CLINICAL PROTOCOL

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

Protocol Number:	218552
Compound/Product Name:	Ibuprofen Arginine Granules
United States (US) Investigational New Drug (IND) Number:	N/A
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This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

Sponsor Name & Legal Registered Address	**Wyeth Pharmaceutical Co., Ltd.** **(hereinafter referred to as "GSK CH")** No. 4 West Baodai Road, Suzhou, Jiangsu, China.
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Document History

Document	Version	Summary of Changes		
Original protocol	1.0	Not applicable		
Revised protocol	2.0	**Change**	**Version 1.0**	**Version 2.0**
		P13: short title	A bioequivalence study of Fenbid Flash ibuprofen arginine granules 400 mg compared to the currently marketed ibuprofen arginine granules 400 mg (Spedifen) in healthy adult subjects	A bioequivalence study of two ibuprofen arginine granules 400 mg under fasting and fed conditions in Chinese healthy adult subjects.
		P18: Table1-1 footnote f; P41: 9.2.11 Electrocardio-gram	12-lead ECGs will be performed with the subject in a supine or semi-supine position having rested in this position for at least 5 minutes before the exam.	12-lead ECGs will be performed with the subject in a sitting position having rested in this position for at least 5 minutes before the exam.
		P18: Table1-1 footnote k; P42: 9.2.12 COVID-19 test	COVID-19 test: At any time during residential period in study, when subjects report symptoms suggestive of COVID-19.	COVID-19 test: At any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by World Health Organization (WHO) or local guidance. In addition, added the abbreviation of WHO to Table 15-1.
		P18: Table 1-1 footnote n; P25: 5.5.1 Meals and Dietary Restrictions	A high-fat/high-calorie breakfast contains about 800-1000 kcal, including about 500-600 kcal from fat (more than 50% of total calories), 150 kcal from protein, 250 kcal from carbohydrates.	A high-fat/high-calorie breakfast contains about 800-1000 kcal, including about 500-600 kcal from fat (more than 50% of total calories), about 150 kcal from protein, about 250 kcal from carbohydrates.
		P23: 5.3 Exclusion Criteria #11	Those who have blood donation (including component donation) or blood loss ≥ 400 mL within 3 months before the study, or have blood transfusion; those who have blood donation (including component donation) or blood loss ≥ 200 mL within 1 month before the study.	Those who have blood donation (including component donation) or blood loss ≥ 400 mL within 3 months before the study, or have blood transfusion; those who have blood donation (including component donation) or blood loss ≥ 200 mL within 1 month before the study (except female physiological blood loss).
		P25: 5.5.3 Activity	Subjects will not be permitted to assume a fully recumbent position for 4 hours following dosing.	Subjects will not be permitted to assume a fully recumbent position for 4 hours following dosing (except when AE requires medical treatment).
		P31: 6.5 Blinding & Allocation/ Randomization	Randomization number consists of one letter R+3 digits number.	Randomization number consists of one letter K+3 digits number in the fasted cohort, and C+3 digits number in the fed cohort.

		P41: 9.2.8 Blood Pressure and Pulse Rate	When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.	<text deleted>
Amended protocol	3.0	**Change**	**Version 2.0**	**Version 3.0**
		P2: Sponsor Information	GlaxoSmithKline Consumer Healthcare (China) Co, Ltd (GSK CH) 8F, The Headquarters building, No. 168 Tibet Road (M), Shanghai, China, 200001 Tel: +86 21 2301 9800	GlaxoSmithKline Consumer Healthcare (China) Co, Ltd (GSK CH) 25/F and 26/F, No.90 Qirong Road, Pudong New Area, Shanghai, China, 200124 Tel: +86 21-2301 9366
		P15: Bioequivalence analysis; P54: 12.3.2-Bioequivalence Analysis	The log-transformed primary PK endpoints….will be analyzed with an analysis of variance (ANOVA) model with treatment, period, sequence and subject within sequence, as fixed effects to calculate the least squares means (LSMs)…. back-transformed values.	The log-transformed primary PK endpoints….will be analyzed with an analysis of variance (ANOVA) model with treatment, period and sequence, as fixed effects to calculate the least squares means (LSMs)…. back-transformed values.
		P18: Table1-1 footnote h; P24: 5.3 Exclusion criteria #20; P39:Table 9-1; P40: 9.2.2 Serology	Serology includes HBsAg, HBcAb, HCV Ab and HIV antibody	Revised Serology including HBsAg, HBcAb, HCV Ab, HIV antibody and Syphilis
		P18: Table 1-1 (footnote k)	COVID-19 tests are to be performed as follows: screening; Day -1; Day 4 or early termination; and at any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by World Health Organization (WHO) or local guidance. And the 2 consecutive tests before the first dose should be separated by > 24 hours.	COVID-19 tests are to be performed as follows: Day -1; and at any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by World Health Organization (WHO) or local guidance.
		P18: Table 1-1 (footnote c)	The subjects will complete a follow-up visit 2 days after last dose of medication, as their end-of-study (EOS) visit. The follow-up visit can be done via telephone if the subject does not need to receive any examination, as judged by the investigator.	The subjects will complete a follow-up visit 2 days after last dose of medication, as their end-of-study (EOS) visit. Due to any unforeseen circumstances if follow-up visit is not completed on day 5, this can be rescheduled and completed in next 2 days i.e., till day 7. The follow-up visit can be done via telephone if the subject does not need to receive any examination, as judged by the investigator.

		P22: 5.2-Inclusion Criteria #7	Subject with two negative polymerase chain reaction (PCR) tests (one at screening and one on Day-1) for active COVID-19, separated by > 24 hours.	Subject with one negative polymerase chain reaction (PCR) or antigen test (on Day-1) for active COVID-19.
		P25: 5.5.1 Meals and Dietary Restrictions; P28: 6.2 Administration	The study drug granules must be mixed and stirred with 240 mL of hot but not boiling water to be completely dissolved	The study drug granules must be mixed and stirred with 240 mL of warm water to be completely dissolved
		P34: 8.1.5-Screening procedures	The following…COVID-19 test and AEs, prior/concomitant medications/treatments collection.	The following…and AEs, prior/concomitant medications/treatments collection.
		P37: 8.2.3-Period 2 [Day 4 (Period 2)]	COVID-19 test	<deleted>
		P38: 8.2.4-End of study	The subjects will complete…medication (Day 5). Subjects will be contacted by telephone by the investigator or his/her authorized staff to complete the following procedures after discharge from the study ward:	The subjects will complete…medication (Day 5). Due to any unforeseen circumstances if follow-up visit is not completed on day 5, this can be rescheduled and completed in next 2 days i.e., till day 7. The follow-up visit can be done via telephone if the subject does not need to receive any examination, as judged by the investigator. The investigator or his/her authorized staff shall complete the following procedures after discharge from the study ward:
		P42: 9.2.12-COVID-19 test	Nasal/nasopharyngeal swab will be collected to test for COVID-19 using PCR test, at times specified in the STUDY PROCEDURES section. Two consecutive negative tests for active COVID-19 separated by > 24 hours are required for inclusion in the study: one test will be done during screening and one test will be done on Day -1. For detection of COVID-19, tests are to be performed as follows: • Screening • At check-in (Day -1) • At discharge from Period 2 (Day 4) or early discontinuation • At any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by WHO or local guidance	Nasal/nasopharyngeal swab will be collected to test for COVID-19 using PCR or antigen test, at times specified in the STUDY PROCEDURES section. For detection of COVID-19, tests are to be performed as follows: • At check-in (Day -1) • At any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by WHO or local guidance

		P42: 9.3.1-Plasma for Analysis of ibuprofen	The actual blood sample requirements for PK analysis shall be dependent on the laboratory manual.	The actual blood sample requirements for PK analysis shall be dependent on the laboratory manual CCI CCI CCI or other contracted central lab etc.).
		P47: 10.4.2 Reporting of a Serious Adverse Event; P48: 10.6 Follow-up of AEs and SAEs; P49: 10.9.2 Action to be Taken if Pregnancy Occurs	Change of safety reporting email box: PPD	Change of safety reporting email box: PPD
		P52: 12.1-Sample Size Determination	This estimates to 78 subjects overall completing the study.	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.

