16.1.1 Protocol and Protocol Amendments

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Study Final Protocol Amendment 2 dated 30-NOV-2022

CLINICAL PROTOCOL 218677

A Randomized, Open label, Single Center, Single Dose, Two Treatment, Two Period, Two Sequence Crossover Bioequivalence Study of Advil PM Liqui-Gels Minis (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) To Advil PM Liqui-Gels (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) in Healthy Adult Subjects Under Fasted Conditions

Protocol Number:	218677
Compound/Product Name:	Advil PM Liqui-Gels Minis
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	Not applicable
Other Regulatory Agency Identified Number:	Not applicable
Phase:	I

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** 184 Liberty Corner Rd., Warren, NJ 07059 United States of America (USA)

Document History

Document	Version	Summary of Changes
Original protocol	2.0	Not applicable (N/A)
Amendment 1	3.0	Added Acceptability to Table 3.1 Objectives and Endpoints Added the ease of swallowing to section 4.1 study design and schedule of activities Updated Table 6.1 with new Product Master Formulation Code (MFC) Updated section 8.2 with timing of acceptability assessment Updated section 9.4 with **a**cceptability of "ease of swallowing" Updated section 12.3.4 with statistical methods for the ease of swallowing assessment
Amendment 2		Updated safety reporting sections 10.4.2, 10.6, 10.9.2 and 10.11 Deleted one duplicated PK timepoint in section 4.1

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 DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A bioequivalence study of Advil PM Liqui-Gels Minis (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) compared to the current marketed Advil PM Liqui-Gels (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) in healthy adult subjects under fasted conditions.

Background and Rationale:

This study will be conducted to support the submission of Advil PM Liqui-Gels Minis (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) which is a size reduction of the currently marketed Advil PM Liqui-Gels, by determining if this product is bioequivalent to the reference product Advil PM Liqui-Gels (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) under fasting conditions. Advil PM Liqui-Gels Minis was developed as a smaller capsule alternative to the currently marketed product.

Bioequivalence studies are most sensitive to detect formulation differences (when such differences exist) after a single dose. The optimal design is therefore a randomized, open-label, 2-treatment, 2-period, 2-sequence, single dose bioequivalence trial in fasted subjects.

Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
Demonstrate the bioequivalence of Advil PM Liqui-Gels Minis (Test) compared to Advil PM Liqui-Gels (Reference)	For ibuprofen and diphenhydramine: • C_{max} (The maximum observed post-dose concentration; obtained without interpolation) • AUC_{0-t} (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule) • AUC_{0-inf} (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0-inf} = AUC_{0-t} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant)

Secondary	
Pharmacokinetics	
Assess the pharmacokinetic (PK) profile	For ibuprofen and diphenhydramine: • λ_z (The terminal elimination rate constant computed as the negative of the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time excluding C_{max}) • t_{max} (The time of the maximum observed post-dose concentration) • $t_{1/2}$ (The elimination half-life computed as $t_{1/2} = \ln(2)/ \lambda_z$) • V_z/F (apparent volume of distribution, as calculated by the dose administered/(λ_z x AUC_{0-inf}) • Cl/F (apparent total clearance, as calculated by the dose administered/ AUC_{0-inf})
Acceptability	
Assess subject acceptability of each of the two products	Ease of swallowing (5-point ordinal scale)
Safety	
Assess the safety profile	• Monitoring and recording of adverse events (AEs) • Physical examination • Vital signs • Laboratory tests

Study Design:

This is a single center, single dose, open-label, randomized, two-treatment, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects with at least a 7-day washout period.

The study is intended to dose in more than one group; all groups will be dosed at the same clinical site and the same protocol requirements and procedures will be followed within each group.

Blood will be sampled regularly at scheduled times for 48 hours following treatment.

Subjects will be randomly assigned to one of 2 treatment sequences and receive a single dose of one of the following treatments in each period following a crossover design:

Treatment A: 2X Advil PM Liqui-Gels Minis; (ibuprofen/diphenhydramine hydrochloride 200mg/25mg) (Test);

Treatment B: 2X Advil PM Liqui-Gels; (ibuprofen/diphenhydramine hydrochloride 200mg/25mg) (Reference).

The study will consist of an ambulant screening day within 28 days prior to first product administration and two study periods. In each period, subjects will be confined from the day before dosing (Day -1) until 48 hours post-dosing (Day 3), during which time PK blood samples will be collected within one hour prior to dosing and at 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 10, 12, 16, 24, 36, and 48 hours following dosing (24, 36, and 48 hours for diphenhydramine only). Carry-over effects will be avoided by a washout interval of at least 7 days between investigational product administrations.

According to data from studies CCI and CCI, ibuprofen t_{max} is expected from CCI hours after dosing. Diphenhydramine t_{max} is expected from CCI CCI hours after dosing. Ibuprofen half-life is expected to be up to CCI hours and diphenhydramine half-life is expected to be up to CCI hours.

Following an overnight fast of at least 10 hours, subjects will receive the investigational product in the fasted state. During each period, the investigational product will be administered by clinical staff and administered along with approximately 240 mL of ambient temperature water. Subjects will be instructed to consume the entire amount of water along with their investigational product. Immediately after dosing subjects will be asked to evaluate the ease of swallowing of each product.

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.

For each subject the duration of study participation is 38 days of which up to 3 days confined in each period (total of up to 6 days confined).

Study Products:

	Test Product	Reference Product
Product Name	Advil PM Liqui-Gels Minis	Advil PM Liqui-Gels

Dose/Application	2X liquid filled capsules	2X liquid filled capsules
Route of Administration	Oral	Oral

Type and Planned Number of Subjects:

A sufficient number of male and female subjects will be screened to randomize approximately 44 to ensure at least 37 evaluable subjects (refer to section 12.1) complete the entire study. An effort will be made to include similar proportions of males and females in the study.

Statistical Methods:

The PK analysis set will be used for the PK evaluations. It includes all subjects of the PK population who complete both treatment periods, and for which the relevant PK parameters (at least one AUC or C_{max}) can be derived. Subjects with baseline concentration >5% of the individual C_{max} for either period will be excluded from the PK analysis set. This analysis set will be used in summaries, the primary PK analysis, and the secondary PK analysis.

The PK parameters that will be used in the primary analyses are $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

For ibuprofen and diphenhydramine separately, a linear mixed effects model will be fit to the log-transformed PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}), as the dependent variable, and treatment, sequence, and period as fixed effects. Subject nested within sequence will be a random effect. The treatment least-squares means (LSMs), difference between treatment LSMs, and 90% confidence interval (CI) for the difference will be computed. The adjusted LSM and LSM difference with 90% CIs for the differences will be exponentiated to provide estimates of the adjusted treatment effects, ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratio. If all study subjects are not recruited from the same enrollment pool and the study doses in more than one group, the statistical model may be modified to reflect the multigroup nature of the study. Bioequivalence will be declared for a given parameter/analyte if the 90% 2-sided CI for the ratio is between 80% and 125% for ibuprofen and diphenhydramine.

