16.1.9 Documentation of Statistical Methods

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Statistical Analysis Plan Version Final 1.0 dated 22-MAR-2023

CCI

Statistical Analysis Plan for Interventional Studies (Early Phase)

Sponsor Name: GlaxoSmithKline Consumer Healthcare (GSK CH)

Protocol Number: 218677

Protocol Title: 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 Version and Date: Amendment 2, 30-Nov-2022

CCI **Project Code:** 222003

Authors: PPD
PPD

Revision History

Version	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	14-Feb-2023	PPD	Initial Draft
1.0	22-Mar-2023	PPD	Incorporation of medical writer input

Approvals

I confirm that I have reviewed this document and agree with the content.

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1. Glossary of Abbreviations

Abbreviation	Description
λ_z	terminal elimination rate constant
$\lambda_{z\ Lower}$	timepoint where ln-linear terminal elimination rate constant calculation begins
$\lambda_{z\ Upper}$	actual sampling time of the last measurable concentration used to estimate the terminal elimination rate constant
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve calculated from time zero to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point
BDR	blind data review
BLOQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	apparent total clearance
C_{max}	maximum observed concentration
CRF	case report form
C(t)	concentration at the last measurable sampling time point
CV	coefficient of variation
ECG	electrocardiogram
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transpeptidase
GSK CH	GlaxoSmithKline Consumer Healthcare
HBc-Ab	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C virus antibodies

Abbreviation	Description
HIV	human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IgM	immunoglobulin M
ln	natural logarithm
LSM	least-squares mean
max	maximum
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum
N	number of subjects
n	number of observations
N/A	not applicable
OT	oral body temperature
PK	pharmacokinetic(s)
PT	preferred term
P-value	probability value
R^2	R-squared
RBC	red blood cell
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	time of maximum observed concentration
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on the following documents:

- Protocol 218677 Amendment 2, dated 30-Nov-2022
- Case Report Form (CRF) version 0.38, dated 13-Dec-2022

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the associated clinical study report. No change will be made without prior approval of the Sponsor.

When applicable, all methodologies and related processes will be conducted according to CCI CCI standard operating procedures (SOPs) as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be presented in a separate document.

2.1 Responsibilities

CCI will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings (TFLs).

2.2 Timings of Analyses

No Interim analysis is planned for this study.

Dry-run Analysis:

A Dry-run analysis is planned for this study using dummy or available data before database softlock. This dry-run analysis will include a set of all unique tables, figures, and listings and are denoted in the accompanying SAP Shells.

Blinded Data Review (BDR):

After completion of database softlock, a BDR will be conducted. The details of the BDR will be compiled in a separate document. The purpose of the BDR is to assign the study populations outlined in Section 6 of this SAP. As this study is open-label, the term “blind” is used to denote that the population determination will be done without respect to treatment.

Topline TLFs:

After completion of database hardlock, a subset of all TLFs will be generated intended to identify key results of the study (i.e. bioequivalence and safety). Please refer to the SAP shell document for more details.

Final Analysis:

The final analysis of safety and PK is planned to be completed after completion of Topline TLFs. The final analysis will include the Topline TLF.

3. Study Objectives

- Primary objective:
  - Demonstrate the bioequivalence of Advil PM Liqui-Gels Minis (Test) compared to Advil PM Liqui-Gels (Reference)
- Secondary objectives:
  - Assess the PK profile
  - Assess subject acceptability of each of the two products
  - Assess the safety profile

4. Study Description

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.

Subjects will be randomly assigned to one of two 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 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. For each subject, the duration of study participation is 38 days with up to 3 days confined in each period (total of up to 6 days confined).

4.1 Subject Selection

Healthy, non-smoking, male and female adult volunteers, aged 18 to 55 years, with body mass index (BMI) 18.5 to 30.0 kg/m^2, will be enrolled in this study. Detail of all the inclusion and exclusion criteria may be found in study protocol, Sections 5.2 and 5.3.

4.2 Determination of Sample Size

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 area under the curve (AUC) and maximum observed post-dose concentration (C_{max}) parameters for both ibuprofen and diphenhydramine components. This assumes a variability (intra-subject coefficient of variation [CV%]) of 25% 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). Considering a drop out or discontinuation rate of approximately 10%, a total of 44 subjects will need to be enrolled.

4.3 Treatment Assignment

Subjects enrolled in this study will be randomized to sequence AB or sequence BA. On Day 1 of each period, subjects will receive either Treatment A or Treatment B, under fasting conditions, according to the assigned sequence.

Reference the table below.

Sequence	Treatment Period 1, Day 1	Treatment Period 2, Day 1
AB	Treatment A (Test): 2X Advil PM Liqui-Gels Minis	Treatment B (Reference): 2X Advil PM Liqui-Gels
BA	Treatment B (Reference): 2X Advil PM Liqui-Gels	Treatment A (Test): 2X Advil PM Liqui-Gels Minis

4.4 Randomization

Randomization schedules will be generated by CCI through SAS® for Windows software, prior to start of the study using block randomization. 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.

Randomization will occur prior to first dosing. Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

4.5 Blinding

This will be an open-label study. Blinding is not considered essential as study measurements (plasma ibuprofen and diphenhydramine concentrations) are biological. 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. Additionally, as the data review for the determination of the populations will be done without respect to treatment, the study statistician and pharmacokineticist participating in the BDR meeting will remain blinded to treatment.

4.6 Subject Withdrawal and Replacement

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. 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.

5. Endpoints

- Primary endpoints:
  - The maximum observed post-dose concentration (C_{max}) for ibuprofen and diphenhydramine
  - The area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point (AUC_{0-t}) for ibuprofen and diphenhydramine
  - The area under the plasma concentration versus time curve calculated from time zero to infinity (AUC_{0-inf}) for ibuprofen and diphenhydramine
- Secondary endpoints:
  - The terminal elimination rate constant (λ_z) for ibuprofen and diphenhydramine
  - The time of the maximum observed post-dose concentration (t_{max}) for ibuprofen and diphenhydramine
  - The elimination half-life ($t_{1/2}$) for ibuprofen and diphenhydramine
  - Apparent volume of distribution (V_z/F) for ibuprofen and diphenhydramine
  - Apparent total clearance (Cl/F) for ibuprofen and diphenhydramine
  - Ease of swallowing (5-point ordinal scale)
  - Monitoring and recording of adverse events (AEs)
  - Physical examination
  - Vital signs
  - Laboratory tests

6. Analysis Populations

Exclusion of any data from the analyses will be determined during a blind data review (BDR) meeting, prior to database lock. Each subject's inclusion or exclusion from each analysis population, along with reasons for exclusions, will be presented by subject in a data listing.

6.1 Screened Population

The screened population is defined as all subjects who were screened with the intentions to receive the investigational product. The screened population will be used for listings that include screen failure subjects and/or eligible subjects who were not randomized and for the assignment to analysis populations.

6.2 Safety Population

The safety population is defined as all randomized subjects who receive at least one dose of study medication. The safety population will be used for all safety summaries and analyses. The safety population will also be used for all listings, unless otherwise specified.

6.3 PK Population

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 PK. PK population will be used for all PK concentration listings.

6.4 PK Analysis Set

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

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.

7. General Aspects for Statistical Analysis

7.1 General Methods

SAS for Windows software will be used to perform all statistical analyses. Unless otherwise stated, all listings will be sorted by treatment group, subject number, and assessment date/time.

The following labels for treatment will be used on all tabulations where the results are displayed by treatment, in the following order:

- Advil PM Liqui-Gels Minis (Test) [A]
- Advil PM Liqui-Gels (Reference) [B]

7.2 Summary Statistics:

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV%), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, arithmetic mean and median will be presented to one more decimal place than the raw data and the SD will be presented to two more decimal places than the raw data. Categorical variables will be summarized with frequency counts and percentages. Percentages (other than PK parameters) will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

For the plasma PK data, the data will be rounded to two decimal places in the listings. The following rules will be applied to following situations:

- λ_z data: Presentation of data in listings and calculated means (arithmetic and geometric), minimum, and maximum - rounded off to 4 decimal digits. Calculated SD will be

presented to 5 decimal places.

- Pharmacokinetic parameters related to time such as T_{max}, $\lambda_{z\ Lower}$, and $\lambda_{z\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits. This applies to presentation in listings and calculated means (arithmetic and geometric), minimum, and maximum. SD will be presented to 4 decimal places.
- Concentration data as well as C_{max}: reported as they appear in the corresponding dataset.