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD

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1 PROTOCOL SUMMARY

1.1 Synopsis

Title: 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.

Short Title:

A bioequivalence study of two ibuprofen arginine granules 400 mg under fasting and fed conditions in Chinese healthy adult subjects.

Background and Rationale:

Ibuprofen arginine granules (Spedifen) was approved in China by the National Medical Products Administration (NMPA) in 2005 (200 mg, H20058759; 400 mg, H20058760; 600 mg, H20058761). A new ibuprofen arginine granules formulation will be investigated in this study to support the generic registration in China. This randomized crossover study is now being conducted to demonstrate the bioequivalence of ibuprofen arginine granules manufactured by the sponsor (test product) and Spedifen (reference product), under fasting and fed conditions.

Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
The objective of this study is 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)	• Primary pharmacokinetic (PK) endpoints in fed cohort: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} • Primary PK endpoints in fasted cohort: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}
Secondary	
Pharmacokinetics	
To assess the PK profile of test and reference product	• Secondary PK endpoints in fed cohort: T_{max}, $t_{1/2}$, λ_z, and $\%AUC_{ex}$ • Secondary PK endpoints in fasted cohort: T_{max}, $t_{1/2}$, λ_z, and $\%AUC_{ex}$
Safety	
To assess the safety profile of test and reference product	• Frequency and nature of adverse events • Physical examination • Vital signs • Laboratory tests • 12-lead electrocardiogram

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 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)

Study Products:

- 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 CCI - one sachet administration containing 400 mg ibuprofen granules

Study Procedure:

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).

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 Pharmacokinetic (PK) blood samples will be collected as follows:

Fasted cohort: PK blood samples will be obtained 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 test or reference product administration.

Fed cohort: PK blood samples will be obtained 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 test or reference product administration.

In order to standardize the conditions on PK sampling days, all subjects should refrain from lying down, eating, and drinking beverages other than water during the first 4 hours after dosing. Aside from time of product administration, water will be allowed ad libitum except within 1 hour before and 1 hour after investigational product administration. No food is allowed within 4 hours after administration. Lunch will be provided approximately 4 hours after dosing. Dinner will be provided approximately 10 hours after dosing.

For each subject the duration of study participation is up to 12 days of which up to 4 days confined.

Type and Planned Number of Subjects:

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 78 subjects overall completing the 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.

Statistical methods

The fasted cohort and fed cohort will be summarized and analyzed separately.

Pharmacokinetic analysis:

Descriptive statistical analysis will be conducted to summarize drug plasma concentration data by treatment groups at each planned sampling time point. Descriptive statistics for plasma concentration will include arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, maximum, minimum, geometric mean, etc. The individual and average concentration-time curve, semi logarithmic concentration-time curve of ibuprofen will be displayed by treatment.

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. Descriptive statistics for the PK parameters will include arithmetic mean, SD, CV%, median, maximum, minimum, geometric mean and geometric CV, etc.

Bioequivalence analysis:

The log-transformed primary PK endpoints (area under the plasma concentration-time curve from time zero to time infinity [$AUC_{0-\infty}$], area under the plasma concentration-time curve from time zero to last observed concentration at time t [AUC_{0-t}], and observed maximum plasma concentration [C_{max}]) will be analyzed with an analysis of variance (ANOVA) model with treatment, period and sequence, as fixed effects to calculate the least squares means (LSMs) between the test product and the reference product, and the geometric mean ratio (GMR) and its 90% confidence interval (CI) will be calculated using back-transformed values. The test and

reference products can be considered equivalent if the 90% CIs of the GMR (T/R) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} are each between 80.00% and 125.00%. Non-parametric analysis will be performed for the secondary PK parameters without logarithmic transformation. For time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$) and terminal elimination rate constant (λ_z), the paired Hodges-Lehmann test (Hodges-Lehmann 's median analysis) will be used. The median of the difference between the test product and the reference product and corresponding 90% CI will be calculated.

Safety analysis:

Adverse events (AEs) will be coded using the preferred terms (PTs) from Medical Dictionary for Regulatory Activities (MedDRA) of the most recent version at the time of database lock and grouped by system organ class (SOC). The severity of AEs will be graded. The number and percentage of subjects will be summarized for all treatment-emergent adverse events (TEAEs, defined as any AE occurring from the start of dosing to the end of the study), serious adverse event (SAEs), investigational product-related TEAEs, investigational product-related SAEs, and TEAEs leading to study discontinuation by medication (T/R) and sequence (TR/RT) based on PT and SOC. In addition, the severity of TEAEs and their relationship to investigational product will also be summarized by medication (T/R) and sequence (TR/RT) based on PT and SOC.

Descriptive statistical analyses will be performed for the baseline values, post-dose values, and changes from baseline for vital signs, physical examinations, laboratory tests, and 12-lead electrocardiogram (ECG).

Criteria for Evaluation

The test product is considered to be equivalent to the reference product if the 90% CI for the GMR (T/R), based on log-transformed data, is 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.

1.2 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure /Assessment	Screening	Period 1		Interval [a]	Period 2		End of study [c]	Early termination [b]
	Within 7 days prior to first dose	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Smoking history and alcohol consumption history	X							
Demographics	X							
Prior/concomitant medications/treatments review	X	X	X	X	X	X	X	X
Height/weight	X							
Physical examination [d]	X	X		X		X		X
Vital signs [e]	X	X	X	X	X	X		X
12-lead ECG [f]	X			X		X		X
Laboratory tests [g]	X			X		X		X
Alcohol breath test	X	X						
Urine drug abuse screening	X	X						
Serology [h]	X							
Blood pregnancy test [i]	X	X				X		X
Hormone test [j]	X							
COVID-19 test [k]		X						
Admission to study ward		X						
Randomization [l]		X						
Investigational product administration [m]			X		X			

Procedure /Assessment	Screening	Period 1		Interval [a]	Period 2		End of study [c]	Early termination [b]
	Within 7 days prior to first dose	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	
High-fat/high-calorie meal [n]			X		X			
AE Collection [o]	X	X	X	X	X	X	X	X
Pharmacokinetic blood sampling [p]			X		X			
Leave study ward						X		

Abbreviations: AE= Adverse Events; ECG= electrocardiogram.

Footnotes:

a. The first dose will be in the morning of Day 1 and the second dose in the morning of Day 3, with a washout period of 2 days.
b. If a subject who has received the investigational product discontinues the study prematurely, an early termination safety assessment is required, while pharmacokinetic blood sampling will no longer be performed. If the subject who discontinues study has completed randomization but has not received the investigational product, safety assessments may be performed as the investigator deems appropriate.
c. The subjects will complete a follow-up visit 2 days after last dose of medication, as their end-of-study (EOS) visit. Due to any unforeseen circumstances if follow-up visit is not completed on day 5, this can be rescheduled and completed in next 2 days i.e., till day 7. The follow-up visit can be done via telephone if the subject does not need to receive any examination, as judged by the investigator.
d. A full physical examination will be required at screening, and an abbreviated physical exam will be performed for all the other visits.
e. Vital signs (blood pressure, pulse, body temperature, respiratory rate) in a sitting position need to be measured.
f. 12-lead ECG parameters include heart rate, PR interval, QRS interval, QT interval and QTcF interval. 12-lead ECGs will be performed with the subject in a sitting position having rested in this position for at least 5 minutes before the exam.
g. Laboratory tests include blood chemistry, hematology, urinalysis, coagulation.
h. Serology: including hepatitis B surface antigen (HBsAg), HBcAb, hepatitis C virus antibody (HCV), human immunodeficiency virus (HIV) antibody and syphilis.
i. Females of childbearing potential should complete the blood pregnancy test at screening, 1 day before dosing in period 1, and Day 4/ early termination.
j. Follicle-stimulating hormone done only in females who have been consecutively amenorrhoeic for 12 months.
k. COVID-19 tests are to be performed as follows: Day -1; and at any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by World Health Organization (WHO) or local guidance.
l. Randomization: After confirmation of subject enrollment on Day -1.
m. In fasted/fed cohort, subjects randomized to TR sequence will receive test product on Day1 and reference product on Day3; subjects randomized to RT sequence will receive reference product on Day1 and test product on Day3.
n. Applicable to fed cohort only. The temporal order should be: vital signs > blood sampling before dosing > high-fat and high-calorie meal > drug administration. A high-fat/high-calorie breakfast contains about 800-1000 kcal, including about 500-600 kcal from fat (more than 50% of total calories), about 150 kcal from protein, and about 250 kcal from carbohydrates.
o. The AEs will be collected from time of informed consent.
p. Fasted cohort: PK samples for determination of ibuprofen in plasma will be taken prior dose, and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120 min, 2.5, 3, 4, 6, 8, and 12 h after oral administration of test product or reference product.
Fed cohort: PK blood samples will be obtained 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 test or reference product administration.