One scale will be used to measure the acceptability of the easiness to swallow. Frequencies (number, percentage) will be tabulated.

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	Treatment Periods 1 and 2[a]				End of Study[*]
Study day	-28 to -2	-1	1	2	3	3
Confinement		x	x	x		
Discharge					x	
Informed consent	x					
Demography	x					
Medical history	x					
Physical examination[b]	x	x				x
Height, weight, BMI	x					
Vital signs (BP, PR, RR, OT)	x	x[c]	x[c]	x[c]	x[c]	x
12-lead ECG	x					
Laboratory tests	x					x
COVID-19 test[d]	x	x			x	x
Serology	x					
Urine pregnancy test[e]	x					x
Serum pregnancy test[e]		x				
FSH[f]	x					
Urine drug screen	x	x				
Urine cotinine test	x	x				
Alcohol breath test	x	x				
Inclusion/exclusion assessment	x	x	x[g]			
Randomization			x[h]			
Drug administration			x			
Acceptability			x			
PK blood sampling[i]			x	x	x	
Concomitant treatments	x	x	x	x	x	x
Adverse events[j]	x	x	x	x	x	x
Study Conclusion						x

Abbreviations: BMI, BP, ECG, FSH, OT, PK, PR, RR

Footnotes:

*These assessments are also to be conducted for subjects who discontinue study drug. End of Study will occur before discharge, on study Day 3 of Period 2.

[a]The washout period between each drug administration will be at least 7 days.

[b]A full physical examination will be performed at screening and a brief physical examination will be performed on Day -1 in each treatment period and at End of Study.

[c]Blood pressure (BP), pulse rate (PR), respiratory rate (RR), oral body temperature (OT): pre-treatment on Day 1 (within 1 hour before drug administration) of each treatment period. Oral body temperature (OT) on Day -1, Day 2 and Day 3 of each treatment period (Note: the oral body temperature obtained on Day 3 of Period 2 can be used as the oral body temperature required at End of Study).

[d]Before the first dosing two consecutive tests (locally approved tests [PCR or Antigen]) separated > 24 hours will be performed: one test at screening within 72 hours of admission and one test at check-in (Day-1). Before the second dosing two consecutive tests (locally approved tests [PCR or Antigen]) separated > 24 hours will be performed: one test during the washout period within 72 hours of admission and one test at check-in (Day-1). If the first test is > 72 hours prior to unit admission, subjects should be advised to self -quarantine until entrance to the unit while awaiting final testing clearance. Subjects who report symptoms suggestive of COVID-19 while in the research unit should be isolated in the unit or at home and tested for COVID-19 infection using an approved molecular test. One test (locally approved tests [PCR or Antigen]) should be performed before releasing the subject from the unit in each period or at early discontinuation (Note: the COVID-19 test performed on Day 3 of Period 2 can be used as the test required at End of Study)

[e]for all females of childbearing potential.

[f]FSH done only in females who have been amenorrhoeic for at least 12 months.

[g]At the discretion of the investigator, subjects could continue the study if any deviation to the inclusion/exclusion criteria does not anticipate to alter study integrity.

[h]Randomization conducted prior to the first dosing (Period 1).

[i]PK blood samples will be collected within one hour prior to dosing and at 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 10, 12, 16, 24, 36, and 48 hours following dosing in each treatment period (24, 36, and 48 hours for diphenhydramine only).

[j]AEs and therefore all serious adverse events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the informed consent form.

2 INTRODUCTION

GSK Consumer Healthcare has developed a reduced filled softgel formulation containing ibuprofen 200 mg and diphenhydramine hydrochloride 25 mg as an analgesic sleep-aid combination product.

2.1 Study Background and Rationale

This study will be conducted to support the submission of Advil PM Liqui-Gels Minis (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) which is a size reduction of the currently marketed Advil PM Liqui-Gels, by determining if this product is bioequivalent to the reference product Advil PM Liqui-Gels (ibuprofen/diphenhydramine hydrochloride 200 mg/25 mg) under fasting conditions. Advil PM Liqui-Gels Minis was developed as a smaller capsule alternative to the currently marketed product.

Bioequivalence studies are most sensitive to detect formulation differences (when such differences exist) after a single dose. The optimal design is therefore a randomized, open-label, 2-treatment, 2-period, 2-sequence, single dose bioequivalence trial in fasted subjects.

2.2 Benefit/Risk Assessment

Complete information for Advil PM Liqui-Gels may be found in the single reference safety document (SRSD), which for this study is the approved US Drug Facts Label for the reference product Advil PM Liqui-Gels.

2.3 Mechanism of Action/Indication

To relieve occasional sleeplessness associated with pain at night, Advil PM Liqui-Gels Minis contains 2 active ingredients per liquid filled capsule: one pain reliever (200 mg ibuprofen) to treat pain and a sleep aid (diphenhydramine hydrochloride 25 mg), with a proposed dose of 2 liquid filled capsules at bedtime to help pain sufferer gently fall and stay asleep.

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) whose mechanism of action is thought to involve inhibition of both isoforms of enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2. Ibuprofen is a racemate; the molecule contains a single stereogenic carbon atom. The anti-inflammatory, antipyretic and analgesic properties of Ibuprofen are thought to be mainly due to inhibition of COX-2, through the (S)-enantiomer of Ibuprofen. The (R)-enantiomer is thought to be pharmacologically inactive. The (R)-enantiomer undergoes some degree of conversion to the (S)-enantiomer after absorption.

Diphenhydramine hydrochloride is available globally in over-the-counter (OTC) allergy, cough, and cold medicines. It is an ethanolamine and first-generation H_1 antagonist that acts as a reversible, competitive inhibitor of histamine binding to the H_1 receptor. H_1 antagonists,

especially ethanolamines, have significant antihistaminic and antimuscarinic activities and concurrent sedative properties.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
Demonstrate the bioequivalence of Advil PM Liqui-Gels Minis (Test) compared to Advil PM Liqui-Gels (Reference)	For ibuprofen and diphenhydramine: • C_{max} (The maximum observed post-dose concentration; obtained without interpolation) • AUC_{0-t} (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule) • AUC_{0-inf} (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0-inf} = AUC_{0-t} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant)
Secondary	
Pharmacokinetics	
Assess the PK profile	For ibuprofen and diphenhydramine: • λ_z (The terminal elimination rate constant computed as the negative of the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time excluding C_{max}) • t_{max} (The time of the maximum observed post-dose concentration) • $t_{1/2}$ (The elimination half-life computed as $t_{1/2} = \ln(2)/ \lambda_z$) • V_z/F (apparent volume of distribution, as calculated by the dose administered/(λ_z x AUC_{0-inf})

	• Cl/F (apparent total clearance, as calculated by the dose administered/ AUC_{0-inf})
Acceptability	
Assess subject acceptability of each of the two products	Ease of swallowing (5-point ordinal scale)
Safety	
Assess the safety profile	• Monitoring and recording of AEs • Physical examination • Vital signs • Laboratory tests

This study will be considered successful if bioequivalence is demonstrated between Advil PM Liqui-Gels Minis (Test) compared to Advil PM Liqui-Gels (Reference).

