Statistical Analysis Plan

An Open-label, Single Dose, Randomized, Cross-over Study to Determine the Fasted State pharmacokinetics of Oxycodone from Oxycodone Tamper Resistant (OTR) Tablet 10 mg and OXYCONTIN® Tablet 10 mg in Chinese Subjects with Chronic Pain

Sponsor:	MundiPharma (China) Pharmaceutical Co. Ltd
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Version History

Version	Date	Reason for Change
0.1	2017-05-04	First version
0.2	2017-06-23	1. Added PK Sampling deviation time window 2. Medical history and current medical conditions definition added 3. Added for detail PK parameter examined criteria
0.3	2017-08-02	1. Updated sample SAS codes used for BE analysis 2. TOST procedure modified as per D J Schuirmann, Vol. 15, No. 6, 1987
0.4	2017-11-21	1. Added the definition of significant adverse events. 2. Deleted AE figures 3. Fisher's exact replaced by McNemar test for Adverse Events and Exposure tables
0.5	2017-12-06	1. Updated wording of PK population definition and bioequivalence analysis population
0.6	2017-12-30	1. Added additional criteria to protocol deviation 2. Updated definition of prior and concomitant to be consistent with protocol.
0.7	2018-01-16	1. Updated signature page
1.0	2018-01-30	Finalization

Table of Content

1. Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the report and analyses of data collected under MundiPharma (China) Pharmaceutical Co. Ltd. for ONF16-CN-101 study. This SAP should be read in conjunction with the study protocol and electronic case report form (CRF). This version of the plan has been developed using the protocol dated May 16, 2016 and eCRF version 2.0 dated Feb 7, 2017. Any further changes to the protocol or eCRF may necessitate updates to the SAP. A final version of this SAP will be issued for sponsor approval prior to database lock.

2. Study Objectives

This open-label, single dose, randomised, cross-over study aims to determine the Fasted-state pharmacokinetics (PK) of oxycodone from OTR tablet 10 mg and OXYCONTIN tablet 10 mg in Chinese subjects with chronic pain.

Primary objective is to confirm the BE of OTR tablet 10 mg and OXYCONTIN tablet 10 mg in a Fasted state.

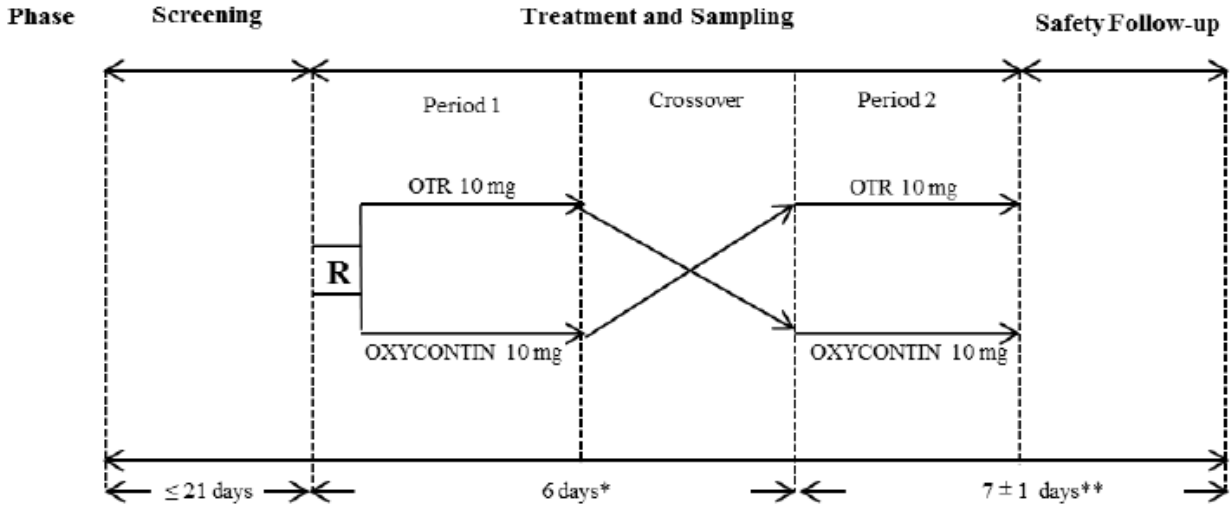
Secondary objective is to assess the safety of OTR tablet 10 mg and OXYCONTIN tablet 10 mg, when given to Chinese subjects with chronic pain in a Fasted state.

