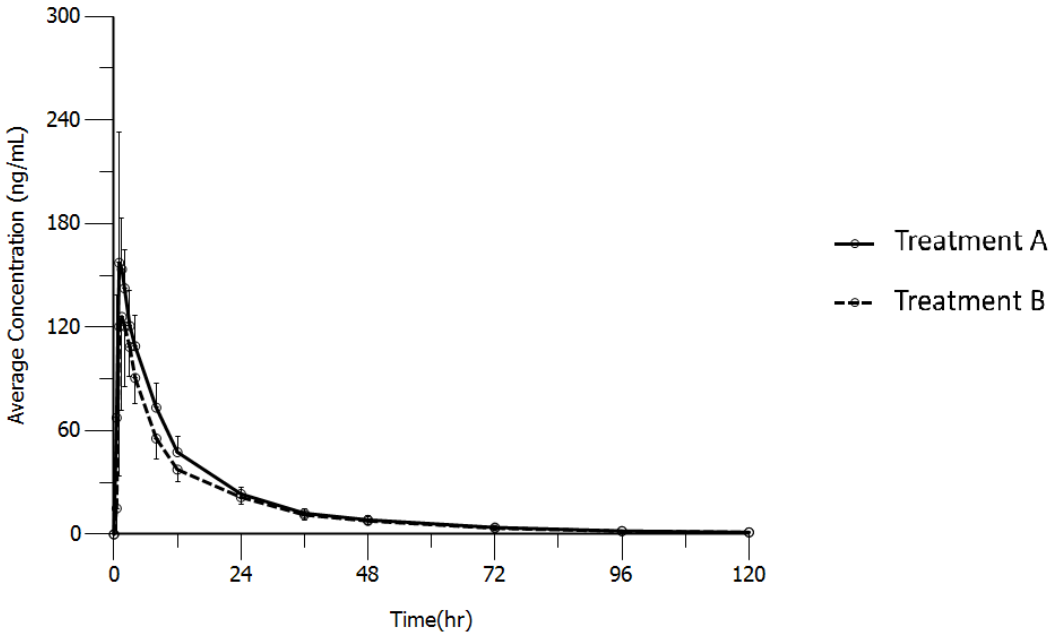
Table 12.4.1:7 Table for frequency of urinalysis results

Table 12.5.1:5 Table for frequency of 12-lead ECG results

Table 12.5.1:6 Table for frequency of physical examination results

Figures

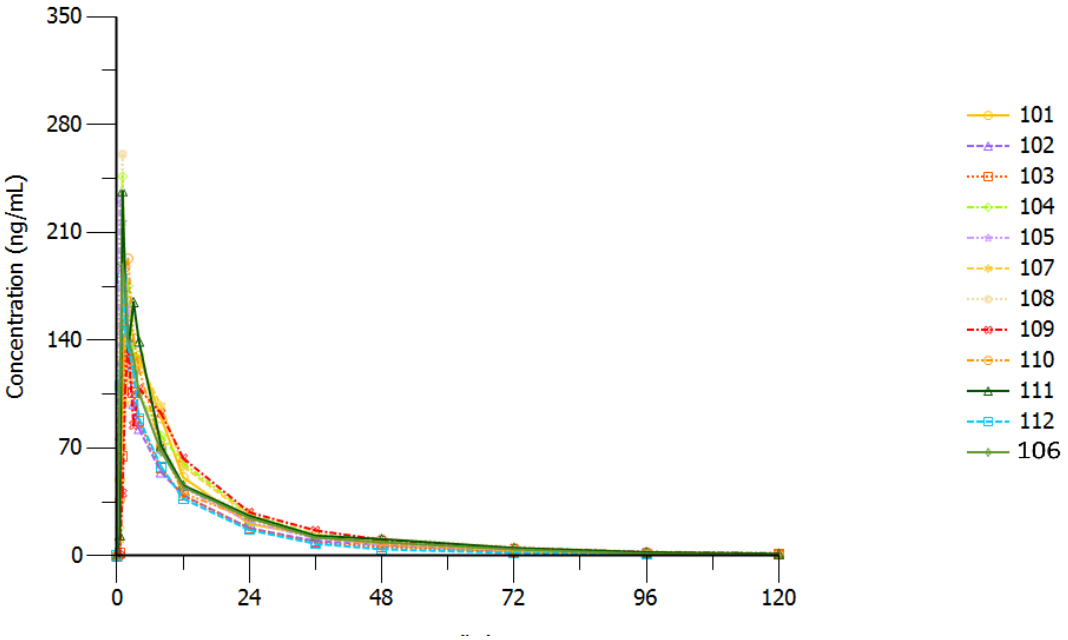
Figure 1.1 Mean plasma drug concentration-time linear curve for oxycodone, naloxone and their metabolites



Similar figures are as follows

Figure 1.2 Mean plasma drug concentration-time semi-logarithmic curve for oxycodone, naloxone and their metabolites

