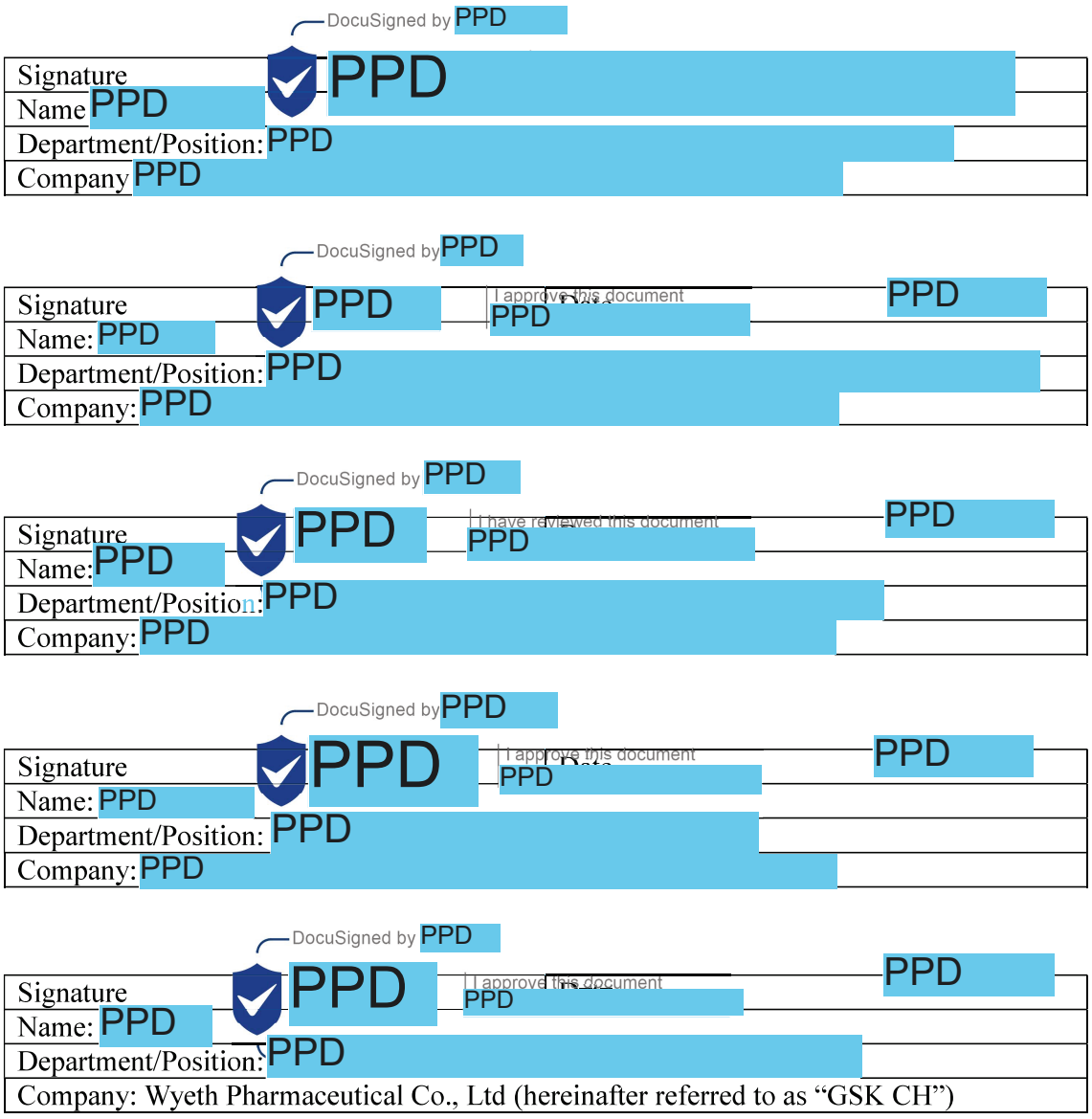
Statistical Analysis Plan

A Randomized, Open-label, Single-center, Single-dose, Two-treatment, Two-sequence, Two-period, Two-cohort, Two-way Crossover Bioequivalence Study of Two Ibuprofen Arginine Granules 400 mg Formulations Under Fasting and Fed Conditions in Chinese Healthy Adult Subjects

Compound/Product Name: Ibuprofen Arginine Granules
Sponsor: Wyeth Pharmaceutical Co., Ltd (hereinafter referred to as "GSK CH")
CRO: CCI [redacted]
Version No.: 1.0
Version Date: 2023-07-06

This document contains confidentiality statements that are not relevant for this publicly available version

Approvals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1. Introduction

The statistical analysis plan (SAP) is intended to describe the statistical methods used in the clinical trial under Protocol No. 218552. The clinical trial is a randomized, open-label, single-center, single-dose, two-treatment, two-sequence, two-period, two-cohort, two-way crossover bioequivalence study of two ibuprofen arginine granules 400mg formulations under fasting and fed conditions in Chinese healthy adult subjects sponsored by Wyeth Pharmaceutical Co., Ltd.