Note: these rules are only intended as a guide and may be changed based on available data for the study and are not meant to override the number of decimal places in the data used as input for analysis. The full unrounded precision will be used for all calculation prior to rounding for display as applicable.

Summary statistics including the geometric mean will be displayed to the same number of decimal places as the arithmetic mean and the coefficient of variation (CV) (%) will be rounded to 1 decimal place.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

All assessments will be presented in the listings.

7.3 Key Definitions

Baseline:

Unless stated otherwise, baseline will be defined for each subject and will be defined as the last non-missing measurement (including repeated and unscheduled assessments) obtained prior to the first study drug administration. Post baseline will be considered as all measurements collected after study drug administration. “Unknown”, “Not Done”, “Not Applicable”, and other classifications of missing data will not be considered when calculating baseline observations unless the finding is a valid categorical observation.

Study day:

Study day will be calculated using first study drug administration (either test or reference) date as the reference date. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date). There will be no study day 0.

Prior medication:

Medication/treatments, including prescription and non-prescription drugs, dietary supplements, and herbal remedies, taken within 90 days prior to signing the informed consent form will be documented as a prior medication/treatment.

Concomitant medication:

Medications/treatments taken after the first dose will be documented as concomitant medication/treatments.

Treatment:

Treatment is assigned as the last received treatment, except in the case of pre-dose measurements. Any non-adverse event assessment occurring on the same calendar date as a given treatment before dosing would be attributed to the same treatment given on that calendar day. If no treatment was applied on the same calendar day, then any measurements pre-dose will not be summarized by treatment. Adverse events will be summarized only by the last received treatment.

7.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in subject listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated shall be presented as "-".

For inclusion in concomitant medication and AE tables, incomplete start and stop dates on the CRF will be imputed as follows:

- If the stop date is incomplete, the following rules will be applied:
    - Missing day: Assume the last day of the month
    - Missing day and month: Assume the last day of the year
    - Missing day, month, and year: Assume that the event/medication is continuing
    - In the case of the death of a subject, and if the imputed end date is after the date of death, the end date will be imputed as the date of death.
- If the stop date is incomplete, imputed end date will be used instead of reported end date.
- If the start date is incomplete, the following rules will be applied:
    - Missing day: Assume the first day of the month; however, if the partial date and the date of first study drug administration lie within the same month and year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of study drug administration. Otherwise, set to the stop date of the event/medication.
    - Missing day and month: Assume January 1st; however, if the partial date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of first study drug administration. Otherwise, set the to stop date of the event/medication.
    - Missing day, month, and year: Assume date of first study drug administration if it is not after the stop date for the event/medication. Otherwise, set the to stop date for the event/medication.

In the case of withdrawal of consent, all data from subjects who withdraw from the study will be included in all safety summaries up to the time of withdrawal. For all other withdrawals, all data captured will be included in the safety summaries.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values below the limit of quantification (BLOQ); reference Section 9.1. 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 if applicable.

8. Study Population

8.1 Subject Disposition

The number of subjects who were screened, enrolled, randomized, not randomized (along with reasons), entered each period, completed each period, did not complete each period (along with reasons), will be presented by sequence and overall (frequency and the percentage of subjects) for the screened population, and presented by subject in a data listing.

8.2 Protocol Deviations

Subject data will be examined for evidence of protocol deviations. All protocol deviations will be categorized and presented by subject for the randomized population in a data listing. Major protocol deviations will be summarized by treatment and overall for the randomized population.

8.3 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented in a data listing. Each subject's inclusion or exclusion from each analysis population will also be presented in a data listing.

8.4 Demographics and Other Baseline Characteristics

All demographics and body measurements will be summarized by sequence group and overall, and they will be presented by subject in a data listing.

Descriptive statistics (n, mean, SD, min, median, and max) will be calculated for continuous variables using the last results obtained prior to study drug administration. Frequency counts and percentages will be tabulated for categorical variables.

All demographic characteristics will be summarized for the safety population and PK population. If the safety population and PK population are the same, the table for the PK population will not be generated.

8.5 Medical History

Details of relevant medical and surgical history (in the last five years), including allergies or drug sensitivity, will be presented by subject in a data listing. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all medical history findings by system organ class (SOC) and preferred term (PT). Output data will include the MedDRA version used in the study.

8.6 Medications

Prior and concomitant medications will be presented by subject in a data listing. The latest version of the World Health Organization Drug Dictionary (WHO DD) will be used to classify medications by anatomical therapeutic chemical (ATC) classification code (2nd level). When 2nd level classification code is not available, 1st level classification will be used instead. Output data will include the WHO DD version used in the study.

8.7 Drug, Cotinine, and Alcohol Screens

A urine drug screen will be performed at screening and Day -1 of each period. Testing includes: Amphetamines, Methamphetamines, Barbiturates, Benzodiazepines, Cocaine, 3,4-methylenedioxymethamphetamine, Methadone, Opiates, Phencyclidine, and Tetrahydrocannabinol.

A urine cotinine test will be performed at screening and Day -1 of each period.

An alcohol breath test will be performed at screening and Day -1 of each period.

The results will be presented by subject in data listings.

8.8 Pregnancy Screening

For all 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. The follicle-stimulating hormone (FSH) level will be tested in females who have been amenorrhoeic for at least twelve consecutive months. All results will be presented by subject in data listings.

8.9 Additional Screening Tests

Serology (HIV antigen and antibody, HBsAg, HBc-Ab (IgG + IgM) and HCV-Ab) tests and electrocardiograms (ECGs) will be performed at screening. COVID-19 test will be performed at 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, and at any time during residential period in the study when subjects report symptoms suggestive of COVID-19. All these data will be presented by subject in data listings.

8.10 Study Drug Administration

The study drug administration details including date and time of administration, Treatment Description (frequency, route, formulating, dose (units)), Fasting status at time of administration, and if a medication/dosing error occurred will be listed by Subject.

9. PK Analyses

Phoenix® WinNonlin® software will be used for all PK analyses. Inferential statistical analyses will be performed using SAS for Windows software. Bioanalysis of all samples should be completed prior to the initiation of the PK and statistical analyses.

All plasma concentration and PK parameter summaries and analyses will be conducted on the PK analysis set. All concentration and PK data, including any data for subjects who are not included in the analysis (e.g., subjects withdrawn from the study due to AEs), will be listed for the PK population. The listing for plasma concentration will include planned timepoint, sample collection (yes or no), date and times of collection, and the calculated time deviations from the planned timepoint.

9.1 Handling of Concentrations Below the Lower Limit of Quantification (BLOQ), No Reportable Concentration Values, and Missing Data

For the analysis of all individual plasma concentrations and all secondary PK parameter, all concentration BLOQ values that occur before the first measurable concentration (i.e. non-BLOQ) will be treated as zero (0). Any BLOQ values after the first measurable concentration will be treated as "Not Detectable" (ND), which will be shown as missing for plasma PK concentrations and PK parameter estimation.

Samples with invalid concentration (due to bioanalytical or clinical issue) will be replaced by "0.00" when it occurs prior to study drug administration. Otherwise, they will be set to missing for tabulation, graphical representation and calculation purposes if it occurs after study drug administration.

Listings will show the actual value of concentration at the timepoint. The value of BLOQ will be displayed as applicable in the listings.

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.

9.2 Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each PK sample collection will be recorded. For all sampling times, the actual sampling time relative to study drug administration will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times, expressed in hours and rounded off to three decimal digits, will be used to calculate the PK parameters. Pre-dose sampling times will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be used in concentration tables and mean graphs, while actual sampling times for post-dose samples will be used in the individual graphs. Actual sampling times for post-dose samples also will be used for PK parameter derivation, unless the actual sampling time is missing, in which case, the nominal time will be used.

9.3 PK Sampling Schedule

Blood samples for the determination of the PK of ibuprofen and diphenhydramine will be collected from each subject during this study according to the following schedule:

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.

9.4 PK Parameters

After database lock and unblinding, the following PK parameters will be calculated, whenever possible, by standard non-compartmental methods for ibuprofen and diphenhydramine:

Primary PK Parameters:

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

Secondary PK Parameters:

Parameter	Definition
λ_z	terminal elimination rate constant, computed as the negative of the slope of the regression line of the natural logarithm (ln) concentration on time
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 as dose administered/(λ_z x AUC_{0-inf})
Cl/F	apparent total clearance, calculated as dose administered/ AUC_{0-inf}

AUC parameters will be calculated using linear up log down trapezoidal method, where the linear trapezoidal rule is used any time the concentration data is increasing, and the logarithmic trapezoidal rule is used any time that the concentration data is decreasing.