Figure 2.1 Individual plasma drug concentration-time linear curves for oxycodone, naloxone and their metabolites



Similar figures are as follows,

Figure 2.2 Individual plasma drug concentration-time semi-logarithmic curve for oxycodone, naloxone and their metabolites

Listing

Listing11.1.1:1 listing of trial completion status

Subject	*Treatment*	*Completion status*	*Completion date*	*Signature of Investigator (Date)*
1001	*Treatment A*	**	**	**
1002	*Treatment A*	**	**	**
1003	*Treatment A*	**	**	**
1004	*Treatment A*	**	**	**
…				

Listing11.1.1:2 Listing of trial protocol deviation

Treatment	*Occasion*	*Subject*	(PI endorsed) measures taken on protocol deviation	Actual situation of deviation events	Nature of protocol deviation	Time of protocol deviation	Protocol requirements for deviation event-related items
**	**	**	**	**	**	**	**
		**	**	**	**	**	**
...							

Listing11.2.1:1 Listing of demographics

Subject	*Age (Years)*	*Gender*	*Race*	*Height (m)*	*Weight (kg)*	*BMI (kg/m^2)*
**	**	**	**	**	**	**
**	**	**	**	**	**	**
…						

Listing11.3:1 Listing of Concomitant Medication

Treatment	*Occasion*	*Subject*	*Does concomitant medication or treatment occur before the first dose?*	*Drug name*	*Dose unit*	*Indication*	*Dosage for single-dose administration*	*Route of administration*	*Does medication continue at ending of this study?*	*Dosing frequency*	*Starting time*	*Ending time*
**	**	**	**	**	**	**	**	**	**	**	**	**
**	**	**	**	**	**	**	**	**	**	**	**	**
**	**	**	**	**	**	**	**	**	**	**	**	**
…												

Listing11.3:2 Listing of past medical history

Subject	*Preferred Term*	*PT annotations*	*Value*
**	Admissions	*Past history of hospitalization*	**
	Operations	*Past history of surgery/trauma*	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**

Subject	*Preferred Term*	*PT annotations*	*Value*
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
	**	**	**
1002	Admissions	*Past history of hospitalization*	**
	Operations	*Past history of surgery/trauma*	**
	**	**	**
	**	**	**
		…	

Listing11.4 Listing of blood collection

Subject	*Treatment*	*Expected delta-time (hr)*	*Actual Time (hr)*	*BiasTime (hr)*	*Flag*	*status*
**	**	0	**	**	**	**
		0.5	**	**	**	**
		1	**	**	**	**
		1.5	**	**	**	**
		2	**	**	**	**
		…				
	**	0	**	**	**	**
		0.5	**	**	**	**
		1	**	**	**	**
		1.5	**	**	**	**
		2	**	**	**	**
		…				
		…				

Listing12.1:1 Listing of individual medication

Subject	*Occasion*	*Treatment*	*Expected time (min)*	*Actual delta time (min)*	*Admin time (Day and Time)*
**	**	**	**	**	**
**	**	**	**	**	**
**	**	**	**	**	**
**	**	**	**	**	**
**	**	**	**	**	**
…					

Listing12.2.2:1 Listing of adverse events

Treatment	*Occasion*	*SubjectNr*	*PT*	*System organ catalog*	*AE severity*	*AE beginning time*	*AE ending time*	*Whether SAE*	*Relationship between AE and treatment*
**	**	**	**	**	**	**	**	**	**
**	**	**	**	**	**	**	**	**	**
**	**	**	**	**	**	**	**	**	**
**	**	**	**	**	**	**	**	**	**
...									

Listing12.4:1 Listing of laboratory haematology test results

Subject	*Treatment*	*Occasion*	*Time (min)*	*Item*	*Value*	*Notes*
**	**	**	**	LabHaem	**	**
	**	**	**	LabHaem	**	**
	**	**	**	LabHaem	**	**
	**	**	**	LabHaem	**	**

Subject	*Treatment*	*Occasion*	*Time (min)*	*Item*	*Value*	*Notes*
			…			

Similar listings are as follows,

Listing12.4:3 Listing of laboratory blood biochemistry test results

Listing12.4:5 Listing of laboratory urinalysis test results

Listing12.5:2 Listing of individual 12-lead ECG determination results

Listing12.5:4 Listing of individual physical examination results

Listing12.4:2 Listing of laboratory haematology test results

Subject	*Treatment*	*Occasion*	*Time (min)*	*Item*	*Unit*	*Value*	*Lower Limit*	*Upper Limit*	*Notes*	*Judge*
**	**	**	**	Item1	**	**	**	**	**	**
				Item2	**	**	**	**	**	**
				Item3	**	**	**	**	**	**
				…						

Similar listings are as follows,

Listing12.4:4 Listing of laboratory blood biochemistry examination results

Listing12.5:1 Listing of individual vital signs results

Listing12.5:3 Listing of individual 12-lead ECG examination results