This SAP (version 1.0, dated 2023-07-06) has been developed based on the study protocol (version 3.0, dated 2023-01-20) and CRF (version 1.0, dated 2023-04-10). Any further changes to the protocol or CRF may update the SAP.

A final version of this SAP will be issued for sponsor approval prior to database lock.

2. Study Objectives

Primary Objective:

To demonstrate the bioequivalence of 400 mg new ibuprofen arginine granules compared to 400mg ibuprofen arginine granules (Spedifen) in two separate conditions (fed cohort and fasted cohort).

Secondary Objectives：

Pharmacokinetics (PK): To assess the PK profile of test and reference product.

Safety: To assess the safety profile of test and reference product.

3. Study Design

3.1 Overall Study Design

The bioequivalence study adopts a single-center, randomized, open-label, single-dose, two-treatment, two-sequence, two-period, two-way crossover design with at least 2-day washout period, in two cohorts under fasting and fed conditions respectively. For this study, it is planned to enroll approximately 84 subjects (the first 34 subjects for the fasted cohort and the subsequent 50 subjects for the fed cohort). Within the fasted cohort and fed cohort, subjects will be randomly assigned to either one of the 2 treatment sequences in a 1:1 ratio, according to the following table.

Fasted cohort		
Sequence	**Period 1**	**Period 2**
TR	Test product (T)	Reference product (R)
RT	Reference product (R)	Test product (T)

Fed cohort		
Sequence	**Period 1**	**Period 2**
TR	Test product (T)	Reference product (R)
RT	Reference product (R)	Test product (T)

Test Product: Ibuprofen arginine granules 400 mg, - one sachet administration containing 400 mg ibuprofen granules. Reference Product: Reference listed drug, ibuprofen arginine granules 400 mg, Spedifen, from CCI - one sachet administration containing 400 mg ibuprofen granules.

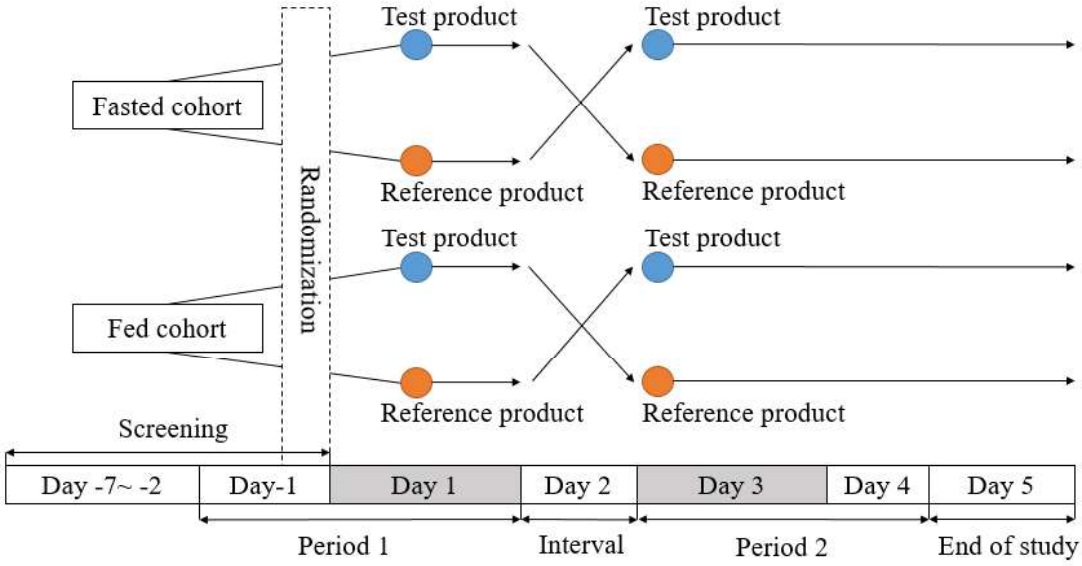
The fasted/fed cohort will consist of an ambulant screening day within 7 days prior to first product administration and two study periods. When screening results are qualified and are reviewed and confirmed for eligibility by the investigator, the subject will be admitted to the study ward on 1 day prior to first administration (Day -1). The first product administration will be on Day 1, and the second product administration on Day 3. Carry-over effects will be avoided by a wash-out interval of at least 2 days between investigational product administrations.