λ_z will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. The best fit method will be used to calculate the λ_z from at least three concentration data points, excluding C_{max}. R^2 adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z must be ≥ 0.8. If the λ_z cannot be measured (e.g.: there are fewer than three non-zero concentrations in the terminal elimination phase), the PK parameters derived from λ_z will be presented in listing(s) but excluded from descriptive statistics in tables. The timepoint where ln-linear λ_z calculation begins ($\lambda_{z\ Lower}$), the actual sampling time of the last measurable concentration used to estimate the λ_z ($\lambda_{z\ Upper}$), and the R^2 adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported.

9.5 Statistical Analysis

For ibuprofen and diphenhydramine, individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scale by treatment for the PK analysis set. The plasma concentrations at each timepoint, and all PK parameters will be summarized by treatment using descriptive statistics (n, arithmetic and geometric means, SD, CV%, min, max, and median) for the PK analysis set.

9.6 Bioequivalence Assessment

The primary objective will be evaluated on the following comparison:

Advil PM Liqui-Gels Minis (Test) versus Advil PM Liqui-Gels (Reference), in terms of Advil PM Liqui-Gels AUC_{0-t}, AUC_{0-inf}, and C_{max}.

For ibuprofen and diphenhydramine separately, a linear mixed effects model will be fit to the natural 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 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. The model will be fit using restricted maximum likelihood, and the Kenward-Roger degrees of freedom approximation. [a] 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.

The SAS code for the analysis model will follow the format given below (The input variables (or datasets) are depicted in slanted red text and have been given generic names).

CCI

If all study subjects are not recruited from the same enrollment pool and the study doses in more than one group, the statistical model will be modified to reflect the multigroup nature of the study. If the group effect is determined to be necessary, the following fixed effect terms will be included in the model: group, sequence, sequence by group, period within group, treatment, and treatment by group. Subject within sequence by group will be entered in the statistical model as a random effect. If the term of treatment by group is found to be not statistically significant (i.e., $p > 0.05$), then the treatment by group term specified in the previous model will be removed. The ratio and 90% CI will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max} as applicable.

The SAS code for the analysis model with group terms will follow the format given below (The input variables (or datasets) are depicted in slanted red text and have been given generic names).

CCI

The bioequivalence 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}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ is between 80% and 125% for ibuprofen and diphenhydramine.

10. Safety

Safety analysis will be performed for all subjects in the safety population.

10.1 Adverse Events (AEs)

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. AEs without an onset date or time, or AEs with an onset date of the date of study drug administration but without an onset time, will be defined as treatment-emergent, unless an incomplete date (e.g., month and year) clearly indicates that the event started prior to administration of study drug, or the AE stop date indicates that the event started and stopped prior to administration of study drug.

Treatment-emergent AEs (TEAEs) and non-TEAEs will be listed by subject and treatment. The latest version of the MedDRA will be used to classify all AEs by SOC and PT. Output data will include the MedDRA version used in the study.

TEAEs will be assigned to the treatment administered immediately prior to the onset. AEs continuing after dosing in the next treatment period will be evaluated on a case-by-case basis. 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 (probable, possible or remote) will be presented in a similar manner. All TEAEs will be also tabulated by severity (mild, moderate, and severe). Any other information collected (e.g. action taken, duration, outcome) will be listed. AEs due to COVID-19, if any, will be listed separately.

The number and percentage of subjects experiencing TEAEs and the number of TEAEs will be tabulated. Subjects who experience the same TEAE (in terms of MedDRA PT) more than once will only be counted once for that event, however, the total number of events will be counted per category. This also applies to sub-categories displayed in the summaries.

The following summaries will be presented by treatment:

- Overall summary of TEAEs

- TEAEs by SOC
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to study drug
- Related TEAEs by SOC and PT.

10.2 Clinical Laboratory Evaluations

Clinical laboratory testing (hematology, chemistry, and urinalysis) will be performed at screening and at the End of Study visit.

The following clinical laboratory assessments will be performed:

Hematology:	Standard blood Hematology will be collected. These include: Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelet count, RBC count, WBC count and differential (Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils).
Chemistry:	Standard serum chemistry will be collected. These include: Albumin, ALP, ALT, AST, Calcium, Chloride, Creatine kinase, Creatinine, GGT, Glucose, Phosphorus, Potassium, Sodium, Total bilirubin, Total protein, Urea (BUN).
Urinalysis:	Standard Urinalysis will be collected. This includes: Bilirubin, Blood (occult), Color and appearance, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific gravity, and Urobilinogen. Microscopic examination will be performed only in the event of abnormal findings.

Clinical laboratory data, including hematology, biochemistry, and urinalysis will be listed. Reference ranges provided by clinical laboratories for each laboratory parameter will be given. If a result falls outside of a provided range, it will be flagged as abnormal (either “Low” or “High”, along with a determination of clinical significance – “CS” for clinically significant or “NCS” for not clinically significant).

10.3 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and oral body temperature (OT). Vital sign measurements will be performed at screening, on Day 1 (within 1 hour before drug administration) of each treatment period, and at the End of Study visit. Additionally, OT will be obtained on Day -1, Day 2 and Day 3 of each treatment period (note: OT performed on Day 3 of Period 2 can be used as the oral body temperature required at End of Study).

Vital sign measurements will be listed, and summarized for each timepoint by treatment or overall as appropriate. Abnormal results will be flagged in the listing (either "Normal", "Abnormal", or "Not Done", along with a determination of clinical significance – "Y" for yes or "N" for no).

10.4 Physical Examination

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.

The results of physical examinations will be listed. Abnormal results will be flagged in the listings.

11. Acceptability

On Day 1 of each period, immediately after dosing, the assessment of acceptability 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").

The results of the ease of swallowing questionnaires will be listed and tabulated by treatment for the safety population.

Frequency counts and percentages will be presented for the categorical response to "Do you agree or disagree that the product is easy to swallow?". The scale ranges from 1 = "not easy to swallow" to 5 = "very easy to swallow" will be summarized by a frequency distribution of response by treatment. Additionally, the 'ease of swallowing' ordinal response (ranks) will be summarized for each treatment using descriptive statistics (n, mean, SD, min, median, and max).

12. Changes from Analysis Planned in the Protocol

No changes were made to planned analyses.

13. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software in accordance with FDA guidelines. Phoenix WinNonlin, version 8.3.4 (Certara USA, Inc., Princeton, NJ) will be used for all PK analyses. This software was validated by CCI in compliance with US 21 CFR Part 11 regulation.

13.1 General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format that can be manipulated in MS Word.
- Numbering of TFLs will follow International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3.[b]

13.2 Table, Listing, and Figure Format

13.2.1 General

- TFLs will be produced in landscape format. The orientation may be changed to portrait, as necessary to allow additional rows to be presented.
- TFLs will be produced using the Times New Roman font, size 10. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all four sides.
- Unless otherwise specified, TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used; see below.
- Standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- TFLs will be produced using sentence case, unless otherwise specified.

13.2.2 Headers and Footers

- Times New Roman font, size 10 will be used for TFL headers and footers.
- All outputs will have the following at the top left of each page: GSK CH Protocol 218677.
- All outputs will have page x of y at the top or bottom right corner of each page. TFLs are individually paginated in relation to total length (i.e., the page number appears sequentially as page x of y, where y is the total number of pages in the output).
- The date and time the output was generated will appear, along with the program name, at the bottom of each page.

13.2.3 Display Titles

Each display title includes the appropriate designation ("Table", "Figure", or "Listing") and a numeral, along with a descriptive name (e.g., Table 10.1-1 Subject Disposition). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained for final determination. Display titles are left aligned, single spaced, and presented in title case. A solid line spanning the margins will separate display titles from column headings.

13.2.4 Column and Row Headings

- Column and row headings are presented in title case, with the exception of complete sentences, which will be presented in sentence case.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of subjects in the analysis population for each group, presented as (N=xx). This is different from the "n" used in descriptive statistics, which represents the number of observations.
- The order of sequences in the tables and listings will be "AB" first, then "BA", followed lastly by "Overall".