2 INTRODUCTION

2.1 Study Rationale

A new ibuprofen arginine granules formulation developed by Wyeth Pharmaceutical Co., Ltd (hereinafter referred to as "GSK CH"), is intended to be registered in China. In order to ensure that this new formulation is clinically equivalent to the original reference product, GSK CH will conduct this bioequivalence study. This study is required to determine whether the test product is bioequivalent to the reference ibuprofen arginine granules under fasting and fed conditions in Chinese healthy adult subjects.

2.2 Background

Ibuprofen, (±)-(R, S)-2-(4-isobutylphenyl)-propionic acid, is a chiral 2-arylpropionic acid derivative nonsteroidal anti-inflammatory drug (NSAID) widely used in the management of mild to moderate pain, fever and inflammation since early seventies [2]. Ibuprofen is a non-selective inhibitor of cycloxygenase-1 and -2 derived prostaglandin biosynthesis [3]. In the clinical practice the drug is usually given by oral route, and the commonest adverse events (AEs) occurring during therapy with ibuprofen include gastrointestinal discomfort, nausea and diarrhea. Nevertheless, systematic review of controlled epidemiological studies have consistently shown that ibuprofen is associated with the lowest relative risk of serious gastrointestinal complications compared with other NSAIDs [4].

Currently, different ibuprofen formulations are available on the market [5]. These formulations differ in terms of pharmaceutical composition that influences the pharmacokinetic (PK) profile and eventually the onset of action of ibuprofen. The formulation of ibuprofen has a significant effect on its rate of absorption and subsequent time to reach maximum concentrations (T_{max}). Ibuprofen is a Biopharmaceutics Classification System (BCS) class II drug (BCS II = low solubility, high permeability) [6]. The ibuprofen acid has low solubility at pH 1.2 and 4.5 and high solubility at pH 6.8. Ibuprofen is highly permeable and is rapidly absorbed as soon as it dissolves. Formulations that aid ibuprofen's rate of dissolution (soluble salt forms) or provide ibuprofen in a 'dissolved' form (gel capsules or effervescent tablets) speed time to maximal concentrations [2],[3],[7],[8].There is one such formulation, ibuprofen arginine, specifically designed to improve the absorption of ibuprofen. Ibuprofen arginine was firstly introduced on the market in 1994 in Spain [9], and is now commercially available in several other European Countries as Spedifen CCI

Ibuprofen arginine granules (Spedifen) was approved in China by the National Medical Products Administration (NMPA) in 2005 (200 mg, H20058759; 400 mg, H20058760; 600 mg, H20058761). A new ibuprofen arginine granules formulation developed by GSK CH will be investigated in this study to support the generic registration in China. This randomized crossover study is now being conducted to evaluate the bioequivalence of ibuprofen arginine granules manufactured by the sponsor and Spedifen manufactured by CCI under fasting and fed conditions.

2.3 Benefit/Risk Assessment

The investigational drug may cause adverse reactions as described in instructions [10], and blood samples drawn during the study procedures may cause some pain, discomfort, bruising and redness/irritation at the site of drawing. Participants will be monitored closely by the site staff during the site visits. If any discomfort occurs during the study, appropriate measures will be taken promptly by investigator.

Participants enrolled into this study are healthy participants. There will be no direct benefits gained from participation in this study. The participants' involvement will be contributing to the PK analysis and safety profile of the ibuprofen arginine granules manufactured by GSK CH compared to reference product (Spedifen).

Complete information for this product may be found in the single reference safety document, which for this study is the Investigator Brochure (IB).

2.4 Mechanism of Action/Indication

Ibuprofen by inhibiting the synthesis of prostaglandin produces analgesic, antipyretic and anti-inflammatory effects. Ibuprofen arginine is an arginine salt of ibuprofen, which can improve the solubility of ibuprofen, and thus leads to more rapid absorption [10],[11]. The analgesic effect is achieved within 15-30 minutes after administration [10],[12].

This product is indicated for the following symptoms: Toothache, dysmenorrhea, pain caused by trauma (such as sports injury), arthralgia and desmalgia, dorsalgia, encephalalgia, neuralgia and fever caused by flu.

The recommended oral dosage for adults aged 12 years old and above is one sachet (400 mg) twice daily. Place this product into a glass, add an appropriate amount of warm water, and take it after the product completely is dissolved. This product takes effect more quickly being taken on an empty stomach.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	**Primary**
The objective of this study is 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)	• Primary PK endpoints in fed cohort: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} • Primary PK endpoints in fasted cohort: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}
Secondary	
Pharmacokinetics	
To assess the PK profile of test and reference product	• Secondary PK endpoints in fed cohort: T_{max}, $t_{1/2}$, λ_z, and $\%AUC_{ex}$ • Secondary PK endpoints in fasted cohort: T_{max}, $t_{1/2}$, λ_z, and $\%AUC_{ex}$
Safety	
To assess the safety profile of test and reference product	• Frequency and nature of adverse events • Physical examination • Vital signs • Laboratory tests • 12-lead electrocardiogram

This study will be considered successful, that is the test product will be considered equivalent to the reference product, if the 90% CI for the geometric mean ratio (GMR) (T/R), based on log-transformed data, is 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.

4 STUDY DESIGN

4.1 Overall Design

The bioequivalence study adopts a single-center, randomized, open-label, single-dose, two-treatment, two-sequence, two-period, two-cohort, two-way crossover design with at least 2-day washout period, 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).

4.2 Scientific Rationale for Study Design

A single-center, randomized, open-label, single-dose, two-period, crossover-controlled design will be used. Healthy adult males and females subjects will be selected in accordance with Technical Guidelines for Human Bioequivalence Studies of Chemical Generics Taking Pharmacokinetic Parameters as Endpoint Evaluation Indicators [1] published by NMPA in 2016 and as per Chinese Pharmacopoeia [13].

A crossover design, using the same subjects to test each product, will be used to reduce variability. The blood sampling time points and the washout interval have been chosen based on the information available particularly on Spedifen's absorption, as well as its elimination.

In accordance with the catalogue of reference preparations for generic drugs, the ibuprofen arginine granules, Spedifen, manufactured by CCI is selected as the reference product.

The mean terminal half-life ($t_{1/2}$) of a single oral dose of ibuprofen arginine is approximately 1.5~2 hours according to the instruction of Spedifen (200 mg), thus the washout period (dosing interval) between 2 doses in the study periods is set to 2 days, much greater than 7-fold $t_{1/2}$.

4.3 Justification for Dose

This is a study to assess the bioequivalence of the test product to a commercial reference product. In accordance with the Chinese guideline of the bioequivalence study, single dose will be used for both test and reference product.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all procedures of the study including the last visit, or the last scheduled procedure shown in the Schedule of Activities.

The end of this study is defined as the date of the last visit of the last subject to complete the study.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

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 78 subjects overall completing the 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.

An enrolled subject is one who has agreed to participate in this clinical study following completion of the informed consent process directly and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

This study can achieve its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in this study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this study.

Subject's eligibility to participate in this clinical study should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria be included into the study:

1. Subject provision of a signed and dated informed consent and/or assent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female.
3. Subject is 18~50 years of age inclusive, at the signing of the informed consent.
4. Subject who is willing and able to comply with scheduled visits, treatment plan, laboratory tests, study restrictions, lifestyle considerations and other study procedures.
5. Healthy subject, which is defined as in general good physical health, as judged by the investigator and no clinically significant relevant abnormalities identified by a detailed medical history, full physical examination, including vital signs, 12-lead electrocardiogram (ECG) and laboratory tests.
6. A subject with a Body Mass Index (BMI) of 19~26 kg/m^2 (including 19, excluding 26) [BMI = weight (kg)/height^2 (m^2)]; and a total body weight $\geq$ 50 kg for males, and $\geq$ 45 kg for females, at screening.
7. Subject with one negative polymerase chain reaction (PCR) or antigen test (on Day-1) for active COVID-19.
8. Female subject of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in the Contraception section of protocol.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. Known or suspected intolerance or hypersensitivity or photosensitivity to the investigational products (or closely related compounds) or any of their stated ingredients.
2. Allergy to skin disinfecting agents, tape, or latex rubber, whenever appropriate substitutions cannot be applied or in the investigator's opinion may pose a risk to the candidate.
3. Diagnosis of long QT syndrome or QTcF > 450 msec at screening.

4. Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 60 or over 90 mmHg, or pulse rate less than 50 or over 100 bpm).
5. Use of any medication (including over-the-counter medications and Chinese herbal and traditional remedies) within 2 weeks before first scheduled study drug administration or within less than 10 times the elimination half-life of the concomitant medication (whichever is longer), or is anticipated to require any concomitant medication during that period or at any time throughout the study. Allowed treatments are:
   - systemic contraceptives and hormone replacement therapy, as long as female subject is on stable treatment for at least 3 months before first scheduled study drug administration and continues treatment throughout the study;
   - occasional use of acetaminophen (up to 2 g in 24 hours).
6. Subject has a history of drug abuse or has positive urine drug abuse screening at screening or on Day-1.
7. Subject reported regular consumption of > 5 cups (1 cup ≈ 250 mL) of coffee or tea per day (or equivalent consumption of ≥ 500 mg caffeine per day using other products). Or consuming any beverages or food containing caffeine, such as coffee, tea, coke, chocolate, etc., within 48 hours prior to screening.
8. Smoking or history of regular use of tobacco- or nicotine-containing products (e.g. nicotinepatch, electronic cigarette) within 6 months prior to screening. Or a subject who is unwilling to abstain from tobacco or nicotine containing product use during the study.
9. Evidence, as reported by an alcohol breath testing, for current alcohol abuse or reports a regular average alcohol consumption exceeding 18 g (women) or 35 g (men) of pure alcohol per day, i.e. 1 drink/day for women or 2 drinks/day for men [1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor] within 6 months prior to screening.
10. Participation in other clinical trials involving investigational drug(s) within 90 days prior to screening.
11. Those who have blood donation (including component donation) or blood loss ≥ 400 mL within 3 months before the study, or have blood transfusion; those who have blood donation (including component donation) or blood loss ≥ 200 mL within 1 month before the study (except female physiological blood loss).
12. Acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. Or any condition not identified in the protocol that in the opinion of the investigator would confound the evaluation and interpretation of the study data or may put the subject at risk.
13. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease within the last 5 years that may increase the risk associated with study participation.
14. Clinically relevant chronic or acute infectious illnesses or febrile infections within two weeks prior to start of the study.
15. Subject with known COVID-19 positive contacts in the past 14 days.

16. Subject with signs or symptoms highly suggestive of COVID-19 (including not limited to fever, cough, chills, new loss of taste or smell, etc.)* that also align with the clinical judgement of the investigator, within 14 days of inpatient admission. **as defined by World Health Organization (WHO) or local guidance.*
17. Any vaccination, including COVID-19 vaccine, within 14 days prior to the first dose of investigational products.
18. Any surgical or medical condition which may significantly alter the absorption, distribution, metabolism or excretion of any drug substance but not limited to any of the following:
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling or gastric banding (note: this is not applicable for minor abdominal surgery without significant tissue resection, *e.g.,* appendectomy and herniorrhaphy);
    - History of inflammatory bowel disease;
    - History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of eGFR $<$ 90 mL/min/1.73m^2 or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria);
    - History or current evidence of ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if more than one of the following lab value deviations are found: 1) AST ($\geq$ 1.2 ULN), ALT ($\geq$ 1.2 ULN), 2) GGT ($\geq$ 1.2 ULN), ALP ($\geq$ 1.2 ULN), 3) bilirubin ($\geq$ 1.5 ULN) or CK ($\geq$ 3 ULN). A single deviation from the above values is acceptable and will not exclude the candidate, unless specifically advised by the investigator;
    - Evidence of urinary obstruction or difficulty in voiding at screening;
    - History or clinical evidence at screening of pancreatic injury or pancreatitis.
19. Pregnant or lactating women, or subjects intending to become pregnant over the duration of the study;
20. Positive results (or out of normal range) any of the virology tests for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody or syphilis .
21. Subject reports consumption of any drug metabolizing enzyme (e.g. CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements (e.g. broccoli, Brussels sprouts, grapefruit, grapefruit juice, star fruit, St. John's Wort etc.) within 2 weeks prior to screening until admission to the unit.
22. Performance of strenuous physical exercise (body building, high performance sports) from 2 weeks prior to admission.
23. Those who are not suitable for participation in this study as determined by the investigator.

5.4 Randomization Criteria

In each cohort, subjects will be randomized into the study provided they have satisfied all subject selection criteria. Subjects are assigned to TR sequence or RT sequence in a 1:1 ratio according to the randomization schedule.

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
- In the fasted cohort, after an overnight fasting for at least 10 hours, the subjects will take the test product or the reference product according to the randomization schedule with 240 mL of warm water under fasting condition on Day 1 during each period. The study drug granules must be mixed and stirred with 240 mL of warm water to be completely dissolved. The oral solution will then be left to cool down, to allow a rapid (less than 1 minute) and continuous ingestion by the subject.
- In the fed cohort, after an overnight fasting for at least 10 hours, the subjects will take a high-fat/high-calorie breakfast (completed within 30 minutes) and then take the test product or the reference product according to the randomization schedule on Day 1 in each period. The study drug granules must be mixed and stirred with 240 mL of warm water to be completely dissolved. The oral solution will then be left to cool down, to allow a rapid (less than 1 minute) and continuous ingestion by the subject.

  A high-fat/high-calorie breakfast contains about 800-1000 kcal, including about 500-600 kcal from fat (more than 50% of total calories), about 150 kcal from protein, and about 250 kcal from carbohydrates.
- Water consumption requirements: Water is prohibited from 1 hour before dosing to 1 hour after dosing on Day 1 in each cycle (except for water for dosing). Water is provided ad libitum at other times.
- Food consumption requirements: No food is allowed within 4 hours after administration.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 10 hours after dosing.
- Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals.
- Subjects will not be allowed to eat or drink beverages or food supplements (e.g. broccoli, Brussels sprouts, grapefruit or grapefruit-related citrus fruits (e.g. Seville oranges, pomelos, papaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits and St. John's Wort etc.) from admission to the clinic site until collection of the final PK blood sample.
- Meals intake during the study will also be standardized.

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will be prohibited from consuming alcohol and consuming any beverages or food containing caffeine, such as coffee, tea, coke, chocolate, etc., from screening until collection of the final PK blood sample.
- Subjects will abstain from the use of tobacco or nicotine containing products including nicotine patches and other delivery devices (such as electronic cigarettes or vaporizers) from screening and throughout the study.

5.5.3 Activity

- Subjects will not be permitted to assume a fully recumbent position for 4 hours following dosing (except when any AE(s) require(s) medical treatment).

- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for the duration of the study. Walking at a normal pace will be permitted.

5.5.4 Contraception

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for 30 days after the last dose of investigational product. The investigator or his or her designee will educate the subjects about highly effective methods of contraception (see below) and requirements about contraception during the informed consent process, admission education and during the study. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness as deemed appropriate by the investigator;
2. Intrauterine contraceptive device (IUD);
3. Male condom or female condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository);
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate;
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label);
6. Female who meets the criteria for non-childbearing potential as described below:

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level ≥ 40 mIU/mL;
- Have undergone a documented hysterectomy and/or bilateral oophorectomy.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, any protocol deviations and any AEs or incidents as applicable.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number for the sponsor's appropriately qualified medical personnel is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects will be provided with investigator's contacts in the informed consent form (ICF).

5.8 Rater/Clinical Assessor Qualifications

No rater/clinical assessor qualifications are required for this study.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonisation (ICH) guidelines, and GSK CH policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Product Supplies

The selection of the batches of Test and Reference product will be based on assay content to ensure that the products do not differ by more than 5%.