3. Study Design

Study Design	Open-label, single dose, randomised, cross-over study
Study Population	Subjects with histories of chronic pain
Geographic Regions	1-2 sites in China
Investigational Medical Product(s)	**Test Group**: OTR tablet 10 mg. Oxycodone Hydrochloride Controlled-release Tablets containing 10 mg oxycodone hydrochloride, manufactured by Purdue Pharma L.P., U.S. The OTR tablet 10 mg will be administered orally once on the morning of Day 1 of each period, in a Fasted state. **Reference Group**: OXYCONTIN tablet 10 mg. Oxycodone Hydrochloride Prolonged-release (PR) Tablets containing 10 mg oxycodone hydrochloride manufactured by Bard Pharmaceuticals Ltd., U.K. The OXYCONTIN tablet 10 mg will be administered orally once on the morning of Day 1 of each period, in a Fasted state.
Treatment and Study Duration	Screening should be performed within 21 days before the randomization. The randomized subjects will be administered the test and reference treatments in a randomized order. There will be two study periods (Period 1 and Period 2), with a minimum of 6 days washout between the two doses. Subjects will cross over to receive the alternative study drug upon completing Period 1. PK blood sampling will continue for up to 32 hours after dosing with the study treatment in each period. Subjects will stay in the unit for safety monitoring until 72 hours after each dosing of the study drug in each period. Subjects will have a safety follow-up visit via telephone at 7±1 days after the last dose of study drug in the case of completion or early discontinuation from the study. Total duration of the study is up to 35 days.
Planned Number of Subjects	A total of 24 subjects with histories of chronic pain will be randomized to receive the study drug to achieve 18 subjects (9 subjects per treatment sequence) to complete the study with valid pharmacokinetic (PK) data.
Randomisation and Blinding	Subjects will be randomized into either the treatment sequence of OTR-OXYXONTIN or OXYCONTIN-OTR group in a 1:1 ratio at Day -1 of Period 1. This is an open-label study, and thus blinding not applicable.
Other Features (as	NA

appropriate)	

Figure 1: Study Flowchart



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

Protocol Amendment Version History

Version	Date	Reason for Change
1.0	2016-05-16	NA

3.1 Sample Size Consideration

The study is designed to have a power of ≥95% to demonstrate a bioequivalence (BE) (AUCt and Cmax) of OTR tablet 10 mg, in terms of oxycodone, with OXYCONTIN tablet 10 mg in a fasted state.

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

A total of 24 subjects was randomised to receive study drug (12 subjects per treatment sequence) with the aim that 18 subjects will provide valid PK data (9 subjects per treatment sequence) and PK parameters (Cmax and AUCt). This will provide ≥ 95% power to show BE simultaneously in both parameters, Cmax and AUCt, between test and reference formulation, assuming a true ratio of 1, a within standard deviation (SD) of the period differences of 0.24 on the log scale for AUCt and 0.20 on the log scale for Cmax, both PK parameters are not anti-correlated, and 90% CI for the ratios of the population means within the BE limits of 80.00% and 125.00%. The within SD of the period differences was based on Purdue Pharma BE study OTR1003 in healthy volunteers taking oxycodone.

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

3.2 Randomization

Twenty-four subjects will be enrolled and randomly assigned to two sequences of treatments (receiving OTR 10 mg before OXYCONTIN 10 mg or receiving OXYCONTIN 10 mg before OTR 10 mg) in a 1:1 sequence ratio. Every 4 subjects will be grouped as a block. Subjects in every block will be randomized with a 1:1 sequence ratio into receiving OTR 10mg before OXYCONTIN 10mg or into receiving OXYCONTIN 10mg before receiving OTR 10mg.

4. Study Variables

4.1 Pharmacokinetic Parameters

- Maximum concentration（Cmax）
- Area under the concentration-time curve from time 0 to last quantifiable concentration (AUCt)
- AUC from time 0 to infinity (AUCINF)
- Terminal rate constant（LambdaZ）
- Time to maximum concentration（tmax）
- Terminal half-life（t1/2z）

4.2 Safety Variables

- Adverse events (AEs), Serious adverse events (SAEs)
- Laboratory values
- Vital signs
- Electrocardiogram (ECG)

5. Definitions

Baseline is defined as last value prior to first dose of investigational medicinal product (IMP).

Change from baseline will be calculated as follows:

Change from baseline = post-baseline assessment value - the baseline assessment value.

Age (in years) is defined as the date of informed consent relative to the date of birth, will be auto-calculated during the eCRF collection.