13.2.5 Body of the Data Display

13.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left aligned
- Whole numbers (e.g., counts) are right aligned

13.2.5.2 Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all groups in a given category that is between the minimum and maximum level for that parameter. See the example for the frequency distribution for symptom severity below.

Severity Rating	N
Severe	0
Moderate	8
Mild	3

- Where percentages are presented in these tables, 0% will not be presented, therefore, counts of zero will be presented as "0", not "0 (0%)".
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least one subject represented in one or more groups are included.

- If data for a given parameter is unavailable for one or more subjects, then an Unknown or Missing category is included.
- P-values are presented in the format: 0.xxxx, where xxxx is the value. If the p-values are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values are presented in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the group that has an observation will be the denominator. Percentages after zero counts are not displayed, and percentages equating to 100% are presented as "100%" (without decimal places).
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented in alphabetical order.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant group (or overall) for the analysis population presented. However, careful consideration is required in many instances, due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject is included in the summary statistics for all relevant categories or just one category and the criteria for selecting the criteria.
- Where a category with a subheading (such as SOC) must be split over more than one page, present the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading will only be presented on the first relevant page.

13.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are presented as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

13.2.5.4 Figure Conventions

- For safety figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis, unless otherwise specified.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Units will be included where available.

13.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left aligned, with single spacing, immediately below the solid line beneath the data display.
- Informational footnotes begin with "Note:". Reference footnotes begin with a reference number or letter (e.g., 1, 2, 3 or a, b, c).
- Each new footnote starts on a new line, where possible.
- Subject-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

14. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures, and statistical analyses. These are developed and undergo quality control in accordance with the latest versions of CCI and CCI

15. Reference List

[a]Kenward, M. G., & Roger, J. H. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics, 53(3), 983-997. doi:10.2307/2533558

[b]International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1996). Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3).

CCI . Standard Operating Procedure, Developing Statistical Programming Specifications for Early Phase Studies CCI .

CCI . Standard Operating Procedure, Developing Statistical Programs for Early Phase Studies CCI .

End of document

Table/Figure/Listing Shells Version Final 1.0 dated 22-MAR-2023

Statistical Analysis Plan (Table/Figure/Listing Shells)

Sponsor Name: GlaxoSmithKline Consumer Healthcare (GSK CH)

Protocol Number: 218677

Protocol Title: 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 Version and Date: Amendment 2, 30-Nov-2022

CCI **Project Code:** 222003

Authors: PPD
PPD

Signature Approvals

I confirm that I have reviewed this document and agree with the content.

CCI Approval		
PPD	Signature: PPD Email:	
Name, Title PPD	Signature	Date (DD-Mmm-YYYY)
PPD PPD	Signature: PPD Email:	
Name, Title PPD	Signature	Date (DD-Mmm-YYYY)
PPD	Signature: PPD Email:	
Name, Title PPD	Signature	Date (DD-Mmm-YYYY)
PPD PPD	Signature: PPD Email:	
Name, Title PPD	Signature	Date (DD-Mmm-YYYY)
GSK CH Approval		
PPD PPD	Signature: PPD Email:	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

All Tables and Listings marked with an * are to be included as part of the topline report.

1. CSR In-text Tables

Table 10.1-1 Subject Enrollment and Disposition (Screened Population)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
Screened n	-	-	xx
Enrolled n (%)	-	-	xx (xx.x)
In the Safety Population n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Dose n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
In the PK Population n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline Concentration > 5% of C_{max} n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Emesis Within 2 Times Median T_{max} n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Subjects in the PK Analysis Set n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Not Available in Both Periods n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Parameter Not Estimable in Both Periods n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Excluded from PK Population n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Randomized n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standby n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
(cont.)			
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N= number of subjects in the safety population; n= number of subjects; n (%)= number and percent of subjects; AE= adverse event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: The overall column includes subjects from both sequence groups.
Data Sources: Table 14.1.1

Table 11.4.1-1 Summary of Ibuprofen Pharmacokinetic Parameters by Treatment (PK Analysis Set)

		Treatment A (Test)				Treatment B (Reference)			
Analyte	Parameter(unit)	N	Geometric Mean	SD	CV%	N	Geometric Mean	SD	CV%
Ibuprofen	AUC_{0-t} (ng*h/mL)								
	AUC_{0-inf} (ng*h/mL)								
	C_{max} (ng/mL)								
	$\%AUC_{ex}$ (%)								
		Treatment A (Test)				Treatment B (Reference)			
	Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
	t_{max} (h)								
	λ_z (/h)								
	$t_{½}$ (h)								

Note: N: Number of subjects; CV: Coefficient of variation; SD: Standard Deviation; AUC_{0-t} = The area under the concentration-time curve, from time 0 to the last measurable timepoint; AUC_{0-inf} = The area under the plasma concentration-time curve, from time 0 to infinity; $\%AUC_{ex}$ = Percentage of AUC_{0-inf} obtained by extrapolation; C_{max} = Maximum observed concentration; T_{max} = Time to reach C_{max}; $t_{½}$ = Elimination half-life; λ_z = Elimination rate constant.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels.

Data Source: Table 14.2.1-2

CCI

Table 11.4.1-2 Summary of Diphenhydramine Pharmacokinetic Parameters by Treatment (PK Analysis Set)

		Treatment A (Test)				Treatment B (Reference)			
Analyte	Parameter(unit)	N	Geometric Mean	SD	CV%	N	Geometric Mean	SD	CV%
Diphenhydramine	AUC_{0-t} (ng*h/mL)								
	AUC_{0-inf} (ng*h/mL)								
	C_{max} (ng/mL)								
	$\%AUC_{ex}$ (%)								
		Treatment A (Test)				Treatment B (Reference)			
	Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
	t_{max} (h)								
	λ_z (/h)								
	$t_{½}$ (h)								

Note: N: Number of subjects; CV: Coefficient of variation; SD: Standard Deviation; AUC_{0-t} = The area under the concentration-time curve, from time 0 to the last measurable timepoint; AUC_{0-inf} = The area under the plasma concentration-time curve, from time 0 to infinity; $\%AUC_{ex}$ = Percentage of AUC_{0-inf} obtained by extrapolation; C_{max} = Maximum observed concentration; T_{max} = Time to reach C_{max}; $t_{½}$ = Elimination half-life; λ_z = Elimination rate constant.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels.

Data Source: Table 14.2.1-2

CCI

Table 11.4.1-3 Assessment of Bioequivalence (PK Analysis Set)

Analyte	Parameter (Unit)	Geometric LSM A	Geometric LSM B	Ratio (A/B)[a]	90% CI[b] Lower	90% CI[b] Upper	Intra-subject CV%[c]	Inter-subject CV %[c]	P-value Treatment	P-value Period	P-value Sequence
Ibuprofen											
	AUC_{0-t} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
	AUC_{0-inf} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
	C_{max} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
…											

Abbreviations: PK= pharmacokinetic(s); LSM= least-squares means; CI= confidence interval; CV= coefficient of variation CV%= coefficient of variation (percent); p-value= probability value; AUC_{0-inf}= area under the plasma concentration versus time curve calculated from time zero to infinity; AUC_{0-t}= area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point; C_{max}= maximum observed post-dose concentration

[a] Calculated using LSM according to the formula exp(Difference) * 100.

[b] Calculated according to the formula (exp(Difference) ± $t(df_{Residual})$ * $SE_{Difference}$) * 100.

[c] Calculated according to formula √(exp (variance component) – 1) * 100.

Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data source: Table 14.2.1-3

CCI

Table 12.2.3-1 TEAEs by Severity and Relationship to the Study Drug (Safety Population)

Category	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
TEAEs	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Severity:				
Mild	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Moderate	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Severe	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Relationship to Study Drug:				
Probable	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Possible	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Remote	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Unrelated	n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

Abbreviations: TEAE= treatment-emergent adverse event; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

CCI

2. Summary Tables

Table 14.1-1 Subject Enrollment and Disposition (Screened Population)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
Screened n	-	-	xx
Enrolled n (%)	-	-	xx (xx.x)
In the Safety Population n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Dose n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
In the PK Population n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline Concentration > 5% of C_{max} n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Emesis Within 2 Times Median T_{max} n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Subjects in the PK Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Not Available in Both Periods	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Parameter Not Estimable in Both Periods	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Excluded from PK Population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomized n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Randomized n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Standby n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Period 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
(cont.)			
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Washout Period n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Entered Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Did Not Complete Period 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Did Not Meet Study Criteria n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Informed Consent n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Due to COVID-19 Pandemic n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N= number of subjects in the safety population; n= number of subjects; n (%)= number and percent of subjects; AE= adverse event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: The overall column includes subjects from both sequence groups.