The drug will be administered as follows:

Fasted cohort: After an overnight fasting (water is allowed) of at least 10 hours, subjects will take 1 sachet (400 mg ibuprofen) of test (T) or reference (R) product with 240 mL of water in the morning on Day 1 under fasting condition, and cross-over 2 days later. Fed cohort: After an overnight fasting (water is allowed) of at least 10 hours, subjects will firstly take a high-fat/high-calorie breakfast exactly 30 minutes prior to dosing in the morning and finish eating within 30 minutes, then take 1 sachet (400 mg ibuprofen) of test (T) or reference (R) product with 240 mL of water under fed condition on Day 1, and cross-over 2 days later.

The study schematic is shown in Figure 1.

Figure 1. Study Schematic



3.2 Sample Size Determination

For this study, it is planned to enroll approximately 84 subjects (34 subjects for the fasted cohort and 50 subjects for the fed cohort) to achieve 32 subjects completing in the fasted cohort and 46 subjects completing in the fed cohort respectively. This estimates to overall 78 completer and evaluable subjects. Due to the unpredictability of the adverse covid situation, the enrolment of subjects may be higher than specified in the protocol to meet the number of completer and evaluable subjects required for this study.

In the fasted cohort, at least 17 subjects will be assigned to either TR or RT sequence and similarly in the fed cohort at least 25 subjects will be assigned to either TR or RT sequence.

The study will be deemed successful if the test product is equivalent to the reference product defined as the 90% confidence interval (CI) for the GMR (T/R), based on log-transformed data, being completely contained within the acceptance interval of 0.8000 to 1.2500 for the primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) in both fasted cohort and fed cohort respectively.

Considering a 2 × 2 crossover study design and using the information from the literature most similar to this study (refer to literature data of fasting condition [1]), the following estimates were used to calculate the intra-coefficient of variation (CV) of ibuprofen: GMR = 0.95, alpha = 0.05, power = 80%, N = 22 and the upper and lower limit range for determining the bioequivalence: 80.00 ~ 125.00%. The intra-CV was estimated to be 22.1%.

In this literature, since the 90% CI for C_{max} was outside the acceptance internal of 0.8000

to 1.2500 the data was calculated for parameters AUC_{0-t}, $AUC_{0-\infty}$. No data on fed status was reported in this literature however it seems that some factors will increase the variability after meal consumption.

Another reference that was considered for making intra-CV assumptions was public assessment report [2]. The intra-CV for C_{max} was back calculated using the following estimates: GMR = 0.95, alpha = 0.05, power = 80%, N = 24 and the upper and lower limit range for determining the bioequivalence: 80.00 ~ 125.00 %. The intra-CV for C_{max} was estimated to be 23.2%. From experience on previous studies, it is also believed that C_{max} intra-CV would be typically higher than AUC.

From above references and discussion and the likely impact of food on the CV, this protocol assumes a higher intra-CV estimate of 28% for the fed cohort and 23% intra-CV for the fasted cohort, for the calculation of sample size for this study.

For the fasted cohort, to calculate the sample size for this study the following estimates were then used: GMR = 0.95, alpha = 0.05, power = 90%, intra-CV = 23% and the upper and lower limit range for determining the bioequivalence: 80.00 ~ 125.00% which calculates 32 subjects per cohort.

Similarly for the fed cohort, to calculate the sample size for this study the following estimates were then used: GMR = 0.95, alpha = 0.05, power = 90%, intra-CV = 28% and the upper and lower limit range for determining the bioequivalence: 80.00 ~ 125.00% which calculates 46 subjects per cohort.

As the cohorts are independent, the overall power of the study was estimated to be 80% (0.9*0.9) which meets the minimum threshold requirement as per ICH guidelines.

3.3 Randomization and Blinding

The order in which all eligible subjects will enter the different sequence (TR or RT) will be determined according to the randomization list providing by CRO statistical programmer. Statistical programmer will use SAS (9.4 or above) to generate the randomization list. Block randomization will be used for randomization.

Subjects will be assigned to TR sequence or RT sequence in a 1:1 ratio by randomization number at the site in both fasted and fed cohorts. Randomization number for fasted cohort consists of one letter K + 3 digits number while randomization number for fed cohort consists of one letter C + 3 digits number. Randomization will be based on the randomization list taking the lowest numerical number when assign a subject .