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = (Weight (kg))/〖Height(m)〗^2

Duration will be calculated as follows:

Duration = last observation date – first observation date +1

Study Day and Treatment Day are defined as follows:

Study date:

If study date < randomisation date then study day = study date – randomisation date

If study date >= randomisation date then study day = study date – randomisation date + 1

Treatment Day = treatment date – date of first dose of IMP +1

6. Analysis Set

Enrolled (ENR) Population

The enrolled population is defined as all subjects who signed inform consent form (ICF).

Intention to treat (ITT) Population

The ITT population is defined as all randomised subjects.

Safety Population

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

PK Population

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

Exclusions from each population will be agreed at the Data Review Meeting (DRM) meeting.

Subjects in the safety population will be analysed ‘as treated’. For all other populations, subjects will be analysed ‘as randomised’, unless stated otherwise.

7. Interim Analysis

No interim analysis is planned.

8. Data Review

Final data for analysis should always be 100% cleaned prior to receipt by Clinical Programming. The purpose of this section is to indicate the history of the data and the process used to ensure that the data are acceptable for statistical analysis prior to database lock

8.1 Data Handling and Transfer

Refer to Data Management Plan.

8.2 Data Screening

Beyond the data screening built into the Data Management Plan, the programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into

Statistical Analysis Software (SAS) logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run (if included in the study contract) on clean subjects and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the sponsor in a data review meeting (DRM) to identify any final data issues and seek corrections prior to database lock. The statistician and the sponsor must approve database lock.

9. Statistical Methods

9.1 General Consideration

9.1.1 General Guideline

In general, all the tables are summarised by treatment sequence or treatment where appropriate. Continuous data will be summarised using the following descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarised as the number and percentage of subjects in each category (including the category ‘missing’ if applicable).

All data will be listed. The data will be sorted by treatment sequence, subject number and date of assessment (if applicable).

9.1.2 Missing Data or Missing Date

9.1.2.1 Handling of Missing Dates

In general, for the subject data listings, no imputation of missing or incomplete dates will be applied.

Partial Dates for Date of Birth

The following conventions will be used for imputing partial dates:

- If only the day is missing, the 15th will be used to replace the missing day.
- If both the day and the month are missing, the 1st July will be used to replace the missing day and month.

Partial Dates for Adverse Events and Previous/Concomitant Medications

For completely missing AE (or medication) start dates, the event will be considered as treatment emergent for both period 1 and period 2 (for AEs) or concomitant (for medications) unless the end date rules out the possibility.

For partial missing start dates (month and/or year is missing), AE (or medication) will be assigned the period with which the available start and stop dates are consistent. If the partial missing AE (or medication) start dates do not allow for identification of ‘treatment-emergent’ (or ‘period 1/period 2 treatment-emergent’ or ‘concomitant’) from the month and/or year alone, a conservative approach will be taken to ensure that these AEs (or medications) are defined as treatment emergent for period 1, period 2, or both period 1 and period 2 (or as concomitant) unless the end date rules out the possibility.

9.1.2.2 Handling of Missing Values

No missing data will be imputed.

9.1.2.3 Assessment Windows

According to protocol section 10.1, the study visits are scheduled at the exact day during the treatment period, and just allow ±1 day window for follow -up visit.

No assessment windows will be slotted for this study. In general, only data recorded at the nominal visit will be presented for by-visit summaries, data will be assigned using the visit numbers as per the eCRF, and baseline visit will be the last non-missing results prior to IMP at Period 1.

For shift tables (change from baseline to the worst/end of study), a conservative approach will be used where the worst/latest post-baseline result including unscheduled visits will be selected.

All data will be listed.

9.1.3 Software Version

All analyses will be conducted using SAS version 9.4.

9.2 Disposition

The number and percentage of subjects who were screened and randomized will be presented for ENR, also the number and percentage of subjects having failed screening will be presented along with a summary of the primary reason of screening failure. For the subjects who were randomised, summaries will be presented for the number and percentage of subjects who randomised, completed the study, and withdrew early from the study by corresponding reasons for withdrawal by treatment sequence for ITT.

All disposition information will be listed.

9.3 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics are based on ITT.

9.3.1 Demographics

Subject demographics and baseline characteristics will be summarized by treatment sequence for the ITT with descriptive statistics. Continuous variables will use Wilcoxon rank sum test method to estimate the difference between two treatment sequences; Categorical variables will use Fisher-exact method. The results of these tests will be provided including p-value for descriptive purposes and will not be used as a formal basis to determine the factors to be included in statistical models. Since this is a crossover study for BE analysis, any baseline imbalances of factors between treatment sequences will not affect the results in conclusion. Additional analyses may be performed to adjust these imbalance baseline differences as an ad-hoc analysis after database lock.