Data Sources: Listing 16.2.1-1, Listing 16.2.3-1, Listing 16.2.3-2, and Listing 16.2.5-2

Table 14.1-2 Summary of Major Protocol Deviations (Randomized Population)

Assessment Type Assessment Category	Treatment A (Test) (N=xx) n (%) E	Treatment B (Reference) (N=xx) n (%) E	Overall (N=xx) n (%) E
Total Number of Protocol Deviations	xx	xx	xx
Medical History	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Category>	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			...

Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Source: Listing 16.2.2-1

Table 14.1.3-1 Demographics and Baseline Body Measurements (Safety Population)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
Age (years)[a]			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Median	xx.x	xx.x	xx.x
Max	xx	xx	xx
Sex n (%)			
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Is subject of childbearing potential?[b] n (%)			
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)
Achieved Postmenopausal Status	xx (xx.x)	xx (xx.x)	xx (xx.x)
Surgically sterile	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity n (%)			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race n (%)			
Am Indian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hawaiian	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	xx (xx.x)	xx (xx.x)	xx (xx.x)
Multiple	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)

Category	Sequence AB (N=xx)	Sequence BA (N=xx)	Overall (N=xx)
(cont)			
Height (cm)			
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx
Min	xx.x	xx.x	xx.x
Median	xx.xx	xx.xx	xx.xx
Max	xx.x	xx.x	xx.x
Weight (kg)			
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx
Min	xx.x	xx.x	xx.x
Median	xx.xx	xx.xx	xx.xx
Max	xx.x	xx.x	xx.x
BMI (kg/m^2)			
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx
Min	xx.x	xx.x	xx.x
Median	xx.xx	xx.xx	xx.xx
Max	xx.x	xx.x	xx.x

Abbreviations: N= number of subjects in the population; n (%)= number and percent of subjects; n= number of observations; SD= standard deviation; min= minimum; max= maximum; Am Indian= American Indian or Alaskan native; Black= Black or African American; Hawaiian= native Hawaiian or other pacific islander; BMI= body mass index
[a] Age at the time of informed consent or reconsent (whichever date occurs last)
[b] Percentage is based on the number of females.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: The last result (scheduled or unscheduled) obtained at screening was used to generate this table.
Note: The overall column includes subjects from both sequence groups.
Note: Repeat as Table 14.1.3-2 for PK Population if PK Population differs from the Safety Population.
Data Source: Listing 16.2.4-1 and Listing 16.2.4-2

Table 14.2.1-1 PK Concentrations (PK Analysis Set)

Analyte Visit, Timepoint (Hours Post-dose) Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)
Ibuprofen		
Day 1, Pre-dose		
n	xx	xx
Mean	xxxx.xx	xxxx.xx
SD	xxxx.xxx	xxxx.xxx
CV%	xxx.x	xxx.x
Geometric mean	xxxx.xx	xxxx.xx
Min	xxxx.xx	xxxx.xx
Median	xxxx.xx	xxxx.xx
Max	xxxx.xx	xxxx.xx
Day 1, x.xx		
n	xx	xx
Mean	xxxx.xx	xxxx.xx
SD	xxxx.xxx	xxxx.xxx
CV%	xxx.x	xxx.x
Geometric mean	xxxx.xx	xxxx.xx
Min	xxxx.xx	xxxx.xx
Median	xxxx.xx	xxxx.xx
Max	xxxx.xx	xxxx.xx
…		

Abbreviations: PK= pharmacokinetic(s); N= number of subjects in the population; n= number of observations; SD= standard deviation; CV%= coefficient of variation (percent); min= minimum; max= maximum; '-'= not calculated
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-1

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Table 14.2.1-2 PK Parameters (PK Analysis Set)

Analyte Parameter (Unit) Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)
Ibuprofen		
AUC_{0-inf} (xx)		
n	xx	xx
arithmetic Mean	xxxx.xx	xxxx.xx
SD	xxxx.xxx	xxxx.xxx
CV%	xxx.x	xxx.x
Geometric mean	xxxx.xx	xxxx.xx
Min	xxxx.xx	xxxx.xx
Median	xxxx.xx	xxxx.xx
Max	xxxx.xx	xxxx.xx
AUC_{0-t} (xx)		
n	xx	xx
Mean	xxxx.xx	xxxx.xx
SD	xxxx.xxx	xxxx.xxx
CV%	xxx.x	xxx.x
Geometric mean	xxxx.xx	xxxx.xx
Min	xxxx.xx	xxxx.xx
Median	xxxx.xx	xxxx.xx
Max	xxxx.xx	xxxx.xx
…		

Abbreviations: PK= pharmacokinetic(s); N= number of subjects in the population; λ_z= terminal elimination rate constant; AUC_{0-inf}= area under the plasma concentration versus time curve calculated from time zero to infinity; AUC_{0-t}= area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point; Cl/F= apparent total clearance; C_{max}= maximum observed post-dose concentration; $t_{1/2}$= elimination half-life; t_{max}= time of the maximum observed post-dose concentration; V_z/F= apparent volume of distribution; n= number of observations; SD= standard deviation; CV%= coefficient of variation (percent); min= minimum; max= maximum; '-'= not calculated
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-2

CCI

Table 14.2.1-3 Assessment of Bioequivalence (PK Analysis Set)

Analyte	Parameter (Unit)	Geometric LSM A	Geometric LSM B	Ratio (A/B)[a]	90% CI[b] Lower	90% CI[b] Upper	Intra-subject CV%[c]	Inter-subject CV %[c]	P-value Treatment	P-value Period	P-value Sequence
Ibuprofen											
	AUC_{0-t} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
	AUC_{0-inf} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
	C_{max} (xx)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xx.x	xx.x	0.xxxx	0.xxxx	0.xxxx
…											

Abbreviations: PK= pharmacokinetic(s); LSM= least-squares means; CI= confidence interval; CV= coefficient of variation CV%= coefficient of variation (percent); p-value= probability value; AUC_{0-inf}= area under the plasma concentration versus time curve calculated from time zero to infinity; AUC_{0-t}= area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point; C_{max}= maximum observed post-dose concentration

[a] Calculated using LSM according to the formula exp(Difference) * 100.

[b] Calculated according to the formula $(\exp(\text{Difference}) \pm t(df_{Residual}) * SE_{Difference}) * 100$.

[c] Calculated according to formula $\sqrt{(\exp(\text{variance component}) - 1)} * 100$.

Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data source: Listing 16.2.6-1

CCI

Table 14.3.1-1 Overall Summary of TEAEs (Safety Population)

Category	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
Number of TEAEs	E	xx	xx	xx
Subjects with at least one TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Drug-related[a] TEAEs	E	xx	xx	xx
Severe TEAEs	E	xx	xx	xx
Serious TEAEs	E	xx	xx	xx
Subjects discontinued due to TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deaths	E	xx	xx	xx

Abbreviations: TEAE= treatment-emergent adverse event; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
[a] Relationship to study drug is categorized as "Possible" or "Probable"
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

CCI

Table 14.3.1-2 TEAEs by SOC (Safety Population)

MedDRA® SOC	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
SOC 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
…				

Abbreviations: TEAE= treatment-emergent adverse event; SOC= system organ class; MedDRA= Medical Dictionary for Regulatory Activities; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

CCI

Table 14.3.1-3 TEAEs by SOC and PT (Safety Population)

MedDRA® SOC MedDRA PT	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
SOC 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
…				

Abbreviations: TEAE= treatment-emergent adverse event; SOC= system organ class; PT= preferred term; MedDRA= Medical Dictionary for Regulatory Activities; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

CCI

Table 14.3.1-4 TEAEs by SOC, PT, and Severity (Safety Population)

MedDRA® SOC MedDRA PT Severity	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
TEAE				
Mild	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Moderate	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Severe	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 1				
PT 1				
Mild	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Moderate	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Severe	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
…				

Abbreviations: TEAE= treatment-emergent adverse event; SOC= system organ class; PT= preferred term; MedDRA= Medical Dictionary for Regulatory Activities; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

Table 14.3.1-5 TEAEs by SOC, PT, and Relationship to the Study Drug (Safety Population)

MedDRA® SOC MedDRA PT Severity	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
TEAE				
Probable	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Possible	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Remote	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Unrelated	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 1				
PT 1				
Probable	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Possible	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Remote	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
Unrelated	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
…				

Abbreviations: TEAE= treatment-emergent adverse event; SOC= system organ class; PT= preferred term; MedDRA= Medical Dictionary for Regulatory Activities; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

Table 14.3.1-6 Related TEAEs by SOC and PT (Safety Population)

MedDRA® SOC MedDRA PT	Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
Related TEAE	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
SOC 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 1	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
PT 2	n (%) E	x (xx.x) x	x (xx.x) x	x (xx.x) x
…				

Abbreviations: TEAE= treatment-emergent adverse event; SOC= system organ class; PT= preferred term; MedDRA= Medical Dictionary for Regulatory Activities; N= number of subjects in the population; n (%)= number and percent of subjects with TEAEs; E= event
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Related is defined as a relationship to study drug probable, possible or remote.
Note: Each subject contributes once to each of the incidence rates, regardless of the number of occurrences.
Note: The overall column includes subjects from both treatment groups.
Note: SOCs and PTs were coded using MedDRA version X.X.