4 STUDY DESIGN

4.1 Overall Design

This is a single center, single dose, open-label, randomized, two-treatment, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects with at least a 7-day washout period.

The study is intended to dose in more than one group; all groups will be dosed at the same clinical site and the same protocol requirements and procedures will be followed within each group.

Blood will be sampled regularly at scheduled times for 48 hours following treatment.

A sufficient number of male and female subjects will be screened to randomize approximately 44 to ensure at least 37 evaluable subjects (refer to section 12.1) complete the entire study. An effort will be made to include similar proportions of males and females in the study.

Subjects will be randomly assigned to one of 2 treatment sequences and receive a single dose of one of the following treatments in each period following a crossover design:

Treatment A: 2X Advil PM Liqui-Gels Minis; (ibuprofen/diphenhydramine hydrochloride 200mg/25mg) (Test);

Treatment B: 2X Advil PM Liqui-Gels;(ibuprofen/diphenhydramine hydrochloride 200mg/25mg) (Reference).

The study will consist of an ambulant screening day within 28 days prior to first product administration and two study periods. In each period, subjects will be confined from the day

before dosing (Day -1) until 48 hours post-dosing (Day 3), during which time PK blood samples will be collected within one hour prior to dosing and at 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 10, 12, 16, 24, 36, and 48 hours following dosing (24, 36, and 48 hours for diphenhydramine only). Carry-over effects will be avoided by a wash-out interval of at least 7 days between investigational product administrations.

According to data from studies CCI and CCI, ibuprofen t_{max} is expected from CCI hours after dosing. Diphenhydramine t_{max} is expected from CCI CCI hours after dosing. Ibuprofen half-life is expected to be up to CCI hours and diphenhydramine half-life is expected to be up to CCI hours.

Following an overnight fast of at least 10 hours, subjects will receive the investigational product in the fasted state. During each period, the investigational product will be administered by clinical staff and administered along with approximately 240 mL of ambient temperature water. Subjects will be instructed to consume the entire amount of water along with their investigational product. Immediately after dosing subjects will be asked to evaluate the ease of swallowing of each product.

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.

Figure A- study design

Screening	Periods 1 and 2[a]	End of study
Day -28 to -2	Day -1 to 3	Day 3 of Period 2

[a]Washout period of at least 7 days between each dosing

For each subject the duration of study participation is 38 days of which up to 3 days confined in each period (total of up to 6 days confined).

4.2 Scientific Rationale for Study Design

This will be an open label study. Blinding is not considered essential as study measurements (plasma ibuprofen and diphenhydramine concentrations) are biological.

A crossover design, using the same subjects to test each product, will be used to reduce variability.

The blood sampling times have been chosen based on the information available particularly on ibuprofen and diphenhydramine absorption, as well as their elimination.

Non-smokers have been chosen as the population for this study to reduce variability.

The following guidance have been followed for designing the study:

- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (FDA 2014)
- Bioavailability Studies Submitted in NDAs or INDs — General Considerations (FDA 2019)

4.3 Justification for Dose

This is a study to assess the bioequivalence of the test product to a commercial reference product.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases 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 in the study.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

A sufficient number of male and female subjects will be screened to randomize approximately 44 to ensure at least 37 evaluable subjects (refer to section 12.1) complete the entire study. An effort will be made to include similar proportions of males and females in the study.

An enrolled subject is one who has agreed to participate in the 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 fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the 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 protocol.

Subject eligibility to participate in the 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 to be eligible to be included into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.

2. Male or female subject who, at the time of screening, is between the ages of 18 and 55 years, inclusive.
3. Subject who is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
4. Healthy subject, which is defined as in general good physical health, as judged by the investigator and no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests.
5. Body Mass Index (BMI) of 18.5 to 30.0 kg/m^2; and a total body weight ≥50.0 kg for males and ≥45.0 kg for females.
6. Female subject of childbearing potential 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 subject who is not of childbearing potential must meet requirements in section 5.5.4.
7. Subject with two negative tests (one at screening within 72 hours of admission and one one at check in Day-1 in Period 1) for active COVID-19, separated by > 24 hours.

5.3 Exclusion Criteria

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

1. Subject who is an investigational site staff member directly involved in the conduct of the study and his/her family members, site staff member otherwise supervised by the Investigator, or subject who is a GSK employee directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.
3. Acute or chronic medical or psychiatric 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.
4. Pregnant female subject as confirmed by a positive pregnancy test or intending to become pregnant over the duration of the study.
5. Breastfeeding female subject.
6. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients (D&C red no. 33, FD&C blue no. 1, gelatin, medium-chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitol sorbitan solution).

7. Any history of asthma, urticaria, or other significant allergic diathesis or allergic reaction to any other pain reliever/fever reducer. Subject with uncomplicated seasonal allergic rhinitis can be accepted if expected allergy season is clearly outside enrollment/treatment period.
8. Diagnosis of long QT syndrome or QTcF > 450 msec for males and > 470 msec for females at screening.
9. Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or pulse rate less than 50 or over 100 bpm).
10. Unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
11. Use of any medication (including OTC medications and herbal remedies) within 2 weeks or within less than 10 times the elimination half-life of the respective drug (whichever is longer) before first scheduled study drug administration, 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 daily).
12. Evidence or history of clinically significant laboratory abnormality, 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.
13. Clinically relevant chronic or acute infectious illnesses or febrile infections within two weeks prior to start of the study.
14. 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 or gastrointestinal bleeding including peptic ulcers;
    - History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine (> 1.43 mg/dL) or BUN

(≥ 35 mg/dL) 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 (≥ 1.2 ULN), ALT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) total bilirubin (> 2.00 mg/dL) or creatine kinase (≥ 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 (e.g. due to benign prostate hyperplasia) or difficulty in voiding at screening;
- Diagnosis of angle-closure (narrow angle) glaucoma;
- History or clinical evidence at screening of pancreatic injury or pancreatitis.