The clinical study is an open-label study, in which all personnel (except bio-analysis and

testing personnel), such as clinical investigator, project manager, project monitor, data management personnel, will not be blinded. Blind analysis techniques will be used by the analysis and testing personnel, who does not know which investigational product the subjects are given in each period during the analysis. Also personnel involved in any data analysis (data management, statistician etc.) should be using anonymized subject data.

4. Study Endpoints

4.1 Pharmacokinetics Endpoints

1）Primary PK Endpoints

- C_{max}：observed maximum plasma concentration.
- AUC_{0-t}：area under the plasma concentration-time curve from time zero to last observed concentration at t.
- $AUC_{0-\infty}$：area under the plasma concentration-time curve from time zero to time infinity.

2）Secondary PK Endpoints

- T_{max}: time to reach maximum concentration
- $t_{1/2}$: terminal half-life
- λ_z: terminal elimination rate constant
- $\%AUC_{ex}$: percentage of extrapolated area of $AUC_{0-\infty}$, calculated as below:

  $\%AUC_{ex} = (1 - AUC_{0-t} / AUC_{0-\infty}) \times 100\%$

4.2 Safety Analysis Endpoints

- Frequency and nature of adverse events
- Physical examination
- Vital signs
- Laboratory tests
- 12-lead electrocardiogram

5. Definition

5.1 Baseline

Baseline (the first period baseline) is defined as the last non-missing measurement prior to first dose of investigational drug in the first period. The second period baseline is defined as the last non-missing measurement prior to first dose of investigational drug in the second period.

5.2 Change from Baseline

Change from baseline will be calculated as follows:

$$Change\ from\ the\ first\ period\ baseline = Post\ baseline\ measurement - First\ period\ baseline\ measurement$$

$$Change\ from\ the\ second\ period\ baseline = Post\ baseline\ measurement - second\ period\ baseline\ measurement$$

5.3 Study Day

Study day：Study day will be calculated from the date of the first administration of study drug, the date of the first administration of study drug is referred to as Day 1.

If the date of any event during the study is on or after the date of the first administration of study drug:

$$Study\ Day = Date\ of\ event - Date\ of\ the\ first\ adminstration\ of\ study\ drug + 1$$

If the date of event is prior to the date of the first administration of study drug:

$$Study\ Day = Date\ of\ event - Date\ of\ the\ first\ adminstration\ of\ study\ drug$$

6. Populations for Analysis

Prior to the lock of database, subjects for each analysis set will be identified mutually by principal investigator, sponsor, and biostatistician during the data review meeting.

Analysis Population: Analysis populations include randomized population, safety analysis population, pharmacokinetic concentration set, and bioequivalence set.

Randomized Population: Randomized population includes all randomized subjects. This will be the population used for analysis of dropout rate, demography, and baseline characteristics.

Safety Analysis Population (SS): Safety analysis population is defined as all subjects who received at least one dose of study drug after randomization and who have safety evaluation. This will be the population used for safety analysis. Analysis will be performed according to the actual treatment received.

Pharmacokinetic Concentration Set (PKCS): PKCS includes all randomized subjects who have received at least one dose of investigational product with available data of concentration for at least one component tested after administration. This is to provide descriptive statistics of the PK concentration data of subjects.

Pharmacokinetic Parameter Set (PKPS): PKPS is defined as the evaluable PK parameter data set obtained from subjects randomized who received at least one dose of investigational product. This is to provide descriptive statistics of the evaluable PK parameter data of subjects.

Bioequivalence Set (BES): BES will include subjects who receive at least one study period and have at least one evaluable PK parameter for ibuprofen. BES will be used in bioequivalence analysis for ibuprofen.

However, the subjects or subject's period will be excluded from BES, if one of the following is true for the specific period.

1. The pre-dose concentration is greater than 5% of observed maximum plasma concentration (C_{max})
2. Vomiting occurs at or before 2 times median T_{max} of subjects in the same treatment group
3. With major PD which will affect PK results.

7. Interim Analysis

There will be no interim analysis in this study.

8. Data Review

The data used for analysis should be cleaned. Prior to the data review meeting, the clinical pharmacologist may obtain the PK analysis data from the data management team for pre-analysis, depending on the specific requirements to help discuss the division of the analysis data set and other abnormal PKs data during the data review meeting. The result of pre-analysis data will further be provided for statistical programmer for programming testing and

verification of PK parameter unit. The analysis of the PK parameter will be performed after the database lock.