Data Source: Listing 16.2.7-1

CCI

Table 14.3.4-1 Vital Signs (Safety Population)

Parameter (Unit) Visit Statistic	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)	Overall (N=xx)
Systolic BP (mmHg)			
Screening			
n	-	-	xx
Mean	-	-	xx.x
SD	-	-	xx.xx
Min	-	-	xx.x
Median	-	-	xx.x
Max	-	-	xx.x
Day 1 (Pre-dose)			
n	xx	xx	-
Mean	xx.x	xx.x	-
SD	xx.xx	xx.xx	-
Min	xx.x	xx.x	-
Median	xx.x	xx.x	-
Max	xx.x	xx.x	-
…			

Abbreviations: N= number of subjects in the population; n= number of observations; SD= standard deviation; min= minimum; max= maximum;
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Baseline is defined as the last result (scheduled or unscheduled) obtained prior to study drug administration.
Note: The overall column includes subjects from both treatment groups.

Data Source: Listing 16.2.8-5

Table 14.3.4-2 Acceptability (Safety Population)

Category	Treatment A (Test) (N=xx)	Treatment B (Reference) (N=xx)
Do You Agree or Disagree That the Product Is Easy to Swallow? n (%)		
Agree	xx (xx.x)	xx (xx.x)
Disagree	xx (xx.x)	xx (xx.x)
Rank the "Ease of Swallowing" of the Product from 1 to 5. n (%)		
1 (Not Easy to Swallow)	xx (xx.x)	xx (xx.x)
2 (Somewhat Easy to Swallow)	xx (xx.x)	xx (xx.x)
3 (Average to Swallow)	xx (xx.x)	xx (xx.x)
4 (Above Average to Swallow)	xx (xx.x)	xx (xx.x)
5 (Very Easy to Swallow)	xx (xx.x)	xx (xx.x)
n	xx	xx
Mean	xx.x	xx.x
SD	xx.xx	xx.xx
Min	xx.x	xx.x
Median	xx.x	xx.x
Max	xx.x	xx.x

Abbreviations: N= number of subjects in the population; n (%)= number and percent of subjects; n= number of observations; SD= standard deviation; min= minimum; max= maximum
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.5-3

3. Figures

Figure 14.2.1-4 PK Concentrations by Subject - Linear Scale (PK Population)

Plot of plasma concentrations over time per subject

Figure Description: The plasma concentration over time for each treatment will be presented. The figure will display values for only one subject on a single page.

For each figure, the X axis will be the Actual timepoint. The Y axis will be the concentration, in units.

X axis title: Visit, Timepoint (Hours Post-dose)
Y axis title: Concentration (Unit)

Abbreviations: PK= pharmacokinetic(s)
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-1

CCI

Figure 14.2.1-5 PK Concentrations by Subject – Semi-Log Scale (PK Population)

Plot of plasma concentrations over time per subject

Figure Description: The plasma concentration (log-scale) over time for each treatment will be presented. The figure will display values for only one subject on a single page.

For each figure, the X axis will be the Actual timepoint. The Y axis will be the concentration, in units.

X axis title: Visit, Timepoint (Hours Post-dose)
Y axis title: Concentration (Unit)

Abbreviations: PK= pharmacokinetic(s)
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-1

CCI

Figure 14.2.1-6 Mean PK Concentrations - Linear Scale (PK Analysis Set)

Plot of mean plasma concentrations over time

Figure Description: The mean plasma concentration over time (±SD) will be presented. The figure will display values for all treatment groups on a single page. Straight lines will connect the values within each treatment group. Different symbols and line types will be used to distinguish between each treatment group. The SD at each point will be added.

For each figure, the X axis will be the scheduled timepoint. The Y axis will be the concentration, in units.

X axis title: Visit, Timepoint (Hours Post-dose)
Y axis title: Concentration (Unit)

Abbreviations: PK= pharmacokinetic(s); SD= standard deviation
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-1

CCI

Figure 14.2.1-7 Mean PK Concentrations - Semi-Log Scale (PK Analysis Set)

Plot of mean plasma concentrations (log-scale) over time

Figure Description: The mean plasma concentration (log-scale) over time will be presented. The figure will display values for all treatment groups on a single page. Straight lines will connect the values within each treatment group. Different symbols and line types will be used to distinguish between each treatment group.

For each figure, the X axis will be the scheduled timepoint. The Y axis will be the concentration, in units.

X axis title: Visit, Timepoint (Hours Post-dose)
Y axis title: Concentration (Unit)

Abbreviations: PK= pharmacokinetic(s)
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Data Source: Listing 16.2.6-1

CCI

4. Listings

Listing 14.3.2-1 Deaths Occurring After Treatment Administration (Safety Population)

*If any Deaths or other Serious and Significant Adverse Events, follow similar format to that of 16.2.7-1

Listing 14.3.2-2 Non-Fatal Serious Adverse Events Occurring After Treatment Administration (Safety Population)

*If any Deaths or other Serious and Significant Adverse Events, follow similar format to that of 16.2.7-1

Listing 14.3.2-3 Adverse Events Causing Discontinuation of Study Treatment (Safety Population)

*If any AE causing discontinuation of the study 16.2.7-1

Listing 16.1.9-1 Linear Mixed Effects Model Output for the Assessment of Bioequivalence - Ibuprofen (PK Analysis Set)

The Mixed Procedure

Parameter = C_{max}

Class Level Information

Class	Levels	Values
CTRTA	2	T R
SUBJID	xx	xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx
APERIOD	2	1 2
ACTARMCD	2	TR RT

Covariance Parameter Estimates

Cov Parm	Estimate
SUBJID(ACTARMCD)	0.xxx
Residual	0.xxxx

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
CTRTA	1	xx	xx.xx	0.xxxx
APERIOD	1	xx	xx.xx	0.xxxx
ACTARMCD	1	xx	xx.xx	0.xxxx

The Mixed Procedure

Parameter = C_{max}

Estimates					
Label	Estimate	Standard Error	DF	t Value	Pr > |t|
Test vs Reference	x.xxxx	0.xxxx	xx	x.xx	0.xxxx

Least Squares Means									
Effect	CTRTA	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
CTRTA	T	x.xxxx	0.xxxx	xx.x	xx.xx	<0.0001	0.1	x.xxxx	x.xxxx
CTRTA	R	x.xxxx	0.xxxx	xx.x	xx.xx	0.xxxx	0.1	x.xxxx	x.xxxx

Repeat listing for AUC_{0-t} and AUC_{0-inf}.
If the study is deemed to require the groups, a group effect will also be added as applicable.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Listing 16.1.9-2 Linear Mixed Effects Model Output for the Assessment of Bioequivalence - Diphenhydramine (PK Analysis Set)

The Mixed Procedure

Parameter = C_{max}

Class Level Information		
Class	Levels	Values
CTRTA	2	T R
SUBJID	xx	xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx
APERIOD	2	1 2
ACTARMCD	2	TR RT

Covariance Parameter Estimates	
Cov Parm	Estimate
SUBJID(ACTARMCD)	0.xxx
Residual	0.xxxx

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
CTRTA	1	xx	xx.xx	0.xxxx
APERIOD	1	xx	xx.xx	0.xxxx
ACTARMCD	1	xx	xx.xx	0.xxxx