15. Subject with signs and symptoms suggestive of COVID-19 (i.e. fever, cough, etc.)* within 14 days of inpatient admission. **as defined by WHO or local guidance*
16. Subject with known COVID-19 positive contacts in the past 14 days.
17. Any vaccination, including COVID-19 vaccine, within 14 days prior to the first dose.
18. History of drug abuse within 1 year prior to screening or recreational use of soft drugs (such as marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening.
19. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%).
20. Positive urine drug screen or alcohol breath test at screening.
21. Subject reported regular consumption of beverages or food containing xanthine derivatives or xanthine-related compounds (e.g., coffee, tea, caffeine-containing sodas and chocolate), equivalent to ≥ 500 mg xanthine per day.
22. Current smoker, defined as the use of tobacco or nicotine products during the 3 months prior to screening until admission to the unit or a positive urine cotinine test at screening.
23. 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 admission to the unit.

24. Positive results in any of the serology tests for HIV antigen and antibody, HCV-Ab, HBsAg and HBc-Ab (IgG + IgM).
25. Performance of strenuous physical exercise (body building, high performance sports) from 2 weeks prior to admission and throughout the entire study.
26. 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 subject.
27. 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.
28. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to dosing.
29. Hemoglobin value < 12.0 g/dL for males and < 11.5 g/dL for females.
30. Subject who has previously been enrolled in this study.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

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 and 10 hours prior to the collection of the pre-dose PK sample. Water is permitted until 1 hour prior to investigational product administration.
- Water may be consumed without restriction beginning 1 hour after dosing.
- Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 10 hours after dosing.
- An evening snack may be permitted approximately 2 hours after the evening meal.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (e.g. Seville oranges, pomelo, papaya, pineapple, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits) from 2 weeks prior to admission to the unit until collection of the final PK blood sample.

- Subjects will not be allowed to eat food containing poppy seeds from 24 hours prior to admission of each period.
- Meals intake during the study will be standardized.

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 48 hours prior to admission to the clinical site and continue abstaining from alcohol until collection of the final PK sample of each study period. Subjects may undergo an alcohol breath test at screening, at admission of each period, and at the discretion of the investigator.
- Subjects will abstain from food or beverages containing xanthine derivatives or xanthine-related compounds (coffee, black/green tea, chocolate) or energy drinks for 48 hours prior to the start of dosing until collection of the final PK sample of each study period.
- 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.
- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests and throughout the entire study. Walking at a normal pace will be permitted.

5.5.4 Contraception

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 (including self-reported) hysterectomy and/or bilateral oophorectomy.

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

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, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. 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 partner sterilization with absence of sperm in the post-vasectomy ejaculate (self-reported);
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed [self-reported] in accordance with the device's label);

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) may not be re-screened.

Subjects who have successfully completed the screening procedures but were not selected for a given group (e.g., reserve subjects) may be invited to another screening session for participation in a subsequent group.

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 electronic investigator study master file.

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 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 a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

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 Harmonization (ICH) guidelines, and GSK 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.

This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

The selection of the Reference product (the currently marketed and commercially available Advil PM Liqui-Gels), will be based on assay content to ensure that this product does not differ by more than 5% from that of the batch used as Test product (Advil PM Liqui-Gels Minis).

The following study products (including retention samples) will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Investigational/Study Product Supplies

	Test Product	Reference Product
Product Name	Advil PM Liqui-Gels Minis	Advil PM Liqui-Gels
Pack Design	Bottles	Bottles
Dispensing Details	Two liquid filled capsules once	Two liquid filled capsules once
Product Master Formulation Code (MFC)	CCI [redacted]	Commercial Product
Dose/Application	2X liquid filled capsules	2X liquid filled capsules
Route of Administration	Oral	Oral
Usage Instructions	• Administer study medication with 240 mL of ambient temperature water • Instruct subjects to consume the entire amount of water along with their investigational product	• Administer study medication with 240 mL of ambient temperature water • Instruct subjects to consume the entire amount of water along with their investigational product
Return Requirements	All unused samples and empty packaging bottles to be returned	All unused samples and empty packaging bottles to be returned
Retain samples	To keep at site	To keep at site

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item*	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Alere 10 Drugs Integrated E-Z Split Cup	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
BD Vacutainer®, Urine Collection Tubes and Kits, BD Medical	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Alere hCG Combo Cassette 20/10 mIU/mL Pregnancy Tests REF#CCI	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
COT Cotinine Test Device DCT-102	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Sarstedt Microtube 2mL PP REF:CCI	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Vacuette tube K2EDTA 3 mL 13x75 lavender cap-black ring, non-ridged	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
VACUETTE® Blood Collection Tubes Serum CAT Serum Sep Clot Activator 3.5 mL	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Urine Collection Cup with Transfer Device	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Urine Collection Tube Plastic 10 mL	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Regular Polyester Swab with Plastic Applicator	Biomedical Laboratory	Commercial pack	Use as per study schedule	Discard/destroy at biomedical laboratory facility using biomedical laboratory disposal procedures	To keep at site

Smiths Medical Peripheral IV Catheter Protectiv® Plus 20 G x 1"	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
BD Peripheral IV Catheter Insyte™ Autoguard™ BC 18 G x 1.16" Winged, Safety	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
3M Tegaderm Transparent Dressing 2 3/8 x 2 3/4"	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Surgical Tape Transparent Plastic 1" X 10 Yard	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Kendall Underpad Tendersorb 23 x 36 ", Disposable	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Medline OnGuard Blood Collection Tube Holder	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
3M Compression Bandage Coban™ NonWoven Material / Elastic Fibers 1" X 5 Yard NonSterile	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
BD IV Flush Solution,PosiFlush™ Sodium Chloride, Preservative Free 0.9% Intravenous, Prefilled Syringe 3 ml in 10 mL	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Medline MediGuard ES S, M, L ,X-L Powder-Free Nitrile Exam Gloves	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Kendall Alcohol Prep-Pads, Medium,Sterile	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
Gauze Sponge 2 x 2" 8-Ply Non-Sterile	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
BD Vacutainer® Eclipse™ Blood	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site

Collection Needle 21 G x 1¼", Safety Shield					
Dukal Dawnmist Tourniquet, Flat, White	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
covidien Sharps Container Monoject™, 14 Quart Red Base /Translucent Lid Vertical Drop Chimney	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
K-Shield Advantage Winged Blood Collection Set 21 G x 3/4" Safety Shield	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site
BD Vacutainer® Blood Collection Tube, Discard Tube, Plain, Plastic, Hemogard™, 6 mL 13 X 100 mm	Site/CRO	Commercial pack	Use as per study schedule	Discard/destroy at site using site disposal procedures	To keep at site

Equivalent items can also be used based on supplier availability. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the study in time for study close out visit. Sundry items will be supplied by the site/vendor and will be discarded or destroyed at the clinical site.