The following study products will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Study Product Supplies

	Test Product	Reference Product
Product Name	Ibuprofen Arginine Granules	Ibuprofen Arginine Granules (Spedifen)
Pack Design	Sachet	Sachet
Dispensing Details	Period 1- one sachet Period 2- one sachet	Period 1- one sachet Period 2- one sachet
Strength	400 mg (calculated with ibuprofen)	400 mg (calculated with ibuprofen)
Product Master Formulation Code (MFC)	CCI [redacted]	Commercial Product
Route of Administration	Oral	Oral
Manufacturer	Wyeth Pharmaceutical Co., Ltd.	CCI [redacted]
Storage	This product is sealed and stored at ambient temperature (10-30℃).	This product is sealed and stored at ambient temperature (10-30℃).

Return Requirements	Unused (excluding samples retained by the study site)	Unused (excluding samples retained by the study site)

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

Granules will be supplied to the clinical site as packaged carton for dispensing by the pharmacy.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

All products supplied are for use only in this clinical study and should not be used for any other purpose.

6.1.2 Preparation and Dispensing

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

Study product will be dispensed by qualified site personnel. An additional member of site staff should ensure the dispensing procedures are completed accurately.

6.2 Administration

Only subjects enrolled in the study may receive study products and only authorized site staff may supply or administer study products. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff only.

In the fasted cohort, after an overnight fasting for at least 10 hours, subjects will take one sachet of either the test product (400 mg ibuprofen) or one sachet of the reference product (400 mg ibuprofen) according to the randomization schedule. The study drug granules must be mixed and stirred with 240 mL of warm water to be completely dissolved. The oral solution will then be left to cool down, to allow a rapid (less than 1 minute) and continuous ingestion by the subject.

In the fed cohort, after an overnight fasting for at least 10 hours, subjects will take a high-fat/high-calorie breakfast (completed within 30 minutes) 30 minutes exactly before administration and then take either one-sachet of the test product (400 mg ibuprofen) or one-sachet of the reference product (400 mg ibuprofen) according to the randomization schedule under fed condition on Day 1 during each period. The study drug granules must be mixed and stirred with 240 mL of warm water to be completely dissolved. The oral solution will then be left to cool down, to allow a rapid (less than 1 minute) and continuous ingestion by the subject.

After administration, the study personnel will examine the subject's oral cavity to ensure the subject's compliance with the dosing.

6.2.1 Medication/Dosing Errors

Dosing errors may result, in this study, from the administration or consumption:

- of the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such dosing errors occurring to a study subject are to be captured in the case report form (CRF). In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours from its first knowledge.**

Dosing errors are reportable irrespective of the presence of an associated AE, including:

- Dosing errors involving subject exposure to any of the study products;
- Potential dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a dosing error is accompanied by an AE, as determined by the investigator, the dosing error and, any associated AE(s) are to be captured in the CRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study. Limited quantities of the study product(s) will be supplied, and closely monitored by the site for each subject.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and SAE, if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Study Product Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected products must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected products prior to sponsor approval will be considered a protocol deviation.

6.4 Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

In accordance with Chinese Good Clinical Practice (GCP) [14] and Technical Guidelines for Human Bioequivalence Studies of Chemical Generic Drugs Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators [1], the study site should retain samples of the test and reference products in accordance with relevant requirements. The retained sample shall be from the same batch as the drug administered in the study, and the quantity of the retained drugs shall be adequate for 5 full inspections according to the specifications. Retained samples will be stored by the study site until least 2 years after the product is marketed. The study site may entrust a qualified independent third party to store the retained samples, but the samples may not be returned to the sponsor or a third party with related interests.

At the end of the study, the principal investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products. The study product accountability record for returned study products (excluding samples retained by the study site) will then be completed. All unused study product for this clinical study, excluding samples retained by the study site, will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

This 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, statisticians etc.) should be using anonymised subject data.
Subjects will be assigned to TR sequence or RT sequence in a 1:1 ratio by randomization number at the site in fasted and fed cohorts. Randomization number consists of one letter K+3 digits number in the fasted cohort, and C+3 digits number in the fed cohort. Randomization will be based on the randomization scheme taking the lowest available number when assigning a subject.

6.6 Breaking the Blind

Not applicable.

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel. A mouth check will be performed to ensure consumption of the medication.

6.8 Concomitant Medication/Treatment(s)

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. The study Sponsor should be immediately informed. Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about medications/treatments at each site visit.

Prohibited medications: barbiturates, benzodiazepines ,cocaine, methadone, phencyclidine.

Medication/treatments taken within 90 days of signing the ICF and finished before the first dose will be documented as prior medication/treatments. Medications/treatments taken after the first dose will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety

- Positive test for COVID-19, conducted during the study, at times deemed necessary by investigator
- Withdrawal of informed consent
- Subject lost to follow-up
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF.

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit, the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return for a final visit and follow-up with the subject regarding any unresolved AEs.

Early termination safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following: vital signs, physical examination, 12-lead ECG, laboratory tests, blood pregnancy test (women of childbearing potential), COVID-19 test, and collection of concomitant medications/treatments and AE(s).

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations as long as the subject's safety was preserved.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities of protocol.

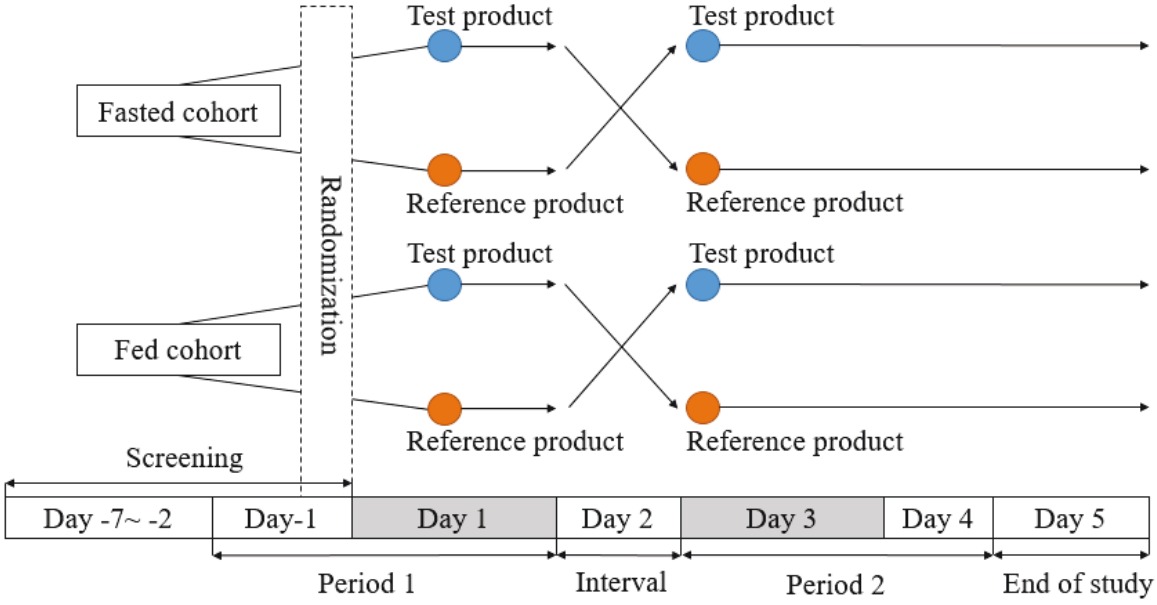
Adherence to the study design requirements, including all procedures are essential and required for study conduct.

The study visit plan includes:

- Screening (within 7 days prior to first dose);

- Period 1 (Day -1 and Day 1);
- Interval (Day 2): If the interval between 2 doses exceeds 2 days, the second dose and subsequent visits will be postponed accordingly;
- Period 2 (Day 3 to 4);
- End of study (Day 5).

Figure 1 Study Schematic



8.1 Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will be screened within 7 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed:

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the ICF will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the ICF will be captured as this is the point at which all AEs will be captured from. The date and time of consent will be captured in the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded in the CRF: gender, year of birth, ethnicity, and race.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2016.