The following demographics and baseline characteristics will be summarised appropriately for the study:

- Age (years)
- Gender – Female, Male
- Ethnicity – Han, Other
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Numeric Rating Scale Score: the average pain over the last 24 hours

All demographic and baseline characteristics will be listed.

9.3.2 Protocol Deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria if subject successfully passed screening and protocol requirements and will be divided into major protocol deviations and minor protocol deviations. Major protocol deviations are those that are considered to have a significant effect on the BE analyses and hence would exclude the subject from the BE analyses. Minor protocol deviations are those not considered to significantly affect the BE analyses and hence do not warrant subjects' exclusion.

The following criteria might be considered as major protocol deviations:

(1) Failure to comply with the inclusion or exclusion criteria

(2) Received incorrect treatment (i.e. actual treatment taken differs from the randomised treatment scheduled)

(3) Received study prohibited concomitant drugs

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

(5) Failure to comply with study restrictions, including food and beverages restrictions and Alcohol, Caffeine, and Smoking Restrictions.

The evaluable subjects set must be finalized at the DRM (or earlier), prior to database lock.

The number and percentage of subjects with protocol deviations (major/minor) will be summarised by protocol deviation category for each treatment sequence and overall based on the ITT.

All protocol deviations will be listed. Listings of food and beverages restrictions and Alcohol, Caffeine, and Smoking Restrictions will be presented respectively.

9.3.3 Medical History and Current Medical Conditions

Medical history and current medical conditions will be defined using the stop date recorded, relative to the date of V1-Screening. A medical history will be defined as any medical condition resolved up to, but not including the date of V1-Screening. A current medical condition will be defined as any condition going at the date of V1-Screening. Medical history and current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 19.1,

The number and percentage of subjects with medical history/current medical conditions will be summarised by system organ class (SOC) and preferred term (PT) for each treatment sequence and overall based on the ITT.

All medical history and current medical conditions will be listed.

9.3.4 Prior and Concurrent Therapies

Therapies will include medication and non-pharmacological therapies.

A prior therapy will be defined as any therapy taken up to, but not including the informed consent date. A concomitant therapy will be defined as any therapy either ongoing at the date of informed consent or with an onset date time on or after informed consent to the completion of the study. Medications will be assigned an 11-digit code using the World Health Organisation Drug Dictionary Enhanced (WHO-DDE) drug codes of the most recent version (WHO-DD June 2016), and will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Non-pharmacological therapies will be coded using MedDRA version 19.1.

The number and percentage of subjects taking prior and concomitant medications will be summarised by ATC anatomical class (ATC level 1), pharmacological class(ATC level 3), pharmacological sub-class(ATC level 4), and preferred term for each treatment sequence and overall based on the ITT.

A listing of prior and concomitant medications will be provided. A listing of non-pharmacological therapies will also be provided.

9.4 Pharmacokinetic Analysis and Bioequivalence Analysis

PK analysis will be performed on the PK population.

9.4.1 Drug Concentration Measurements and Analysis

Plasma concentration for analyte oxycodone will be summarised descriptively by nominal time-point and treatment as continuous data (i.e. n, mean, standard deviation, standard error, median, minimum, and maximum) for subjects in the PK population. Concentrations that are below the lower limit of quantitation will be assigned a value of 0 for the purposes of computing descriptive statistics.

The following PK sampling window will be used to identify any significant sampling deviation, and significant deviations will be discussed at the DRM.

Table 1. PK Sampling deviation time window

Planned PK sampling time	Sampling deviation without significance
0 h (predose)	Within 30 min before administration
> 0 h and ≤ 1 h	±1 min

> 1 h and ⩽ 4 h	±2 min
> 4 h and ⩽ 8 h	±5 min
> 8 h and ≤24 h	±10 min
> 24 h	±20 min

Additionally, plasma concentrations for analyte oxycodone will be presented graphically in the following way using both a linear and log linear scales.

- The mean plasma concentration data of each treatment will be plotted over time
- For each treatment, the mean and individual plasma concentration data for each subject will be plotted over time
- For each subject, the individual plasma concentration data for each treatment will be plotted over time

All plasma concentrations will be listed for Safety population.

9.4.2 Pharmacokinetic Analysis

PK parameters for oxycodone will be derived using non-compartmental methods with WinNonlin software (Pharsight Corporation, v6.3 or above). The following PK parameters will be calculated for each subject.