6.1.1 Dosage Form and Packaging

Liquid filled capsules will be supplied to the clinical site as packaged bottles 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 Global 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 CCI , prior to the start of the study, using validated software.

Study product will be dispensed by qualified site personnel per the dosage/administration instructions. 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.

Following an overnight fast of least 10 hours, subjects will receive investigational product. Investigator site personnel will administer investigational product during each period with ambient temperature water to a total volume of 240 mL and will instruct subjects to consume the entire amount of water along with their investigational product. A hand and mouth check will be performed to ensure consumption of the medication.

Subjects will swallow the investigational product whole and will not manipulate or chew the medication prior to swallowing. To standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required by procedures), eating, and drinking beverages for the first 4 hours after dosing. Water may be given after 1 hour post-dosing.

6.2.1 Medication/Dosing Errors

Medication/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 medication/dosing errors occurring to a study subject are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Medication/dosing errors are reportable irrespective of the presence of an associated AE, including:

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

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated AEs 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.

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 Investigational/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, including any actions taken, must be documented as a protocol deviation and reported to the sponsor.

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

6.4 Investigational/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.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty packaging bottles), 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

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

Dummy randomization will be supplied by CCI to the Sponsor. Upon confirmation of general layout, an unblinded statistician not directly involved in the study will generate the final randomization.

CCI will provide the final randomization schedule to the investigator and, in accordance with the randomization numbers and treatment allocations, the subject will receive the study treatment sequence assigned to the corresponding randomization number.

Treatments will be provided in an open-label manner. However, the analytical laboratory will remain blinded to treatment during the analysis of the plasma samples.

6.6 Breaking the Blind

Not applicable given the open-label study design.

6.7 Compliance

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

6.8 Concomitant Medication/Treatment(s)

Subjects will abstain from all concomitant treatments, 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 when the integrity of the study is at jeopardy. Any medications, treatments, or vaccine (including OTC 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.

Medication/treatments taken within 90 days of signing the informed consent form will be documented as a prior medication/treatment. 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 or sponsor for safety, behavioral reasons, major non-compliance with protocol requirements, 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
- Pregnancy
- Withdrawal of informed consent

- Subject lost to follow- up

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 repeatedly 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 and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved AEs.

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion, which could include the following:

- urine pregnancy test,
- physical examination,
- safety laboratory tests,
- seated blood pressure, respiratory rate, oral body temperature and pulse rate measurements.

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 so 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 section.

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

8.1 Screening

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

Subjects will be screened within 28 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. The informed consent form will be signed and dated by the subject. A copy will be given to the subject, and the original signed and dated ICF will be maintained in the subject's records.

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. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

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 informed consent form 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: year of birth, gender, 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, 2005.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information, as specified in Section 5, will be documented in the CRF.

8.1.4 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 5 years), including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 90 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.5 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Considerations and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.1.6 Screening Procedures

The following procedures will be completed:

- Obtain written informed consent and record in the CRF.
- Review inclusion and exclusion criteria and record in the CRF.
- Collect demography, including year of birth, gender, ethnicity and race and record in the CRF.
- Collect height and weight and calculate BMI. The results for each measurement will be recorded in the CRF.
- Obtain medical history as related to the inclusion/exclusion criteria, including any relevant medical or surgical history, allergies or drug sensitivity, history of drug and alcohol use. Significant findings that are present before consent must be included in the CRF.

- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 90 days prior to consent, and record in the CRF.
- Obtain seated blood pressure, pulse rate, respiratory rate, and oral body temperature. The results for each measurement will be recorded in the CRF.
- Conduct full physical examination. Any clinically relevant findings will be noted in the AE CRF page and enrollment will be based upon investigator judgement.
- Contraceptive review.
- Collect single 12 lead ECG. Results (normal or abnormal) and clinical significance will be recorded on the CRF.
- Following at least a 4 hour fast, collect blood and urine specimens for the following, and recorded on the CRF:
  - Safety laboratory tests and serology;
  - Urine drug screening;
  - Alcohol screening;
  - Cotinine screening;
  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months;
  - Urine pregnancy test for all females of childbearing potential.
- 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.
- Collect nasal/nasopharyngeal swab sample for COVID-19 test within 24 to 72 hours prior to check-in (Day -1) in Period 1. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.

8.2 Study Periods

For each study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible:

- Vital signs: obtain as close as possible to scheduled time, but prior to blood specimen collection;
- PK blood specimens: obtain at scheduled time.

Obtain all other procedures as close as possible to the scheduled time but may be obtained before or after blood.

8.2.1 Day -1

In each period, subjects will be admitted to the clinical site the day prior to Day 1 dosing.

The following procedures will be completed following admission to the clinical site:

- Review inclusion and exclusion criteria and record in the CRF.
- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Brief physical examination including evaluation of general appearance, heart, lung. The results will be recorded in the CRF.
- Collect urine for drug screening. The results will be recorded in the CRF.
- Collect urine for cotinine screening. The results will be recorded in the CRF.
- Obtain blood for serum β-hCG for all females of childbearing potential. The results will be recorded in the CRF (note: blood for serum β-hCG can be obtained at admission or in the morning of Day -1).
- Collect nasal/nasopharyngeal swab sample for COVID-19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.
- Confirm proper contraception is being used and the results will be recorded on the CRF.
- Collect alcohol breath test. Result will be recorded on the CRF.
- Meals as required in section 5.5.1. Time and consumption of meals will be recorded on CRF.
- Subjects will begin fasting at least 10 hours prior to dosing on Day 1.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- 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.

8.2.2 Day 1

Prior to dosing in each period, within one hour of study drug administration, the following procedures will be completed:

- Obtain seated blood pressure, pulse rate, respiratory rate, and oral body temperature. The results for each measurement will be recorded in the CRF.
- Review inclusion and exclusion criteria and record in the CRF.

- Randomization (conducted prior to the first dosing in Period 1).
- Collect a blood sample for PK analysis. Time of blood sampling will be recorded in the CRF.
- After all pre-dose procedures have been completed, administer the investigational product (see Investigational/Study Products section) and record in the CRF.

After dosing, the following procedures will be completed:

- Acceptability: ease of swallowing (5-point ordinal scale).
- Collect blood samples for PK analysis at the following time points after dosing on Day 1: 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 10, 12, and 16 hours. The time tolerance window for blood samples will be ±1 minute for all samples collected before 8 hours post-dose and ±3 minutes for subsequent samples. Time of blood sampling will be recorded in the CRF.
- Meals as required in section 5.5.1. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- 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 Day 2

The following procedures will be completed on Day 2 of each period:

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Collect blood samples for PK analysis (for diphenhydramine only) at 24 and 36 hours post dosing of Day 1 continuing into Day 2. The time tolerance window for blood samples will be ±3 minutes. Time of blood sampling will be recorded in the CRF.
- Meals as required in section 5.5.1. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- 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 Day 3

The following procedures will be completed on Day 3 of each period:

- Obtain oral body temperature. The results for each measurement will be recorded in the CRF.
- Collect blood samples for PK analysis (for diphenhydramine only) at 48 hours post dosing of Day 1 continuing into Day 3. The time tolerance window for blood samples will be ±3 minutes. Time of blood sampling will be recorded in the CRF.
- Meals as required in section 5.5.1. Time and consumption of meals will be recorded on CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- 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.
- Collect nasal/nasopharyngeal swab sample for COVID-19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.
- After all procedures are completed, subjects are discharged from the clinical site.