8.1 Data Handling and Transfer

The data from eCRF will be exported from EDC system and delivered to statistical programming team as SAS datasets by data management team. The PK analysis data will be provided for the PK analyst by the data management team. The PK parameters calculated by PK analyst will be sent to the statistical programming team in EXCEL for further statistical analysis.

8.2 Data Screening

Beyond the data screening based on the CCI Data Management Plan, the CCI CCI programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Any data issues identified as 'Error' will be output into SAS logs and extracted from the logs by a SAS macro and sent to Data Management for validation.

Prior to the database lock, further data screening will be provided for the TFLs which is generated by analysis dataset after data cleaning. The TFLs will be discussed with the sponsor in a data review meeting to identify any data issues and implement corrections prior to the database lock.

9. Statistical Methods

9.1 General Considerations for Statistical Analyses

9.1.1 General Principles

SAS Version 9.4 or above will be used for statistical analyses.

For quantitative data, descriptive summary will include the number of subjects, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), maximum, minimum, geometric mean, CV% and geometric CV% where geometric mean, CV% and geometric CV% are summarized for PK parameters only. Unless otherwise specified, the number of decimal places for the minimum and maximum will be the same as the original data recorded in the database. The mean, geometric mean and median (Q1, Q3) will retain one decimal place more than original data recorded in the database. The SD will retain two decimal places

more than original data recorded in the database. The CV% and geometric CV% will retain one decimal place. All statistics contain a maximum of four decimal places.

For categorical data, descriptive summary will include the number of subjects and percentage. The percentage will retain one decimal place. No percentage will be presented if frequency equals 0.

The confidence interval will retain four decimal places. If P-value is greater than or equal to 0.0001, it will retain four decimal places. If P-value is less than 0.0001, it will be presented as '<0.0001'.

Throughout the statistical methods the fasted cohort and fed cohort will be summarized and analyzed separately.

9.1.2 Handling of Missing Data

Handling of missing values: The missing value will not be filled in or imputed and the outliers will be checked.

Handling of missing dates: Due to the short study period, missing date in adverse events will be checked but not be filled in or imputed. For missing dates in medical history and medication history, they will also not be filled in or imputed. The dates in the listing will be presented as they are in the CRF.

9.1.3 Output of Statistical Results

All statistical results will be output using SAS 9.4 or above. TFL templates are presented in a separate document. The templates will be used to direct statistical programmer's work. For any modifications in templates that will not have essential effects on this plan, the SAP will not require modification and approval.

9.2 Subject Disposition

The summary of subject disposition is based on all subjects. Total number of subjects screened, subjects enrolled, subjects screened failure, and main reasons for screen failures (didn't meet inclusion criteria and/or did meet exclusion criteria, withdrawal of informed consent or other reasons) will be listed. The number and percentage of subjects who complete the study, subjects who withdraw the trial and the main reasons for withdrawal from the trial (protocol violation that may impact the subject's safety, withdrawal of informed consent, etc.) will be calculated by sequence group (TR: Test product – Reference product, RT:

Reference product – Test product). The number and percentage for subject distribution in each analysis population will also be calculated by sequence group (TR/RT).

The listing of subject disposition sorted by sequence group and subject screening number will be provided.

9.3 Demographic and Baseline Characteristics

The summary of demographic and other baseline characteristics is based on randomized population.

9.3.1 Demographic

Demographic and baseline characteristics will be summarized with descriptive statistics by sequence group (TR/RT). The following information will be included in the table:

- Age (years)
- Gender
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Past history (Transfusion/blood donation history (in the last 3 months), Allergy history, Childbearing history, Family history, Drug abuse history, COVID-19 history and COVID-19 positive contact history)
- Smoking history
- Alcohol consumption history

The listing of demographic and baseline characteristics sorted by sequence group and subject randomization number will be provided.

9.3.2 Protocol Deviation

Protocol deviation (PD) is defined as any condition that doesn't comply with the protocol and ICH GCP. PD can be classified into major PD or minor PD by severity.

Major PD is the deviation from the protocol that may affect the subject's rights, safety, or wellbeing and/or the completeness, accuracy, and reliability of the study data. This may also be defined in the study plans, as agreed upon by the sponsor.

Minor PD is the deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately. This may also be defined in the study plans, as agreed upon by the sponsor.

The number and percentage of subjects with at least one major or minor PD will be summarized by sequence group (TR/RT). The listing of protocol deviations sorted by subject randomization number will be provided.

All protocol deviations will be finally reviewed prior to the database lock.