- Cmax：Maximum concentration (ng/mL) obtained directly from the observed concentration versus time data for all analytes.
- AUCt：Area under the concentration-time curve from time 0 (immediately predose on Day 1) to last quantifiable concentration (h*ng/mL), calculated by linear up/log down trapezoidal summation.
- AUCINF：AUC from time 0 (immediately predose on Day 1) to infinity (h*ng/mL), calculated by linear up/log down trapezoidal summation.
- LambdaZ：Apparent terminal rate constant (1/h) estimated by log-linear least-squares regression of the terminal part of the concentration-time curve for all analytes (at least 3 timepoints to the last quantifiable concentration at this study).
- t1/2z：Apparent terminal half-life (h), determined as Ln2/LambdaZ.
- tmax：Time to maximum concentration (h) obtained directly from the observed concentration versus time data using actual draw times.
- R2: Coefficient of determination from the linear regression used to determine LambdaZ.

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, tmax, LambdaZ, t1/2Z, and R2) for analyte oxycodone will be summarised descriptively by treatment for subjects in the PK population using the following descriptive statistics: n, mean, standard deviation, standard error, median, minimum, and maximum. For AUCt, AUCINF, and Cmax, the geometric mean, the standard deviation of geometric mean, and the geometric coefficient of variation (CV) will also be presented. Non-quantifiable PK parameter values below the limit of quantification (BLQ) will be set to equal zero for the analysis and will be set to missing for log-transformed data.

9.4.3 Bioequivalence Analysis

Only subjects who provide valid PK data for both the test and reference treatment will be included in the BE analysis. Subject who have major protocol deviations must be excluded from the BE analysis, when agreed on the DRM.

Primary Analysis

Log transformed data for oxycodone AUCt, and Cmax will be analysed using an analysis of variance (ANOVA) model, with fixed terms for treatment, period, treatment sequence and subject within sequence. Treatment population geometric means will be estimated from the exponential of the treatment Least Square (LS) means. Ratios of treatment population geometric means will be estimated by exponentiating the difference (test-reference) between treatment LS means, and 90% confidence intervals (CI) for the ratios will be calculated. For each comparison of interest, the exponentiated LS Mean and ratio will be presented along with its 90% CI for the AUCt, and Cmax parameters. Also, intra-subject variablity will be presented for each parameter per China Food and Drug Administration (CFDA) requirement. BE of test and reference will be confirmed for a PK parameter of analyte oxycodone if the 90% CI for the ratio (test/reference) falls completely within the BE acceptance range of 80.00% to 125.00%. BE of test and reference will be confirmed in all if it can be confirmed with AUCt and Cmax.

The sample SAS code as below

```
proc mixed data=xxx;
        class sequence subject period treat;
        model Y = sequence period treat subject(sequence);
        estimate 'Study - Ref' treat 1 -1 / cl alpha=0.1;
        lsmeans treat;
 run;
```

Where Y denotes the response measure (e.g., log(AUCt), log(Cmax)) being analyzed.

In additional, with the Mean Squared Error (MSE) estimated from ANOVA model, Schuirmann's Two One-Sided Test (TOST) will be performed for Cmax and AUCt at the alpha of 0.05 level (Donald J. Schuirmann, 1987). The TOST Procedure, as its name implies, consists of decomposing the interval hypotheses H_o and H_1 into two sets of one-sided hypotheses.

$$H_{01}: \quad \mu_T - \mu_R \leq \theta_1$$

$$H_{11}: \quad \mu_T - \mu_R > \theta_1$$

and

$$H_{02}: \quad \mu_T - \mu_R \geq \theta_2$$

$$H_{12}: \quad \mu_T - \mu_R < \theta_2$$

The two sets of one-sided hypotheses can be tested with ordinary one-sided t tests, where $\bar{X}_T$-$\bar{X}_R$ is the difference between Cmax (or AUCt) of products T and R in the log scale, the limits θ_1 and θ_2 ($\theta_1 < \theta_2$) are the pre-defined equivalence interval(ln(0.8) and ln(1.25)), *s* is the square root of the error mean square ($\sqrt{}$MSE) from the crossover design analysis of variance, $t_{1-\alpha(\nu)}$ is the point that isolates probability α in the upper tail of the Student's t distribution with ν degrees of freedom, where ν is the number of degrees of freedom associated with the error mean square.

$$t_1 = \frac{(\bar{X}_T - \bar{X}_R) - \theta_1}{s\sqrt{2/n}} \geq t_{1-\alpha(\nu)} \quad \text{and} \quad t_2 = \frac{\theta_2 - (\bar{X}_T - \bar{X}_R)}{s\sqrt{2/n}} \geq t_{1-\alpha(\nu)}$$

Example SAS code can be found in Appendix 2.

Secondary Analysis:

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

For tmax, with orginial value, nonparametric method (Hodges-Lehmann's median analysis) (Lingling Han, 2015) will be used to determine the difference between two treatments (study-reference) and its 90% asymptotic CI.