8.1.3 Inclusion/Exclusion Criteria

The investigator and/or medically qualified designee will review inclusion/exclusion criteria as specified in STUDY POPULATION, medical history, smoking history and alcohol consumption history, prior/concomitant medications/treatments to confirm subject eligibility to participate in the clinical study. This will be documented in the CRF.

8.1.4 Medical History and Prior Medication/Treatment

Details of relevant medical history (in the last 5 years), transfusion/blood donation history (in the last 3 months), allergy history, surgical history, childbearing history, family history, menstrual history（female), drug abuse history, smoking history, alcohol consumption history, COVID-19 history and COVID-19 positive contact history (in the past 14 days) will be documented in the electronic CRF (eCRF).

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the 90 days prior to signing the ICF and finished before the first dose, will be documented in the eCRF.

8.1.5 Screening procedures

The following screening procedures should be completed 7 days prior to first administration: Height/weight measurement, full physical examination, vital signs examination, 12-lead ECG, laboratory tests (blood chemistry, hematology, urinalysis, coagulation), alcohol breath test, urine drug abuse screening, serology, blood pregnancy test (only in females of childbearing potential), hormone test (only in females who have been consecutively amenorrhoeic for 12 months), and AEs, prior/concomitant medications/treatments collection.

8.2 Study Period

8.2.1 Period 1

Day -1 (Period 1)

The fasted and fed cohorts will follow the same procedures on Day -1.

On Day -1, subjects will be admitted to the study ward, the following procedures will be performed: concomitant medications/treatments review, abbreviated physical examination, vital signs examination, alcohol breath test, urine drug abuse screening, blood pregnancy test (only in females of childbearing potential), COVID-19 test, and collect AEs. The inclusion/exclusion criteria will be reviewed again. Enrolled subject will be randomized on Day -1.

Day 1 (Period 1)

The fasted and fed cohorts have different procedures on Day 1.

Fasted cohort:

Within 2 hours before dosing:

- Vital signs (blood pressure, pulse, body temperature, and respiratory rate);
- PK blood sampling, completed within 2 hours prior to investigational product administration.

Administration of investigational product:

- See Administration for details.

Post-dose:

- A standard lunch will be provided approximately 4 hours after dosing, a uniform standard dinner will be provided approximately 10 hours after dosing, and water is not allowed until 1 hour after dosing;
- PK blood sampling (5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120 min, 2.5, 3, 4, 6, 8, and 12 h after oral administration, the blood collection window is detailed in Table 9-2);
- Collection of concomitant medications/treatments;
- Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF;
- Vital signs (3 [± 0.5], 6 [± 0.5] hours post-dose);
- Subjects will be remained in the study ward.

Fed cohort:

Within 2 hours before dosing:

- Vital signs (blood pressure, pulse, body temperature, and respiratory rate);
- PK blood sampling, completed within 2 hours prior to investigational product administration;
- High-fat/high-calorie breakfast (started exactly 30 minutes before dosing and completed within 30 minutes);

Administration of investigational product:

- See Administration for details.

Post-dose:

- A standard lunch will be provided approximately 4 hours after dosing, a uniform standard dinner will be provided approximately 10 hours after dosing, and water is not allowed until 1 hour after dosing;
- PK blood sampling (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 in Table 9-2);
- Collection of concomitant medications/treatments;
- Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF;
- Vital signs (3 [± 0.5], 6 [± 0.5] hours post-dose);
- Subjects will be remained in the study ward.

8.2.2 Interval

Day 2

The fasted and fed cohorts will follow the same procedures on Day 2.

Subjects will remain in the study ward on Day 2. They will be received the following examinations:

- Abbreviated physical examination;
- Vital signs (blood pressure, pulse, body temperature, respiratory rate);
- Laboratory tests (see Table 9-1 for specific tests);
- 12-lead ECG;
- Collection of concomitant medications/treatments;
- AE monitoring, and spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.3 Period 2

Day 3 (Period 2)

The fasted and fed cohorts have different procedures on Day 3.

Fasted cohort:

Within 2 hours before dosing:

- Vital signs (blood pressure, pulse, body temperature, and respiratory rate);
- PK blood sampling, completed within 2 hours prior to investigational product administration.

Administration of investigational product:

- See Administration for details.

Post-dose:

- A standard lunch will be provided approximately 4 hours after dosing, a uniform standard dinner will be provided approximately 10 hours after dosing, and water is not allowed until 1 hour after dosing;
- PK blood sampling (5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120 min, 2.5, 3, 4, 6, 8, and 12 h after oral administration, the blood collection window is detailed in Table 9-2);
- Collection of concomitant medications/treatments;
- Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF;
- Vital signs (3 [± 0.5], 6 [± 0.5] hours post-dose);
- Subjects will be remained in the study ward.

Fed cohort:

Within 2 hours before dosing:

- Vital signs (blood pressure, pulse, body temperature, and respiratory rate);
- PK blood sampling, completed within 2 hours prior to investigational product administration;
- High-fat/high-calorie breakfast (started exactly 30 minutes before dosing and completed within 30 minutes);

Administration of investigational product:

- See Administration for details.

Post-dose:

- A standard lunch will be provided approximately 4 hours after dosing, a uniform standard dinner will be provided approximately 10 hours after dosing, and water is not allowed until 1 hour after dosing;
- PK blood sampling (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 in Table 9-2);
- Collection of concomitant medications/treatments;
- Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF;
- Vital signs (3 [± 0.5], 6 [± 0.5] hours post-dose);
- Subjects will be remained in the study ward.

Day 4 (Period 2)

The fasted and fed cohorts will follow the same procedures on Day 4.

On Day 4, subjects can leave the study ward after completing the following examinations:

- Abbreviated physical examination;
- Vital signs (blood pressure, pulse, body temperature, respiratory rate);

- 12-lead ECG;
- Laboratory tests (see Table 9-1 for specific tests);
- Blood pregnancy test (female subjects of childbearing potential only);
- Collection of concomitant medications/treatments;
- AE monitoring, and spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

8.2.4 End of study

The subjects will complete an end-of-study (EOS) visit 2 days after last dose of study medication (Day 5). Due to any unforeseen circumstances if follow-up visit is not completed on day 5, this can be rescheduled and completed in next 2 days i.e., till day 7. The follow-up visit can be done via telephone if the subject does not need to receive any examination, as judged by the investigator. The investigator or his/her authorized staff shall complete the following procedures after discharge from the study ward:

- Concomitant medications/treatments;
- Spontaneous reporting of AEs and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed and any AEs recorded in the CRF.

Subjects may be asked to return to the ward for follow-up if deemed necessary by the investigator.

8.3 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page. And efforts should be made to complete the **early termination** safety assessment as described in Lost to Follow up of protocol.

If a subject has any clinically significant, study-related abnormalities or AEs at the end of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the STUDY PROCEDURES of this protocol.

9.2 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the STUDY PROCEDURES of this protocol.

9.2.1 Laboratory Tests

The following laboratory tests/analytical measures will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in STUDY PROCEDURES of this protocol. Specific clinical laboratory tests are detailed in Table 9-1.

Table 9-1 Laboratory Tests

Blood chemistry Creatine kinase Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transpeptidase Total protein Albumin Total bilirubin Direct bilirubin Urea Creatinine Total cholesterol Triglycerides Serum calcium Phosphorous Sodium, potassium, chlorine Fasting glucose	**Hematology** Red blood cell count (RBC) Hematocrit Hemoglobin White blood cell count (WBC) Differential white blood cell count (including percentages and absolute counts of neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count
Blood Pregnancy test (for women of childbearing potential only) **Hormone test** (postmenopausal women only) Follicle stimulating hormone (FSH)	**Urinalysis** Urine white blood cells (dry chemistry) Nitrite Urine pH Urine specific gravity Urine protein Urine glucose Urine ketones Urobilinogen Urine bilirubin Urine occult blood White blood cells (sediment) Red blood cells (sediment)
Routine coagulation test Plasma prothrombin time Activated partial thromboplastin time (APTT) International normalized ratio (INR) Fibrinogen (FIB)	**Serology** HBsAg HBcAb HCV Ab HIV antibody Syphilis
Urine drug abuse screening	**Alcohol breath test**

Morphine Amphetamines/methamphetamine Ketamine Methylene dioxymetham-phetamine Tetrahydrocannabinolic acid	breath alcohol concentration

Additional laboratory results may be reported on these samples because of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests or results would not require additional collection of blood. Unscheduled clinical lab tests may be obtained at any time during the study to assess any perceived safety concerns.