8.2.5 Washout Period

The washout period between each drug administration will be at least 7 days. The following procedure will be completed during the washout period:

- Collect nasal/nasopharyngeal swab sample for COVID-19 test within 24 to 72 hours prior to check-in (Day -1) in Period 2. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.

8.2.6 End of Study

The exit examination procedures will be done before check-out from the clinic, on study Day 3 of Period 2.

- Obtain seated blood pressure, pulse rate, respiratory rate and oral body temperature. The results for each measurement will be recorded in the CRF. (Note: the oral body temperature obtained on Day 3 of Period 2 can be used as the oral body temperature required at End of Study)
- Conduct brief physical examination. The results will be recorded in the CRF.
- Collect nasal/nasopharyngeal swab sample for COVID-19 test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF. (Note:

the COVID-19 test performed on Day 3 of Period 2 can be used as the test required at End of Study)

- Obtain blood and urine samples for safety laboratory tests.
- Collect urine pregnancy test for all females of childbearing potential. The results will be recorded in the CRF.
- Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.
- 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.

8.3 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.

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.

8.4 Follow-up Visit

The study site may contact a subject to follow up an AE post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

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 section 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 section 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.

Table 9-1 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Drug, cotinine, and alcohol screens**
Hematocrit Hemoglobin MCH MCHC MCV Platelet count RBC count WBC count and differential: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Albumin ALP ALT AST Calcium Chloride Creatine kinase Creatinine GGT Glucose Phosphorus Potassium Sodium Total bilirubin Total protein Urea (BUN)	Bilirubin Blood (occult) Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination[a]	Amphetamines /methamphetamines Barbiturates Benzodiazepines Cocaine MDMA Methadone Opiates PCP THC Urine cotinine test Alcohol breath test
Serology	**Hormone panel - females only**	**Other tests**	
HBsAg HBc-Ab (IgG + IgM) HCV-Ab HIV antigen/antibody	Serum FSH[b] Serum pregnancy test[c] Urine pregnancy test[d]	COVID-19 PCR or antigen	

Definitions: ALP= alkaline phosphatase; ALT= alanine transaminase; AST= aspartate transaminase; BUN= blood urea nitrogen; HBc-Ab= Hepatitis B core antibody; HBsAg= hepatitis B surface antigen; HCV-Ab= hepatitis C virus antibodies; HIV= human immunodeficiency virus; FSH= follicle-stimulating hormone; GGT= gamma-glutamyl transpeptidase; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; MDMA= 3,4- methylenedioxymethamphetamine; PCP= phencyclidine; RBC= red blood cell; THC= tetrahydrocannabinol; WBC= white blood cells.

[a]In the event of abnormal findings (per safety laboratory internal protocols)

[b]FSH done at screening only in females who have been amenorrhoeic for at least 12 months

[c]All female subjects of childbearing potential will be tested for serum human chorionic gonadotropin (hCG) at Day -1 of each period

[d]All female subjects of childbearing potential will undergo a urine pregnancy test at Screening and End of Study

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 would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive investigational product.

Any remaining serum/plasma from samples collected for clinical safety labs will be destroyed at the end of the study.

9.2.2 Serology

Virus serology will be performed at times specified in the Study Procedures section of this protocol for HIV antigen and antibody, HBsAg, HBc-Ab (IgG + IgM) and HCV-Ab. In case of a positive finding in virus serology screen, the subject must be excluded from trial participation.

9.2.3 Urine drug screen

Urine will be collected at times specified in the Study Procedures section of this protocol. 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 test

An alcohol breath test will be conducted at times specified in the Study Procedures section of this protocol. In case of a positive finding in the alcohol test, the subject must be discontinued from the trial.

9.2.5 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at screening and End of Study and a serum pregnancy test will be performed on Day -1 of each period. Results will be obtained prior to dosing during each period.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

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 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.

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 include head, ears, eyes, nose, throat, mouth, skin, heart and lung examinations, lymph nodes, abdominal, musculoskeletal, vascular, and neurological systems.

A brief physical examination will be focused on general appearance, heart and lung examinations, as well as towards subject reported symptoms.

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 centimeters (cm) and body weight in kilograms (kg) to the nearest 0.1 kilogram 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 will be calculated in 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.

Seated blood pressure should be measured with the subject's arm supported at the level of the heart with feet flat on the floor and recorded to the nearest mmHg after a minimum 5 minutes of rest.

Subjects should be instructed not to speak during measurements.

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. 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.

9.2.9 Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in seated 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 after the 5 minutes of rest.

9.2.10 Temperature

Body temperature will be measured orally.

No eating or drinking is allowed for 15 minutes prior to the measurement.

9.2.11 Electrocardiogram

A standard 12 lead ECG will be performed at screening after the subjects have been resting for at least 5 minutes in a supine position. 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 findings must be discussed with the GSK CH Clinical Project Lead (CPL) prior to enrolling the subject in the study. Subjects should be in a quiet environment and not speak during the resting period or measurement.

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 Procedure 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 at screening within 72 hours of admission and one test will be done on Day -1 in Period 1.

For detection of COVID-19, test/s are to be performed as follows:

- During the screening
- At check-in (Day -1 of each period)
- During the washout period
- At discharge from Period 1 and End of Study or early discontinuation
- At any time during residential period in study, when subjects report symptoms suggestive of COVID-19

If the first test is > 72 hours prior to unit admission, subjects should be advised to self-quarantine until entrance to the unit while awaiting final testing clearance. Subjects who report symptoms suggestive of COVID-19 while in the research unit should be isolated in the unit or at home and tested for COVID-19 infection using an approved molecular test.

9.3 Pharmacokinetics (PK)

Thirty-two (32) blood samples will be collected for PK analysis: within one hour prior to dosing (pre-dose) and at 10, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 6, 8, 10, 12, 16, 24, 36, and 48 hours following dosing in each treatment period (24, 36, and 48 hours for diphenhydramine only). Time zero ("0") as reference for post-dose PK samplings is defined as the time of drug administration. Time zero 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 and Diphenhydramine

During all study periods, blood samples (3 mL for ibuprofen and 3 mL for diphenhydramine) to provide a minimum of 1 mL plasma for PK analysis of each analyte will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the protocol.