The Mixed Procedure

Parameter = C_{max}

Estimates					
Label	Estimate	Standard Error	DF	t Value	Pr > |t|
Test vs Reference	x.xxxx	0.xxxx	xx	x.xx	0.xxxx

Least Squares Means									
Effect	CTRTA	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
CTRTA	T	x.xxxx	0.xxxx	xx.x	xx.xx	<0.0001	0.1	x.xxxx	x.xxxx
CTRTA	R	x.xxxx	0.xxxx	xx.x	xx.xx	0.xxxx	0.1	x.xxxx	x.xxxx

Repeat listing for AUC_{0-t} and AUC_{0-inf}.
If the study is deemed to require the groups, a group effect will also be added as applicable.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Listing 16.2.1-1 Subject Disposition (Screened Population)

Subject Number	Sequence	Last Period Prior to Discontinuation	Last Treatment Prior to Discontinuation	Did the subject complete the study? (Y/N)	Date of Withdrawal or Completion	Last Date of Participation	Reason for Non-Completion
xxxxx	N/A	N/A	N/A	N	ddmmmyyyy	N/A	Subject Did Not Meet Study Criteria
xxxxx	AB	Period 1	Treatment A	N	ddmmmyyyy	ddmmmyyyy	Withdrawal By Subject
xxxxx	AB	Period 2	Treatment B	Y	ddmmmyyyy	ddmmmyyyy	N/A
…							

Abbreviations: Y= yes; N= no; N/A= not applicable
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.2-1 Protocol Deviations (Randomized Population)

Subject Number	Treatment/Sequence	Period, Visit	Date of Deviation	Deviation Category	Deviation Classification[a]	Description of Deviation
xxxxx	-/AB	Period 1, Day 1	ddmmmyyyy	xxxxxxxxxxxxx	Minor	xxxxxxxxxxxxx
…						

[a] Major or minor
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.3-1 Inclusion and Exclusion Criteria (Screened Population)

Subject Number	Sequence	Period, Visit	Assessment Date	Did subject meet all eligibility criteria? (Y/N)	Criterion Short Name	Reason Criterion Not Respected
xxxxx	AB	Screening	ddmmmyyyy	Y	N/A	N/A
		Period 1, Day x	ddmmmyyyy	N	Inclusion 1	xxxxxxxxxx
…						

Abbreviations: Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.3-2 Assignment to Analysis Populations (Screened Population)

Subject ID	Treatment Sequence	Included in Safety Population	Reason for Exclusion in Safety Population	Included in PK Population	Reason for Exclusion in PK Population	Included in PK Analysis Set	Reason for Exclusion in PK Analysis Set
xxx	AB	Y					
xxx	BA	Y					
etc.							
xxx*	-	N	Subject did not receive any study medication	N	Subject not in Safety Population	N	Subject not in Safety Population

Programming note: If a subject is not included in the IE domain, then assume subject met all eligibility criteria and add subject to this listing.
*: Screen Failure
Abbreviations: Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.4-1 Demographics (Safety Population)

Subject Number	Sequence	Age (years)[a]	Sex	If female, is subject of childbearing potential? (Y/N) / If N, Reason	Ethnicity	Race
xxxxx	AB	xx	Female	N, Achieved Postmenopausal Status	Not Hispanic or Latino	Am Indian
…						

Abbreviations: Y= yes; N= no
Am Indian= American Indian or Alaskan native; Black= Black or African American; Hawaiian= native Hawaiian or other pacific islander
[a] Age at the time of informed consent or reconsent (whichever date occurs last)
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

Listing 16.2.4-2 Body Measurements (Safety Population)

Subject Number	Sequence	Height (cm)	Weight (kg)	BMI Calculation (kg/m^2)
xxxxx	AB	xxxx	xxxx	xxxx
…				

Abbreviations: BMI= body mass index
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: The BMI is a value derived from the mass (weight) and height of a person, calculated by the following equation: BMI= Weight (kg) / Height (m)^2

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Listing 16.2.4-3 Medical History (Safety Population)

Subject Number	Sequence	MH ID	MH Term	MedDRA® SOC / MedDRA PT	Start Date	End Date	Is the subject taking any medication related to this condition? (Y/N)
xxxxx	AB	xx	TERM 1	SOC 1 / PT 1	ddmmmyyyy	ddmmmyyyy	N
xxxxx	BA	xx	TERM 2	SOC 2 / PT 2	ddmmmyyyy	ONGOING	Y
…							

Abbreviations: MH= medical history; ID= identifier; MedDRA= Medical Dictionary for Regulatory Activities; SOC= system organ class; PT= preferred term; Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: SOCs and PTs were coded using MedDRA version X.X

Listing 16.2.4-4 Prior and Concomitant Medications (Safety Population)

Subject Number	Sequence	Period	ATC Classification Code / Preferred Name / Reported Name	Indication	Dose (Unit) / Form	Frequency / Route	Start Date / Time / End Date / Time	Due to AE ? (Y/N) / If Y, AE ID / Due to MH? (Y/N), If Y, MH ID	P or C
xxxxx	AB	Screening	ATC 1 / Preferred Name 1 / Medication 1	xxxxxxxxxxx	100 (mg) / Tablet	QD / Oral	ddmmmyyyy / hh:mm / ddmmmyyyy / hh:mm	Y, 1 / N	P
…									

Abbreviations: ATC= anatomic therapeutic chemical; AE= adverse event; Y= yes; N= no; ID= identifier; MH= medical history; P= prior; C= concomitant; WHO DD= World Health Organization Drug Dictionary
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: Medications were coded using WHO DD, version MMM YYYY.

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Listing 16.2.4-5 Drug Screen (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected? / If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Result[a]	If Positive, Test Name(s)
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	Negative	N/A
		Period 1, Day x	Y	ddmmmyyyy / hh:mm	Y	Positive	xxxxxxxxx
…							

Abbreviations: Y= yes; N= no
[a] Positive, negative, or valid result not obtained
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.4-6 Alcohol Breath Test (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected? / If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Result[a]
xxxxx	AB	Screening Period 1, Day x	Y Y	ddmmmyyyy / hh:mm ddmmmyyyy / hh:mm	Y Y	Negative Positive
…						

Abbreviations: Y= yes; N= no
[a] Positive, negative, or valid result not obtained
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.4-7 Cotinine Test (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected? / If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Result[a]
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	Negative
		Period 1, Day x	Y	ddmmmyyyy / hh:mm	Y	Positive
…						

Abbreviations: Y= yes; N= no
[a] Positive, negative, or valid result not obtained
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.4-8 ECGs (Safety Population)

Subject Number	Sequence	Period, Visit	Was the ECG Performed? / If No, Reason	Date / Time of Assessment	Interpretation[a]	Parameter (Unit)	Actual Value
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Abnormal CS	Heart Rate (beats/min) PR Interval (msec)	xxx xxx
…							

Abbreviations: ECG= electrocardiogram; NCS= not clinically significant; CS= clinically significant; Y = yes; N = no
[a] Normal or abnormal; if abnormal, CS or NCS
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.5-1 Study Drug Administration (Safety Population)

Subject Number	Period, Visit	Treatment	Was the study drug administered? (Y/N) / If N, Reason	Administration Date / Time	Planned Dose (Unit) / Was the planned dose administered? (Y/N)	Was the subject fasting for 10 hours prior to administration? (Y/N)	Is there any medication/dosing error? (Y/N)	Was the drug administered with 240 mL of water at ambient temperature? (Y/N)
xxxxx	Period 1, Day 1	Treatment A	Y	ddmmmyyyy / hh:mm	xxxxxx (xx) / Y	Y	N	Y
…								

Abbreviations: Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.5-2 Subject Randomization (Screened Population)

Subject Number	Was the subject randomized? (Y/N) / If N, Reason	Randomization Date / Time	Randomization Number	Sequence
xxxxx	Y	ddmmmyyyy / hh:mm	xxxxxxxx	AB
…				

Abbreviations: Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

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Listing 16.2.5-3 Acceptability (Safety Population)

Subject Number	Treatment	Period, Visit	Date / Time of Assessment	Do You Agree or Disagree That the Product Is Easy to Swallow?[a]	'Ease of Swallowing' Rank[b]
xxxxx	Treatment A	Period 1, Day x	ddmmmyyyy / hh:mm	Agree	5
…					

[a] Agree or disagree
[b] 1 (Not easy to swallow), 2 (Somewhat easy to swallow), 3 (Average to swallow), 4 (Above average to swallow), or 5 (Very easy to swallow)
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.6-1 PK Concentrations (PK Population)