9.3.3 Medical/Surgery History

The medical and surgery history will be coded using the preferred terms (PTs) according to the ICH Medical Dictionary for Regulatory Activities (MedDRA, V26.0 or above) and grouped by system organ class (SOC). All medical and surgery history will be summarized by sequence group (TR/RT).

The listing of medical history and surgery history sorted by sequence group and subject randomization number will be provided.

9.4 Pharmacokinetic Analysis

For fasted cohort, PK blood sample will be collected at within 2 hours prior to dosing (pre-dose) and 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120 min, 2.5, 3, 4, 6, 8, and 12 h after oral administration.

For fed cohort, PK blood sample will be collected at within 2 hours prior to dosing (pre-dose) and 10, 30, 45, 60, 75, 90, 120 min, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 h after oral administration.

The blood collection window is detailed as follows:

Planned sampling time point	Time window
0 h (pre-dose)	- 120 minutes
> 0 h and ≤ 60 min post-dose	± 1 minute
> 60 min and ≤ 4 h post-dose	± 2 minutes
> 4 h and ≤ 12 h post-dose	± 5 minutes

9.4.1 Plasma Concentration Analysis

Plasma concentration analysis will be based on PKCS.

Descriptive statistical analysis will be conducted to summarize drug plasma concentration data by treatment group (T: Test product, R: Reference product) at each planned sampling time

point. Descriptive statistics for plasma concentration will include number of subjects, arithmetic mean, SD, CV%, median (Q1, Q3), maximum (observed), minimum (observed), geometric mean. The mean, SD, CV% and geometric mean will be calculated only if at least two-thirds of the individual data meet or exceed the lower limit of quantification (LLOQ) at a specific sampling time point, otherwise only the minimum and maximum will be reported (these rules do not apply to pre-dose time points). Only mean, minimum and maximum will be reported for the pre-dose time points.

Plasma concentration-time curves will be plotted by blood sampling time points and mean concentrations or individual concentrations. The actual blood collection time will be used in the individual plasma concentration-time curves, while the scheduled blood collection time will be used in mean plasma concentration-time curves. Individual or mean plasma concentration-time curves will be plotted linearly and semi-logarithmically. The plasma concentration-time curves for both dose formulations should be graphically displayed in an overlay.

In the linear plot, if one or more BLQs appear in the same subject before the C_{max}, they will be imputed as 0, and post C_{max} BLQs will be presented as missing. In the semi-logarithmical plot, the values imputed as 0 before C_{max} will be presented as missing.

9.4.2 Pharmacokinetic Parameter Analysis

The PK parameter analysis will be based on PKPS.

The non-compartmental analysis modeling in software CCI , CCI) will be used to calculate the PK parameters of ibuprofen according to actual sampling time points. Descriptive statistical analysis will be conducted for all PK parameters by treatment group (T/R). Descriptive statistics for the PK parameters will include number of subjects with non-missing value (Nx), arithmetic mean, SD, CV%, median (Q1, Q3), maximum, minimum, geometric mean, and geometric CV%, etc.

The PK parameters will be calculated as follows:

PK parameter	Calculation method
C_{max}	Observed maximum plasma concentration.
T_{max}	Time to reach C_{max}.
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to last observed concentration at time t, will be calculated by the *linear up log down* trapezoidal rule.

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to time infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, ($C_t$ is the plasma concentration at the last measurable time point).
$t_{1/2}$	Elimination half-life, calculated as below: $t_{1/2} = Ln(2) / \lambda_z$.
λ_z	Terminal elimination rate constant. It will be estimated by log-linear regression of the terminal part of the plasma concentration versus time curve.
$\%AUC_{ex}$	Percentage of extrapolated area of $AUC_{0-\infty}$, calculated as below: $\%AUC_{ex} = (1- AUC_{0-t} /AUC_{0-\infty}) \times 100\%$.

For handling of values below the lower limit of quantification (BLQ):

When calculating individual or average plasma concentration or PK parameters, if one or more BLQs appear in the same subject before the C_{max}, it will be set to 0; if one or more BLQs appear in the same subject after the C_{max}, it will be set to missing.

9.5 Bioequivalence Analysis

Bioequivalence analysis will be based on BES.

The ln-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Ibuprofen will be analyzed by analysis of variance (ANOVA) with treatment, period, sequence as fixed effects and subject within sequence as random effect using PROC MIXED.

For both fasted and fed cohorts, the general approach average bioequivalence (ABE) is constructing a 90% CI for the quantity $\mu_T - \mu_R$ where μ_T and μ_R represent the means of ln-transformed PK parameters for each treatment. If the exponential of lower and upper limits of 90% CI is contained in the interval (80%, 125%), ABE is concluded.