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.

Samples will be analyzed using a validated analytical method in compliance with applicable CCI standard operating procedures.

The PK samples must be processed and shipped as indicated in the Analytical Methodology Information Sheet (AMIS) to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

9.3.2 Shipment of Pharmacokinetic Samples

When applicable, samples will be transported to the assay lab in at least two separate shipments, with each set of aliquots in separate shipments. Once the assay lab confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to keep them frozen for at least 72 hours.

All PK samples will be stored until they are properly disposed of at the end of its retention period (i.e., until 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 from last participant last visit.

9.4 Acceptability of "ease of swallowing"

Immediately after dosing the subject will answer the following questions.

"Do you agree or disagree that the product is Easy to swallow?

Rank the 'ease of swallowing' of the product on the following scale from 1 to 5:

5= very easy to swallow

4 = above average to swallow

3 = average to swallow

2 = somewhat easy to swallow

1 = not easy to swallow

9.5 Blood Volume

The total blood sampling volume for each subject in this study is approximately 417 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total number of PK blood samples will not increase. Additional blood samples may be taken for safety assessments at the discretion of the investigator or GSK CH.

Table 9-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	End of Study	
Safety Labs screening	21	1			21
Safety Labs end of study	12.5			1	12.5
Serum Pregnancy Test	8.5		2		17
PK (ibuprofen)	3		58		174
PK (diphenhydramine)	3		64		192
TOTAL					416.5

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

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 study 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 AE Definition:

- 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 NOT meeting the AE definition:

- 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 signs/symptoms of the disease under study, death due to progression of disease).

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

- **Results in death**
- **Is life-threatening**
  - 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**
  - 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**
  - 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.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - 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.

Note: 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 5 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.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. 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 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 the documented as the AE/SAE where 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 scanned and e-mailed to the Case Management Group mailbox CCI, with copy to the appropriate CH Study Manager, with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed 24 hours** of it being available.

The initial report will be followed up with more information as relevant, or as requested by the CH study manager.

The CH Study Manager will be responsible for forwarding the SAE form to other CH personnel as appropriate.

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10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The investigator or medically qualified designee will make an assessment of intensity 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 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 investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

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. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the approved US Drug Facts Label for the reference product Advil PM Liqui-Gels, 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.

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.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **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 as may be indicated or as requested by GSK CH 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 Case Management Group mailbox CCI , with copy to the appropriate CH Study Manager.

The investigator will submit any updated SAE data to GSK CH within the designated reporting time frames.

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 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.

Both the investigator and the sponsor will comply with all local medical device reporting requirements

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the Case Management Group mailbox CCI , with copy to the appropriate CH Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

The 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 by the investigator to the Case Management Group mailbox CCI with copy to the appropriate CH Study Manager. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

10.10.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.11 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the Case Management Group mailbox CCI [redacted] with copy to the appropriate CH Study Manager with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report

form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

The investigator will follow the following directions regarding the reporting of a device failure (malfunction):

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by GSK CH, return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the investigator site, report the incident to the device manufacturer and follow the manufacturer instructions for the return of the failed device (whilst keeping GSK CH informed).

10.12 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.13 Regulatory Reporting Requirements for Medical Device Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

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 electronic CRF (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, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, 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 can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Subject Number. Any reference made to an individual subject within the study must be done using their unique Subject Number.

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 trial 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 CCI 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 Personally Identifiable Information (PII) (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.

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 WHO Drug Dictionary (WHO DD).

11.2.1 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. A query should be issued to update the verbatim towards a codable description.

The study monitor will perform ongoing review 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 and rights 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.

11.3 External Data

External Data are subject data obtained externally to the CRF. 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

A sufficient number of subjects will be screened to randomize approximately 44 to ensure at least 37 evaluable subjects complete the entire study.

Assuming the true bioavailability of Advil PM Liqui-Gels Minis is within 8.0% of Advil PM Liqui-Gels, a sample size of 37 subjects will provide at least 80% power to establish (using a one-sided alpha of 0.05) that the bioavailability of Advil PM Liqui-Gels Minis is within 80% and 125% of Advil PM Liqui-Gels for the log transformed AUC and C_{max} parameters for both ibuprofen and diphenhydramine components. This assumes a variability (intra-subject coefficient of variation [CV%]) of CCI for the log transformed C_{max} for ibuprofen [the highest observed CV% out of the primary parameters in previous legacy GSK CH studies where Advil PM Liqui-Gels were a treatment arm CCI and CCI]. Considering a drop out or discontinuation rate of approximately 10%, a total of 44 subjects will need to be enrolled.

12.2 Populations for Analysis

The screened population is defined as all subjects who were screened with the intentions to receive with the investigational product.

The safety population is defined as all randomized subjects who receive at least one dose of study medication.

The PK population is defined as all randomized subjects who have at least one post-dose PK value, and who have no major protocol deviations concerning PKs.

The following PK analysis set is defined to address the PK objectives and further PK considerations within this study:

- PK analysis set includes all subjects of the PK population who complete both treatment periods, and for which the relevant PK parameters (at least one AUC or C_{max}) can be derived. Subjects with baseline concentration >5% of the individual C_{max} for either period will be excluded from the PK analysis set. This analysis set will be used in summaries, the primary PK analysis, and the secondary PK analysis.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (SAP), which will be written following finalization of the protocol and prior to study analysis and finalized prior to database lock. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The SAP creation and statistical analysis will be performed by CCI CCI

PK variables will be calculated by CCI .

All concentration and PK data will be listed. This includes any data for subjects who are not included in the analysis (e.g. subjects withdrawn from the study due to AEs).

12.3.1 Primary Analysis(es)

Primary Pharmacokinetics Analysis Variables

For ibuprofen and diphenhydramine, PK parameters will be derived using the actual sampling times after database lock and unblinding and are defined as follows:

- C_{max}: maximum observed post-dose concentration; obtained without interpolation.
- AUC_{0-t}: area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule.
- AUC_{0-inf}: area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0-inf} = AUC_{0-t} + C(last)/\lambda_z$ where C(last) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant.

Statistical Methods:

The BE between Advil PM Liqui-Gels Minis (test) and Advil PM Liqui-Gels (reference) under fasted conditions will be declared as per FDA requirements:

- if the 90% CIs for the ratio of the geometric means of the primary PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} is between 80% and 125% for ibuprofen and diphenhydramine.