BE Analysis Considerations:

The statistical summaries and analyses will exclude PK parameters from the relevant subject period for which any of the following criteria apply: vomiting within 12 hours after dosing, incorrect dosing, incomplete plasma profile which cannot adequately detail the parameter, pre-dose concentration>5% of Cmax.

Pre-dose concentration>5% of Cmax and AUC % Extrapolation>20% will be summarised for PK population.

In addition, the PK parameters AUCINF, t1/2Z and LambdaZ will be examined to see if they are evaluable based on the following criteria:

- Any R2<0.85 will be flagged out in the corresponding listing. If R2 associated with the LambdaZ estimate for any subject is <0.85 then the subject's LambdaZ, and corresponding t1/2Z and AUCINF parameter values for that subject's period will be excluded to perform the sensitivity analysis for the primary BE analysis.

- If a single non-quantifiable (NQ) value occurs between measurable concentrations in a profile, the NQ will be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots.

These exclusions will be identified in the listings of the PK data.

The validity of PK data will be discussed further and evaluated during the data review meeting at the end of the study. In accordance with BE guidelines, only subjects that provide valid PK data for both the test and reference treatments will be included in the statistical analysis.

9.5 Safety Analysis

The summary of safety data will be based on Safety population. Safety data that will be summarised includes exposure, adverse events, clinical laboratory assessments, vital signs and ECGs. All safety analyses will be based on the safety population and will be summarised by treatment unless otherwise stated. Subjects will be assigned to the treatment according to the actual treatment they have received ("as treated").

9.5.1 Treatment Compliance and Exposure

IMP will be summarised as treatment exposure. Treatment exposure will be defined and calculated as the dose of IMP taken by subjects. Treatment exposure will be summarised by treatment. Regarding naltrexone dosing, exposure will be summarised by treatment for each nominal time point. Summary statistics of dosing exposure includes n, mean, minimum and maximum.

Treatment compliance is defined as the subjects who received 10mg study/reference drug at the scheduled visit per protocol. Treatment compliance will be summarized by the number and proportion of subjects who received treatments in compliance with the study protocol in each treatment of the safety population, the difference between the treatments will be tested using Fisher-exact method. P-value will be provided for descriptive purpose. Since it is a crossover study and only subjects that provide valid PK data for both the test and reference treatments will be included in BE analysis, any imbalance between treatment exposures will not affect the results in BE conclusion.

9.5.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 19.1) to give a System Organ Class (SOC) and Preferred Term (PT) for each adverse event (AE).

A treatment emergent AE (TEAE) will be defined as follows:

A TEAE is defined as any AE with an onset datetime 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.

A TEAE will be assigned to treatment period 1 IMP if it had an onset datetime on or after the first dose of IMP in treatment period 1, up to the treatment period 2 IMP given. A TEAE will be assigned to treatment period 2 IMP if it had an onset datetime on or after the first dose of IMP in treatment period 2, up to and including the day of the follow-up visit. If an AE had an onset datetime on or after the first dose of IMP in treatment period 1, and it was ongoing at the start of period 2 and it did not worsen in severity, it will be assigned to treatment period 1.

TEAEs/SAEs collected from dosing of IMP till the last visit will be will be summarised. All AEs (including AEs with an onset data before IMP dosing) will be listed for subjects in the safety population.

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

Overall Summary of Adverse Events

An overall summary of AEs will be presented showing the number and percentage of subjects reporting at least one of the following:

- Any AE
- Any TEAE
- Any related TEAE
- Any severe TEAE
- Any related severe TEAE
- Any serious TEAE
- Any related serious TEAE
- Any significant AE, which is defined as AEs leading to death, leading to withdrawal from study, requiring treatment given, leading to dose reduction, leading to dose interruption and leading to dose discontinuation
  - Any TEAE leading to death
  - Any death because of a related serious TEAE
  - Any TEAE leading to discontinuation from study
  - Any TEAE requiring additional therapy
  - Any TEAE leading to dose reduction
  - Any TEAE leading to dose interruption
  - Any TEAE leading to dose discontinuation

Additionally, the number of reported AEs, reported TEAEs, related TEAEs, severe TEAEs, related severe TEAEs, serious TEAEs, related serious TEAEs and significant AEs will also be presented. The difference between the treatments will be tested using McNemar test.

Analyses of Treatment Emergent Adverse Events

The number and percentage of subjects reporting TEAEs will be summarized by Preferred Term (PT) nested within System Organ Class (SOC). If a System Organ Class (SOC) / Preferred Term (PT) is reported more than once for a subject, the subject will only be counted once for this System Organ Class (SOC) / Preferred Term (PT).