9.2.2 Serology

The following serology tests will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in STUDY PROCEDURES of this protocol: HBsAg, HBcAb, HCV antibody, HIV antibody and Syphilis. In case of a positive (or out of normal range) finding in virus serology screen, the subject must be excluded from trial participation.

9.2.3 Urine Drug Abuse Screening

The following drugs will be screened by appropriately trained staff/clinical examiners, at the times and in the order defined in STUDY PROCEDURES of this protocol: morphine, amphetamines/methamphetamine, ketamine, methylene dioxymetham-phetamine, tetrahydrocannabinolic acid. In case of a positive finding for any substance class, the subject must be discontinued from the trial (or excluded from trial participation in case of positive findings at the screening visit).

9.2.4 Alcohol Breath Test

The alcohol breath test will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in STUDY PROCEDURES of this protocol. In case of the result in the alcohol test is out of the negative range, the subject must be discontinued from the trial.

9.2.5 Pregnancy Testing

For female subjects of childbearing potential, a blood pregnancy test, will be performed on screening, Days -1 and 4/ early termination.

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of institutional review boards/ethics committees (IRBs/ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study, and study termination procedures will be followed.

9.2.6 Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will be required at screening, and an abbreviated physical examination will be acceptable for all the

other visits. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, cardiovascular and neurological systems. An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Any untoward findings identified on physical exams conducted after the administration of the first dose of investigational product will be captured as an AE, if those findings meet the definition of an AE.

9.2.7 Height and Weight

Height in meters and body weight in kilograms (kg) to the nearest 0.1 kg will be measured.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

BMI can be calculated by a calibrated device directly. The unit of BMI is kg/m^2.

9.2.8 Blood Pressure and Pulse Rate

Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary at the discretion of the investigator, to ensure appropriate collection of safety data.

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mmHg after a minimum 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study.

A calibrated blood pressure cuff of the same proper size will be used to measure blood pressure each time. The use of an automated device for measuring blood pressure and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

9.2.9 Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in sitting position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

9.2.10 Temperature

Body temperature will measure the ear temperature.

9.2.11 Electrocardiogram

A standard 12-lead ECG will be performed at screening. Interpretation of the tracing must be made by a qualified physician or designee and documented on the ECG section of the CRF. Each ECG tracing should be kept in the source documents at the study site. Results or any clinically significant abnormalities should be reported in the CRF. Clinically significant abnormalities should also be recorded on the Adverse Event CRF. 12-lead ECG parameters include heart rate, PR interval, QRS interval, QT interval and QTcF interval. 12-lead ECGs will

be performed with the subject in a sitting position having rested in this position for at least 5 minutes before the exam.

9.2.12 COVID-19 test

Nasal/nasopharyngeal swab will be collected to test for COVID-19 using PCR or antigen test, at times specified in the STUDY PROCEDURES section. For detection of COVID-19, tests are to be performed as follows:

- At check-in (Day -1)
- At any time during residential period in study, when subjects report symptoms suggestive of COVID-19 as defined by WHO or local guidance

If transportation is required then to provide transportation reimbursement to subjects to and from the unit to avoid public transportation.

9.3 Pharmacokinetics (PK)

Fasted cohort: 18 blood samples will be collected for PK analysis, within 2 hours prior to dosing (pre-dose), and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120 min, 2.5, 3, 4, 6, 8, and 12 h following dosing in each treatment period. Therefore 36 blood samples will be collected for each subject.

Fed cohort: 18 blood samples will be collected for PK analysis, within 2 hours prior to dosing (pre-dose), and at 10, 30, 45, 60, 75, 90, 120 min, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 h following dosing in each treatment period. Therefore 36 blood samples will be collected for each subject.

Time zero ("0") as reference for post-dose PK samplings is defined as the time of drug administration. All PK blood sampling collection times will be recorded in the CRF. A dead-volume intravenous catheter will be used for blood collection to avoid multiple skin punctures, when appropriate. Otherwise, blood samples will be collected by direct venipuncture.

9.3.1 Plasma for Analysis of ibuprofen

During all study periods, blood samples (3 mL) to provide approximately 1.5 mL plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylene diamine tetraacetic acid (K_2EDTA) at times specified in the protocol. All centrifuged plasma samples will be divided into 2 parts and stored in a freezer at the test facility for PK analysis. The actual blood sample requirements for PK analysis shall be dependent on the laboratory manual CCI [redacted] or other contracted central lab etc.).

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within allowable time windows will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g. CRF).

Table 9-2 Table of Permissible Deviation for Blood Collection Time

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

Planned sampling time point	Time window
> 60 min and ≤ 4 h post-dose	± 2 minutes
> 4 h and ≤ 12 h post-dose	± 5 minutes

The specific biological sample handling procedures shall be detailed in the laboratory manual.

9.3.2 Shipment of Pharmacokinetic Samples

The actual shipment of blood sample requirements shall be dependent on the laboratory manual. All PK samples will be stored until they are properly disposed of at the end of its retention period (i.e., 2 years after clinical study report is issued), or useful life (i.e., until expiry of stability), upon written request by Sponsor, or upon receipt of a request to destroy the PK samples due to withdrawal of consent. No sample will be retained beyond 2 years after clinical study report.

9.4 Blood Volume

The total blood sampling volume for each subject in this study is up to 159 mL. The table below reflects approximate sample volumes needed for each measured endpoint. Additional blood samples may be taken for safety assessments at the discretion of the investigator.

Table 9-3 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs	9	1	2	-	27
Serology	8	1	-	-	8
Blood pregnancy test[a]	4	2	1	-	12
Hormone test[a]	4	1	-	-	4
PK	3	-	36	-	108
TOTAL					143 (minimum) 159 (maximum)

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

Footnotes:

a. Females of childbearing potential should complete the blood pregnancy test. Follicle-stimulating hormone (FSH) done only in females who have been consecutively amenorrhoeic for 12 months.

b. In the event of early termination or reexamination due to abnormal laboratory parameters, the total approximately blood volume should be calculated separately. The blood sample volume required for each examination is the same as the above table.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the investigational product or the study, or that caused the subject to discontinue the study product or study.

10.1 Definition of an Adverse Event (AE)

An 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).

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events that do not meeting the definition of an AE include:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A SAE is a particular category of an AE where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for expected progression of or death due to the pre-existing disease or the disease under study, unless more severe than expected).

A SAE is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**

  Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**

  Note: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Other situations:**

  Note: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent to participate in the study by the completion (signature) of the ICF and until 30 days following last administration of the study product (or last procedure). Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from its first knowledge. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

Spontaneous reporting of AEs and those elicited by asking subjects to respond to non-leading such as “How do you feel” will be assessed and any AE’s recorded in the CRF and reported appropriately.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is not acceptable for the investigator (or medically qualified designee) to send original records or photocopies of the subject’s medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be documented as the AE/SAE when known and not the individual signs/symptoms. (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a

consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be sent to contract research organization (CRO), CCI **immediately and under no circumstance should this exceed 24 hours** of first awareness. CRO will then email the SAE form to the Case Management Group, Global Safety at GSK CH PPD with copy to the appropriate GSK CH Study Manager as soon as possible, **but not later than one business day** after receiving the SAE form from the study site. The GSK CH Study Manager will be responsible for forwarding the SAE form to other GSK CH personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity/Severity

The investigator or medically qualified designee will make an assessment of intensity/severity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

Note: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity/severity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The degree of certainty about causality will be graded using the categories below.

- **Reasonable Possibility that AE is related -Yes**: The AE is known to occur with the study product, there is a reasonable possibility that the study product caused the AE, or there is a temporal relationship between the study product and event.
- **Reasonable Possibility that AE is related -No:** There is not a reasonable possibility that the administration of the study product caused the event, there is no temporal relationship between the study product and event onset, and an alternate etiology is likely.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship and will also consult the IB, Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK CH. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition. All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of

the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE). The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD
The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Safety mailbox at GSK CH PPD

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.8 Regulatory Reporting Requirements for SAEs

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other applicable regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies of a female subject reported while subjects are participating in the study from the signing of informed consent until 30 days after last administration of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will collect pregnancy information on female subject while participating in the study after administration of the study product. The investigator will record pregnancy information on the appropriate form and submit it to CRO within 24 hours of learning of the female subject becoming pregnant.