For ibuprofen and diphenhydramine separately, a linear mixed effects model will be fit to the log-transformed PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}), as the dependent variable, and treatment, sequence, and period as fixed effects. Subject nested within sequence will be a random effect. The treatment LSMs, difference between treatment LSMs, and 90% CI for the difference will be computed. The adjusted LSM and LSM difference with 90% CIs for the differences will be exponentiated to provide estimates of the adjusted treatment effects, ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratio. If all study subjects are

not recruited from the same enrollment pool and the study doses in more than one group, the statistical model may be modified to reflect the multigroup nature of the study. As noted above BE will be declared for a given parameter/analyte if the 90% 2-sided CI for the ratio is between 80% and 125% for ibuprofen and diphenhydramine.

12.3.2 Secondary Analysis(es)

Secondary Pharmacokinetics Analysis Variables

To further assess the PK profiles of ibuprofen and diphenhydramine the following PK parameters will be derived also using actual sampling times:

- λ_z - terminal elimination rate constant computed as the negative of the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time excluding C_{max}.
- t_{max} - time of the maximum observed post-dose concentration.
- $t_{1/2}$ - elimination half-life computed as $t_{1/2} = \ln(2)/ \lambda_z$.
- V_z/F - apparent volume of distribution calculated by the dose administered/(λ_z x $AUC_{0\text{-inf}}$)
- Cl/F - apparent total clearance calculated by dose administered/ $AUC_{0\text{-inf}}$

Statistical Methods:

The PK parameters (λz, t_{max}, $t_{1/2}$, V_z/F, and Cl/F) will be summarized for each treatment and analyte using descriptive statistics same as for the primary PK parameters.

12.3.3 Safety Analysis(es)

The assessment of safety will be based on the frequency and severity of treatment emergent AEs (TEAEs) i.e. AEs that are emergent or that worsen after the first study product (Test or Reference) administration.

The incidence of TEAEs will be summarized by presenting, for each treatment, the number and percentage of subjects having any AE, any AE in each MedDRA System Organ Class (SOC) and having each individual AE. The subset of AEs suspected of a relationship to study drug will be presented in a similar manner. All TEAEs will be also tabulated by severity. Any other information collected (e.g. action taken, duration, outcome) will be listed. AEs will be assigned to the treatment administered immediately prior to the onset. AEs due to COVID-19, if any, will be listed and tabulated separately.

Vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature) data will be reviewed and summarized on an ongoing basis during the study, as applicable, to evaluate the safety of the subjects. Any clinical laboratory or vital signs abnormalities of potential concern

will be described. Safety data will be presented in a tabular format and summarized descriptively, where appropriate.

Medical history and physical examination, as applicable, will be listed with abnormal values flagged.

Laboratory data and ECGs collected at screening and used for inclusion/exclusion criteria will be considered source data, and will not be required to be reported, unless otherwise noted.

12.3.4 Ease of Swallowing

On Day 1 of each period, immediately after dosing, the assessment of 'ease of swallowing' will be done via one question with a categorical response ("Do you agree or disagree that the product is Easy to swallow?") and one question with an ordinal response ("Rank the 'ease of swallowing' of the product on the following scale from 1 to 5").

Descriptive statistics for the categorical response will be summarized by n (frequency count) and percent, for each treatment, separately. Similarly, descriptive measures for the ordinal response will be summarized by a frequency distribution of treatment by response.

In addition, descriptive statistics (n, mean, SD, Min, median, and Max) will be calculated for the ordinal response, for each treatment.

12.3.5 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

Data from subjects who experience emesis during the study should be deleted from statistical analysis if vomiting occurs at or before 2 times median T_{max}. Plasma concentration data from subjects who vomited during the study should be flagged and reported even though they were excluded from the analysis.

12.3.6 Demographic and Baseline Characteristics

Baseline data, relevant screening data, and demographic characteristics will be summarized for all randomized subjects.

12.3.7 Study Drug/Product Compliance and Use of Other Therapies

12.3.7.1 Study Drug/Product Compliance

The number of subjects exposed to each treatment will be tabulated for the safety population. Treatment deviations for individual subjects will be listed and summarized.

12.3.7.2 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the safety population.

12.3.8 Handling of Dropouts and Missing Data

All existing data for subjects who are dropouts from the study will be included in the PK statistical analysis.

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.

Missing values of λ_z can be estimated from the subject's mean λ_z value from the other treatments. If a λ_z value cannot be calculated from the other treatments, then the λ_z will be obtained from the treatment mean value for subjects with non-missing values of λ_z in the period in which it is not available. This estimated λ_z can be used to calculate other λ_z dependent variables. This λ_z value derivation is only applied for pre-dose concentration adjustments.

For ibuprofen and diphenhydramine concentrations:

- Below the limit of quantification (BLOQ) values obtained before the first measurable concentration will be imputed as zero.
- BLOQ values obtained after the first measurable concentration will be "Not detectable" (ND), which will be shown as missing (explanations will be specified in the footnote of TFLs).

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 and rights 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 documents, investigator brochure/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), 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 use of initials should be avoided.

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 documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent 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.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

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 and rights 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 Trial Registers

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

GSK intends to make anonymized subject-level data from this trial 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 trial 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 (CSR) 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 ibuprofen/diphenhydramine hydrochloride formulation 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 authority(ies) 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 trial, 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.

14 REFERENCES

1. Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28. Available on request
2. ICH Topic E6 (R2) Guideline for Good Clinical Practice, Nov 2016.
3. World Medical Association Declaration of Helsinki, 64th General Assembly, Fortaleza 2013.
4. [FDA Draft Guidance, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs— General Considerations March 2014]
5. [FDA Draft Guidance, Bioavailability Studies Submitted in NDAs or INDs— General Considerations February 2019]

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
λ_z	terminal elimination rate constant
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AMIS	analytical methodology information sheet
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-t}	area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t
AUC_{inf}	area under the plasma concentration versus time curve calculated from time 0 to infinity
BDR	blinded data review
BE	bioequivalence
BLOQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
Cl/F	apparent total clearance
C_{max}	maximum observed post-dose concentration
COX	cyclooxygenase
CPL	clinical project lead
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
EC	ethics committee

Abbreviation	Term
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	electronic data capture
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GSK CH	GlaxoSmithKline Consumer Healthcare
HBc-Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV-Ab	hepatitis C virus antibodies
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICF	informed consent form
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	Investigational New Drug
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LSM	least-squares mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDMA	3,4- methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
ND	not detectable
NSAID	nonsteroidal anti-inflammatory drug
OT	oral body temperature
OTC	over-the-counter
PCP	phencyclidine
PII	personally identifiable information

Abbreviation	Term
PK	pharmacokinetic(s)
PR	pulse rate
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	statistical reporting and analysis plan
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference study document
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	elimination half-life
TEAE	treatment emergent adverse event
TFL	tables, figures, and listings
THC	tetrahydrocannabinol
t_{max}	time of the maximum observed post-dose concentration
ULN	upper limit of normal
UK	United Kingdom
USA	United States of America
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHO DD	WHO drug dictionary