All AE summary tables will be sorted by System Organ Class (SOC) and Preferred Term (PT) within System Organ Class (SOC). In addition, the number of reported TEAEs will be summarized in the same manner.

Moreover, the number and percentage of subjects reporting the most frequent TEAEs (Preferred Term ≥ 10% in any treatment) for each treatment period will be summarised by System Organ Class (SOC) and Preferred Term (PT).

TEAE by Severity

The number and percentage of subjects with TEAEs will be summarised by worst severity (mild, moderate, and severe) by Preferred Term (PT) nested within System Organ Class (SOC). Worst severity will be counted if an AE is reported more than once by the same subject for this System Organ Class (SOC) / Preferred Term (PT).

TEAE by Relationship

The number and percentage of subjects with TEAEs will be summarised by relationship to IMP (related and not related) by Preferred Term (PT) nested within System Organ Class (SOC). The highest relationship to IMP will be counted if an AE is reported more than once by the same subject for this System Organ Class (SOC) / Preferred Term (PT).

Deaths, Serious Adverse Events and Significant Adverse Events

The number and percentage of subjects

- with TEAEs leading to death,
- with any Serious TEAEs,
- with any severe TEAEs,
- with any TEAE leading to discontinuation from the study
- with any significant AEs

will be summarised by Preferred Term (PT) nested within System Organ Class (SOC).

AE Listings

The AE dictionary will be listed, presenting the MedDRA system organ class, MedDRA preferred term and investigator terms.

All AEs for enrolled population, AEs leading to death, SAEs, severe AEs, significant AEs and AEs leading to discontinuation from study will be listed. All death information will be listed too.

9.5.3 Laboratory Data

Clinical laboratory data to be summarised includes haematology, blood chemistry, and urinalysis.

Haematology: red blood cells (RBC), haemoglobin, haematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)

Blood Chemistry:

Electrolytes: sodium, potassium, chloride, bicarbonate (HCO_3^-)

Liver function	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin
Renal function	blood urea nitrogen, creatinine
Other	glucose, calcium, albumin, cholesterol, triglycerides, phosphorus (inorganic phosphate), lactate dehydrogenase (LDH), total protein, globulin, uric acid
Urinalysis:	pH, protein, glucose, ketone, occult blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals, specific gravity

Clinical laboratory results recorded at Baseline and V3-Period 2 Day 4 and change from baseline to V3-Period 2 Day 4 will be summarised as continuous data for each parameter by treatment sequence. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

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 to evaluate categorical changes from baseline to end of study value with respect to reference range values (low, normal, high) for each parameter by treatment sequence. The end of study value is defined as the latest value assessed for the subject in the study.

Clinical laboratory values after first dose of IMP will be evaluated for markedly abnormal values. Table 1 presents the criteria (i.e. upper limit, lower limit criteria for each laboratory parameter) that will be used to identify subjects with markedly abnormal laboratory values.

Table 2. Laboratory Ranges Used to Identify Markedly Abnormal Laboratory Values

Laboratory Parameter	**Lower Limit**	**Upper Limit**
Haematology		
Haemoglobin	Male<11 g/dL (110 g/L)	Male>17.5 g/dL (175 g/L)
	Female<10 g/dL (100 g/L)	Female>16.5 g/dL (165 g/L)
Platelets	$<70.0 \times 10^9$/L	$>400 \times 10^9$/L
Leukocytes	$<3.5 \times 10^9$/L	$>10.5 \times 10^9$/L
Lymphocytes	$<1.2 \times 10^9$/L	$>4.5 \times 10^9$/L
Neutrophils	$<2.0 \times 10^9$/L	$>7 \times 10^9$/L
Clinical Chemistry		
Electrolytes		
Sodium (Na^+)	<130 mmol/L	>150 mmol/L
Potassium (K^+)	<3.2 mmol/L	>5.7 mmol/L
Bicarbonate (HCO3-)	≤21.4 mmol/L	>27.3 mmol/L
Liver Function Tests		
Alkaline phosphatase	——	>3 × ULN
AST	——	>3 × ULN
ALT	——	>3 × ULN
GGT (gamma glutamyl trans peptidase, GGTP)	——	>3 × ULN

Total bilirubin	——	>1.5 × ULN
Renal Function Tests		
Creatinine	——	>1.5 × ULN
Other Chemistry		
Calcium	<2.0 mmol/L	>3.0 mmol/L
Phosphorous (inorganic phosphate)	<0.8 mmol/L	—
Glucose	<3.2 mmol/L	>7.0 mmol/L
Uric acid	Male <180 μmol/L Female <120 μmol/L	Male >440 μmol/L Female >320 μmol/L
Cholesterol	<2.3 mmol/L	>6.0 mmol/L
Triglycerides	<0.3 mmol/L	>2.5 mmol/L
Albumin	<3.2 g/dL	>5.5 g/dL

Note: There are no markedly abnormal ranges identified for urinalysis.