The ABE hypothesis tests are:

$$H_{01} : \mu_T - \mu_R \leq ln0.8, \quad H_{A1} : \mu_T - \mu_R > ln0.8$$

and

$$H_{02} : \mu_T - \mu_R \geq ln1.25, \quad H_{A2} : \mu_T - \mu_R < ln1.25$$

By rejecting the null hypothesis, we conclude ABE.

The example of SAS codes can be referred to as follows (assuming Treat=1 represents study product, Treat=2 represents reference product):

CCI

The point estimate of test/reference geometric mean ratio (GMR) will be calculated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$for Ibuprofen by taking the exponential of least square means difference.

90% CIs for the difference between least square means of test and reference formulations will be obtained in ANOVA model for ln-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Ibuprofen. 90% CI for the geometric mean ratio will be calculated by taking the exponential of lower and upper limits of 90% CI, obtained for the least square mean difference. According to the residual obtained from the ANOVA model, the intra-subject CV of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ will also be calculated.

For both fasted and fed cohorts, if 90% CIs for the GMR of (T/R) for the PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are all contained in the interval (80%, 125%), average bioequivalence (ABE) of test product and reference product is concluded.

Besides the ANOVA, two one-sided test (TOST) will be conducted for the difference between least square means of test and reference formulations.

Hodges-Lehmann testing model will be used to perform the non-parameter analysis for the secondary PK parameters including $t_{1/2}$ and T_{max}. The median of the difference between the test product and the reference product and the corresponding 90% CI will be calculated. The result of Hodges-Lehmann test for secondary PK parameters will not contribute towards a conclusion of ABE or not ABE.

9.6 Safety Analysis

Safety analysis will be based on SS.

9.6.1 Study Product Exposure

The number and percentage of subjects who administered the investigational product will be summarized by treatment group (T/R) and period. The listing of exposure to study product sorted by sequence group and subject randomization number will be provided.

9.6.2 Prior/Concomitant Medications

No therapeutic medications are allowed during the study except for contraceptives and hormone replacement therapy, and those used for the treatment of AEs unless they jeopardize the integrity of the study.

Prior medications are defined as non-investigational medications taken within 90 days of signing the ICF and finished before the first dose administered.

Concomitant medications are defined as non-investigational medications taken after the first dose administered.

Prior and concomitant medications will be coded by anatomical therapeutic chemical (ATC) classification system using WHODrug Global (Mar, 2023 or above). Prior and concomitant medications will be summarized by ATC, PT and sequence group (TR/RT).

The listing of prior and concomitant medications sorted by subject randomization number will be provided.

9.6.3 Prior/Concomitant Non-Drug Therapies

Prior non-drug therapies are defined as non-drug therapies taken within 90 days of signing the ICF and finished before the first dose administered.

Concomitant non-drug therapies are defined as non-drug therapies taken after the first dose administered.

Prior and concomitant non-drug therapies will be coded by SOC and PT using ICH MedDRA (V26.0 or above). The listing of prior and concomitant non-drug therapies sorted by subject randomization number will be provided.

9.6.4 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

All AEs will be coded into SOC and PT using ICH MedDRA (V26.0 or above).

The severity of AE will be graded as mild, moderate, and severe. The causality of AE will be divided as related and not related.

In this study, treatment-emergent adverse events (TEAEs) are defined as AEs that occur on or after the first dose administered and before the end (or discontinuation) of the study. Besides, the period of AE should be specified as follows:

- The first period AEs: AEs present after the first dose administered and before the dose administered in the second period.
- The second period AEs: AEs present after the dose administered in the second period.

In situations with missing AE start/end dates/times, available data will be used for TEAE classification and treatment assignment. If the TEAE classification is inconclusive, worst-case will be assumed and the AE will be classified as a TEAE. If the treatment assignment is inconclusive, the earliest of the possible treatments will be assigned. AEs will be summarized by sequence group (TR/RT) and treatment group (T/R).

The number of events will be summarized with number and percentage of the subjects for all AEs, TEAEs, serious AEs (SAEs), investigational product-related TEAEs, investigational product-related SAEs, and TEAEs leading to study discontinuation.

For TEAEs, SAEs, investigational product-related TEAEs, investigational product-related SAEs, and TEAEs leading to study discontinuation, the number of events will be summarized with number and percentage of the subjects by treatment (T/R) and sequence (TR/RT) based on PT and SOC. In addition, the severity of TEAEs and the relationship to investigational product will also be summarized by treatment (T/R) and sequence (TR/RT) based on PT and SOC. Subjects with multiple occurrences of events for a given SOC, PT, or overall will only be counted once at the worst severity and strongest relationship to investigational drug.