If a female subject becomes pregnant, she must stop the study product immediately and withdrawn from the study. The female subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to CRO. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

If the outcome of the pregnancy meets the criteria of SAEs (e.g., spontaneous abortion, stillbirth, death of newborn or congenital anomaly, including aborted fetus, stillbirth, or death of newborn), the investigator needs to follow the procedures for reporting SAEs.

CRO will scan and email the pregnancy form to the Case Management Group, Global Safety mailbox at GSK CH PPD with copy to the appropriate GSK CH Study Manager.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an eCRF, using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified. The CRF and or diary can be used as a source document at the discretion of data management.

Subjects will be sequentially assigned randomization numbers in the order of screening numbers.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each study subject.

For each subject who has given informed consent/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personal Information (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

Refer to the appropriate vendor CRO handbook and study-specific CRF specifications as needed for the study.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using a validated medication dictionary, WHODrug.

11.3 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety, rights and well-being of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.4 External Data

External Data are subject data obtained externally to the CRF and other sources such as patient reported outcome. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 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 [15]), 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 [16]. 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.

12.2 Populations for Analysis

Analysis Populations: Analysis populations includes randomized population, safety analysis population, pharmacokinetic concentration set, pharmacokinetic parameter 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 analyses. 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 subject 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.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). SAS Version 9.4 or above version will be applied for statistical analysis. For quantitate data, descriptive summary including the number of evaluable volunteers, mean, standard deviation (SD), median, maximum and minimum values will be performed. For categorical variables, number of volunteers and proportions will be summarized. Throughout the statistical methods the fasted cohort and fed cohort will be summarized and analyzed separately.

12.3.1 Pharmacokinetic Analysis

12.3.1.1 Concentration Analysis

Plasma concentration analysis of ibuprofen will be based on PKCS. Descriptive statistical analysis will be conducted to summarize drug plasma concentration data by treatment groups at each planned sampling time point. Descriptive statistics for plasma concentration will include arithmetic mean, SD, CV%, median, maximum (observed), minimum (observed), geometric mean, etc. The mean, SD, and CV% 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, and the scheduled blood collection time for 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.

12.3.1.2 Parameter Analysis

The PK parameter analysis of ibuprofen will be based on PKPS. The non-compartmental analysis modeling in software CCI [redacted] 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. Descriptive statistics for the PK parameters will include arithmetic mean, SD, CV%, median, maximum, minimum, geometric mean and geometric CV%, etc.

The PK parameters will be calculated as follows:

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 below:

$AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$ (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.

12.3.2 Bioequivalence Analysis

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 and sequence as fixed effects using PROC MIXED.

For both fasted and fed cohorts, the general approach average bioequivalence (ABE) is constructing a 90% CI for the quantity $\mu_T - \mu_R$. If this CI is contained in the interval (80%, 125%), ABE is concluded.

The ABE hypothesis tests are:

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

and

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

By rejecting the null hypothesis, we conclude ABE.

The point estimates (test/reference GMR) will be calculated for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for Ibuprofen.

90% CIs for the difference between least square means of test and reference formulations will be obtained in ANOVA for ln-transformed PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for Ibuprofen. 90% CI for the geometric least squares mean (LSM) ratio will be obtained by taking the exponent of lower and upper limits of 90% CI, obtained for the least square mean difference.

For Ibuprofen, based on the statistical results of 90% CIs for the GMR of (T/R) for the PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, conclusions will be drawn whether test formulation is bioequivalent to reference formulation. Acceptance range for bioequivalence is 80.00%-125.00% for 90% CIs of the geometric means ratio for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$.

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.

12.3.3 Safety Analysis

Safety analyses will be performed based on SS.

12.3.3.1 Adverse event

AEs will be coded using the preferred terms (PTs) from the ICH MedDRA of the most recent version at the time of database lock, and grouped by system organ class (SOC). The severity of AEs will be graded as mild, moderate, and severe. The number and percentage of subjects will be summarized for all treatment-emergent adverse events (TEAEs), SAEs, investigational product-related TEAEs, investigational product-related SAEs, and TEAEs leading to study discontinuation by medication (T/R) and sequence (TR/RT) based on PT and SOC. In addition, the severity of TEAEs and their relationship to investigational product will also be summarized by medication (T/R) and sequence (TR/RT) based on PT and SOC. AEs due to COVID-19, if any, will be listed and tabulated separately.

12.3.3.2 Laboratory Tests

Descriptive statistical analysis of all laboratory results and changes from baseline will be performed by scheduled time point and group, and laboratory abnormalities (mainly focusing on the occurrence of normal or abnormal results before treatment but abnormal values after treatment) will be summarized by time-point and treatment. Summary statistics will include mean, SD, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

12.3.3.3 12-lead ECG

Descriptive statistical analysis of results of 12-lead ECGs and changes from baseline will be performed by scheduled time point and group, and ECG abnormalities (mainly focusing on the occurrence of normal or abnormal results before treatment but abnormal values after treatment) will be summarized by time-point and treatment. Summary statistics will include mean, SD, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

12.3.3.4 Vital Sign, Physical Examination

The vital sign, physical examination, and other safety-related abnormalities (mainly focusing on the occurrence of normal or abnormal results before treatment but abnormal values with clinical significance after treatment) will be summarized by time-point and treatment. Summary statistics will include mean, SD, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

12.3.4 Exclusion of Data from Analysis

The subjects with protocol deviation will be reviewed at the data review meeting prior to database lock. Exclusion of any data from the analyses will be determined after discussion by biostatisticians, investigator or designee. Any reasons for exclusion from an analysis population will be recorded.

12.3.5 Subject Disposition

The total number of subjects screened, and the number of screening failures will be listed. The number and percentage of subjects who complete the study, and dropout and the main reasons for dropout (lost to follow-up, AEs, poor compliance, etc.) will be calculated by group.

The number and percentage for subject distribution in each analysis population will be calculated by group.

12.3.6 Demographic and Baseline Characteristics

Descriptive statistical analysis will be performed on demographic characteristics such as age, height, sex, weight, and other baseline characteristics such as disease history for all randomized population.

12.3.7 Study Product Compliance and Use of Other Therapies

12.3.7.1 Study Product Compliance

Exposure to study medication during the study period will be presented for the SS. Number and percentage of subjects who administered the investigational product will be summarized by group and study period.

12.3.7.2 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the SS.

12.3.8 Handling of Dropouts and Missing Data

If any concentration data is missing or deviates from the planned time of collection, then the pharmacokineticist may calculate the PK parameters using the available data.

For handling of values BLQ, will refer to Section 12.3.1.

12.3.9 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK CH requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK CH or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety, rights and well-being of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the

regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent and/or assent documents, IB/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), NMPA GCP (2020), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent OR assent documents must be in compliance with GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent OR assent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety, rights and well-being of a subject or the reliability and robustness of the data generated in GSK CH-sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13.4 Posting of Information on Publicly Available Clinical Study Registers

Study information from this protocol will be posted on publicly available clinical study registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

GSK CH intends to make anonymized subject-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually-agreeable location.

GSK CH will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator as per the signed contractual agreement, from the issue of the final Clinical Study Report or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of test product at any time.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authorities and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a study, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

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15 APPENDICIES

15.1 ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 15-1 Abbreviations

Abbreviation	Term
ABE	average bioequivalence
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
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
BCS	biopharmaceutics classification system
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
CRO	contract research organization
CV	coefficient of variation
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio
GSK CH	GlaxoSmithKline Consumer Healthcare
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LLOQ	lower limit of quantification

Abbreviation	Term
LSM	least squares mean
MedDRA	medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
NSAID	nonsteroidal anti-inflammatory drug
PCR	polymerase chain reaction
PK	pharmacokinetics
PKCS	pharmacokinetic concentration set
PKPS	pharmacokinetic parameter set
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum concentration
WBC	white blood cell
WHO	World Health Organization
λ_z	terminal elimination rate constant
$\%AUC_{ex}$	percentage of extrapolated area of $AUC_{0-\infty}$

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