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

All clinical laboratory data will also be presented in the data listings, abnormal clinical laboratory values and markedly abnormal values will be flagged in the listing.

9.5.4 Vital Signs

Vital sign parameters to be summarised include systolic blood pressure, diastolic blood pressure, respiration rate, axillary temperature, and pulse rate and will be assessed at the scheduled time-points at V1, V2-Period 1, and V3-Period 2.

Vital sign variables at each visit, and its change from baseline to each test will be summarised as continuous data using descriptive summary statistics for each parameter by treatment sequence.

Vital sign values for each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. The values will be summarised using shift tables to evaluate categorical changes from baseline to end of study value with respect to reference range values (low than, within, higher than) for each parameter by treatment sequence. The end of study value is defined as the latest value assessed for the subject in the study.

Table 3. Normal Ranges for Vital Signs

Parameter	**Range**
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	60-90 mmHg
Pulse rate	60-100 bpm
Respiration rate	12-20 breaths per minute
Temperature (where applicable)	36 – 37.5 ℃

Vital sign values after first dose of IMP will be evaluated for clinically notable abnormalities. The number and percentage of subjects reporting clinically notable vital sign abnormalities will be summarised for each parameter

by time-point and treatment sequence. Each subject can be counted once in the parameter high and the parameter low categories per time-point, as applicable.

Table 4. Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

Vital Sign Parameter	Criteria	Value	Change From Baseline[a]
Systolic blood pressure	High	≥155 mmHg	Increase of ≥20 mmHg
	Low	<80 mmHg	Decrease of ≥20 mmHg
Diastolic blood pressure	High	≥95 mmHg	Increase of ≥15 mmHg
	Low	≤50 mmHg	Decrease of ≥15 mmHg
Pulse rate	High	≥120 bpm	Increase of ≥15 bpm
	Low	<50 bpm	Decrease of ≥15 bpm
Respiration rate	High	>24 breaths/minute	-
	Low	<8 breaths/minute	-
Axillary temperature	High	>38℃	-
	Low	<36℃	
*Both value and change from baseline criteria must be met to qualify as a clinically notable vital sign abnormality.			

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

All vital sign data will also be presented in the data listings. Abnormal vital signs values and clinically relevant vital sign abnormalities will be flagged in the listing.

9.5.5 ECG

ECG will be recorded at Baseline and V3-Period 2 Day 4.

ECG will be judged by the investigator as clinically significant (yes/no). The number and percentage of subjects with worst post-baseline findings will be summarised by treatment sequence. The worst post-baseline finding refer to the worst evaluation result observed post-baseline including unscheduled visits, with a severity order of abnormal, clinical significant > abnormal, not clinical significant > normal. This will include a summary of frequency counts for the number of subjects who had significant changes from baseline, with respect to those who had no significant findings at baseline to significant findings post-baseline.

The description of the clinically significant ECG findings will be listed.

9.5.6 Physical Examinations

All phyical examination results will be listed.

9.5.7 Other Observations Related to Safety

The following observations will be provided for listing only;

- Allergy history
- β-HCG test
- Urine Drug test
- Alcohol test

10. Validation

To ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

11. Reference

Donald J. Schuirmann, A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability, *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 15, No. 6, 1987

Lingling Han, Calculating the point estimate and confidence interval of Hodges-Lehmann's median using SAS® software. ST-154

Appendix 1 List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutical Chemical
BE	Bioequivalence
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CFDA	China Food and Drug Administration
CI	Confidence Interval
CV	Coefficient of Variation
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
LLN	Lower Limit of Normal
LNH	Low, Normal, High
LS	Least Squares
MedDRA™	Medical Dictionary for Regulatory Activities
MSE	Mean Square Error
NA	Not Applicable
NQ	Non Quantifiable
PK	Pharmacokinetic
PT	Preferred Term
RAS	Random Allocation Schedule
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, and Listings
TOST	Two One-Sided Test
ULN	Upper Limit of Normal
ULQ	Upper the Limit of Quantification
WHO-DD	World Health Organisation Drug Dictionary

Appendix 2 TOST Example SAS code

ANOVA TOST.docx