The listing of all AEs, TEAEs, serious AEs (SAEs), investigational product-related TEAEs, investigational product-related SAEs, and TEAEs leading to study discontinuation will be provided.

9.6.5 Laboratory Tests

Laboratory tests include blood chemistry, hematology, urinalysis, coagulation.

Descriptive statistical analysis of all laboratory tests results and changes from baseline will be summarized by scheduled time point and sequence group (TR/RT). Summary

statistics will include mean, SD, minimum, median (Q1, Q3), and maximum. Shift in clinical significance from baseline will be summarized by timepoint and treatment (T/R). Shift in clinical significance from baseline to the worst post-baseline result will also be summarized by sequence group (TR/RT).

The listing of laboratory tests results and abnormal laboratory results (clinical significance evaluated as 'Abnormal, clinical significance') will be provided.

9.6.6 Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and ear temperature.

Descriptive statistical analysis of all vital signs results and changes from baseline will be summarized by scheduled time point and sequence group (TR/RT). Summary statistics will include mean, SD, minimum, median (Q1, Q3), and maximum. Shift in clinical significance from baseline will be summarized by timepoint and treatment (T/R). Shift in clinical significance from baseline to the worst post-baseline result will also be summarized by sequence group (TR/RT). The listing of vital signs results and abnormal vital signs results (clinical significance evaluated as 'Abnormal, clinical significance') will be provided.

9.6.7 Physical Examination

Shift in clinical significance from baseline will be summarized by timepoint and treatment (T/R). Shift in clinical significance from baseline to the worst post-baseline result will also be summarized by sequence group (TR/RT). The listing of physical examination results and abnormal vital signs results (clinical significance evaluated as 'Abnormal, clinical significance') will be provided.

9.6.8 12-lead ECG

Descriptive statistical analysis of all 12-lead ECG results and changes from baseline will be summarized by scheduled time point and sequence group (TR/RT). Summary statistics will include mean, SD, minimum, median (Q1, Q3), and maximum. Shift in clinical significance from baseline will be summarized by timepoint and treatment (T/R). Shift in clinical significance from baseline to the worst post-baseline result will also be summarized by sequence group (TR/RT).

The listing of 12-lead ECG results and abnormal laboratory results (clinical significance evaluated as 'Abnormal, clinical significance') will be provided.

9.6.9 Admission to/ Leaving Study Ward

The listing of admission to/ leaving study ward sorted by sequence and subject randomization number will be provided.

9.6.10 Other Examinations

The listing of following examinations sorted by sequence and subject randomization number will be provided.

- Urine drug abuse screening
- Alcohol breath test
- Serology
- Blood pregnancy test (For female only)
- Menstrual History (For female only)
- Hormone test (Follicle-stimulating hormone done only in females who have been consecutively amenorrhoeic for 12 months)
- COVID-19 test
- Intake of high-fat/high-calorie breakfast (For fed cohort only)
- Unscheduled visit (if applicable)

10. Quality Control

To ensure that each delivery of TFL is of a high standard, the TFL quality control process will be documented in detail in the Quality Control Tracker.

Appendix 1 Abbreviations

Abbreviation	Term
ABE	average bioequivalence
AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to time infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to last observed concentration at time t
BES	bioequivalence set
BLQ	below the lower limit of quantification
BMI	body mass index
CI	confidence interval
C_{max}	observed maximum plasma concentration
CRF	case report form
CV	coefficient of variation
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification
LSM	least squares mean
MedDRA	medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PKCS	pharmacokinetic concentration set
PKPS	pharmacokinetic parameter set
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Abbreviation	Term
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum concentration
WHO	World Health Organization
λ_z	terminal elimination rate constant
$\%AUC_{ex}$	percentage of extrapolated area of $AUC_{0-\infty}$

Appendix 2 References

[1]. Public Assessment Report-Scientific discussion, Ibuprofen 400 mg/100 ml solution for infusion & Ibuprofen 600 mg/100 mL solution for infusion, ibuprofen arginine, Medicine Online Information Center of AEMPS, January 2017.

[2]. Sádaba B, Campanero MA, Muñoz-Juarez MJ, et al. A comparative study of the pharmacokinetics of ibuprofen arginate versus dexibuprofen in healthy volunteers. Eur J Clin Pharmacol. 2006 Oct;62(10):849-54.