Subject Number	Treatment	Period, Visit	Nominal Timepoint (Hours Post-dose)	Date / Time of Study Drug Administration / Date / Time of Sample Collection	Actual Time[a] (Hours)	Analyte	Concentration (ng/mL)	Excluded? (Y/N) / If Y, Reason
xxxxx	Treatment A	Period 1, Day 1	Pre-Dose	ddmmmyyyy / hh:mm / ddmmmyyyy / hh:mm	0.000	Ibuprofen	xx	Y / Inconclusive
…								

Abbreviations: Y= yes; N= no
[a] Actual time is the difference (in hours) from study drug administration to sample collection
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.6-2 PK Parameters (PK Population)

Subject Number	Treatment	Period, Visit	Analyte	Parameter	Result	Unit	Excluded? (Y/N) / If Y, Reason
xxxxx	Treatment A	Period 1, Day 1	Ibuprofen	AUC_{0-inf}	xxxxxxx	xx	N
				AUC_{0-t}	xxxxxxx	xx	N
				Cl/F	xxxxxxx	xx	N
				C_{max}	xxxxxxx	xx	N
				λ_z	N/A	xx	Y / Not estimable
				$t_{1/2}$	N/A	xx	Y / Not estimable
				t_{max}	xxxxxxx	xx	N
				V_z/F	N/A	xx	Y / Not estimable

…

Abbreviations: PK= pharmacokinetic(s); Y= yes; N= no; AUC_{0-inf}= area under the plasma concentration versus time curve calculated from time zero to infinity; AUC_{0-t}= area under the plasma concentration versus time curve calculated from time zero to the last measurable sampling time point; Cl/F= apparent total clearance; C_{max}= maximum observed post-dose concentration; λ_z= terminal elimination rate constant; $t_{1/2}$= elimination half-life; t_{max}= time of the maximum observed post-dose concentration; V_z/F= apparent volume of distribution; N/A= not applicable
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.7-1 TEAEs (Safety Population)

Subject Number	Treatment / Sequence	AE ID	MedDRA® SOC / MedDRA PT / AE Term	Is the AE related to COVID-19? (Y/N) / If Y, Case Diagnosis	Onset Date / Time / Resolution Date / Time	Severity[a] / Relationship to the Study Drug[b]	Action Taken: Study Treatment / Other	Outcome	Did the AE Cause the subject to be discontinued? (Y/N)	Is the AE serious? (Y/N) / If Y, Reason	Is the AE a TEAE?[c]
xxxxx	Treatment A / AB	xx	SOC 1 / PT 1 / Term 1	Y / Suspected	ddmmmyyyy / hh:mm / ddmmmyyyy / hh:mm	Severe / Unrelated	Dose Reduced / Medication	Recovered/ Resolved	N	Y / Life Threatening	Y
…											

Abbreviations: AE= adverse event; ID= identifier; MedDRA= Medical Dictionary for Regulatory Activities; SOC= system organ class; PT= preferred term; Y= yes; N= no; TEAE= treatment-emergent adverse events
[a] Mild, moderate, or severe
[b] Probable, possible, remote, or unrelated
[c] TEAEs are defined as AEs that are emergent or that worsen after the first study drug (Test or Reference) administration
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: SOCs and PTs were coded using MedDRA version X.X.

CCI

Listing 16.2.7-2 Non-TEAEs (Screening Population)

Subject Number	Sequence	AE ID	MedDRA® SOC / MedDRA PT / AE Term	Is the AE related to COVID-19? (Y/N) / If Y, Case Diagnosis	Onset Date / Time / Resolution Date / Time	Severity[a] / Relationship to the Study Drug[b]	Action Taken: Study Treatment / Other	Outcome	Did the AE Cause the subject to be discontinued? (Y/N)	Is the AE serious? (Y/N) / If Y, Reason
xxxxx	AB	xx	SOC 1 / PT 1 / Term 1	Y / Suspected	ddmmmyyyy / hh:mm / ddmmmyyyy / hh:mm	Severe / Unrelated	Dose Reduced / Medication	Recovered/ Resolved	N	Y / Life Threatening
…										

Abbreviations: AE= adverse event; ID= identifier; MedDRA= Medical Dictionary for Regulatory Activities; SOC= system organ class; PT= preferred term; Y= yes; N= no; TEAE= treatment-emergent adverse events
[d] Mild, moderate, or severe
[e] Probable, possible, remote, or unrelated
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels
Note: SOCs and PTs were coded using MedDRA version X.X.

CCI

Listing 16.2.8-1 Biochemistry (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected?/ If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Parameter (Unit)	Actual Value	Normal Range (Low, High)	Flag [1] / If Abnormal, Interpretation
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	xxxx (xx)	xxx.x	(xxx.x, xxx.x)	L / Abnormal NCS
…									

Abbreviations: NCS= not clinically significant; CS= clinically significant; Y= yes; N= no
[1] Flag is based on laboratory reference normal range. N= Normal; L= Low; H=High; A=Abnormal.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-2 Hematology (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected?/ If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Parameter (Unit)	Actual Value	Normal Range (Low, High)	Flag [1] / If Abnormal, Interpretation
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	xxxx (xx)	xxx.x	(xxx.x, xxx.x)	L / Abnormal NCS
…									

Abbreviations: NCS= not clinically significant; CS= clinically significant; Y= yes; N= no
[1] Flag is based on laboratory reference normal range. N= Normal; L= Low; H=High; A=Abnormal.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-3 Urinalysis: Quantitative (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected?/ If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Parameter (Unit)	Actual Value	Normal Range (Low, High)	Flag [1] / If Abnormal, Interpretation
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	xxxx (xx)	xxx.x	(xxx.x, xxx.x)	L / Abnormal NCS
…									

Abbreviations: NCS= not clinically significant; CS= clinically significant; Y= yes; N= no
[1] Flag is based on laboratory reference normal range. N= Normal; L= Low; H=High; A=Abnormal.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-4 Urinalysis: Categorical (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected?/ If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Parameter (Unit)	Actual Value	Flag [1] / If Abnormal, Interpretation
xxxxx	AB	Screening	Y	ddmmmyyyy / hh:mm	Y	xxxx (xx)	xxxxx	N
…								

Abbreviations: NCS= not clinically significant; CS= clinically significant; Y= yes; N= no
[1] Flag is based on laboratory reference normal range. N= Normal; A=Abnormal.
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-5 Pregnancy Test (Safety Population)

Subject Number	Treatment / Sequence	Period, Visit	Sample Collected? / If No, Reason	Sample Matrix[a]	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Result[b]
xxxxx	Treatment A / AB	Screening	Y	Urine	ddmmmyyyy / hh:mm	Y	Negative
		Period 1, Day x	Y	Serum	ddmmmyyyy / hh:mm	Y	Negative
…							

Abbreviations: Y= yes; N= no
[a] Serum or urine
[b] Positive, negative, or valid result not obtained
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-6 Follicle Stimulating Hormone Test (Safety Population)

Subject Number	Sequence	Sample Collected? / If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Result (mIU/mL)
xxxxx	AB	Y	ddmmmyyyy / hh:mm	Y	xxxx
…					

Abbreviations: Y= yes; N= no
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-7 Serology (Safety Population)

Subject Number	Sequence	Sample Collected? / If No, Reason	Date / Time of Sample Collection	Was the subject fasting at least 4 hours prior to the collection? (Y/N, where applicable)	Are there any out of range values? (Y/N) / If Y, Test Name[a] / If Y, Interpretation[b]
xxxxx	AB	Y	ddmmmyyyy / hh:mm	Y	Y / HBsAg / Abnormal CS
…					

Abbreviations: Y= yes; N= no; HBc-Ab= Hepatitis B core antibody; HBsAg= hepatitis B surface antigen;
HCV-Ab= hepatitis C virus antibodies; HIV= human immunodeficiency virus; CS= clinically significant; NCS= not clinically significant
[a] HBc-Ab, HBsAg, HCV-Ab, or HIV antigen/antibody
[b] Abnormal CS or Abnormal NCS
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-8 COVID-19 Test (Safety Population)

Subject Number	Sequence	Period, Visit	Sample Collected? / If No, Reason	Method[a]	Date / Time of Sample Collection	Result[b]
xxxxx	AB	Screening	Y	RT-PCR	ddmmmyyyy / hh:mm	Negative
		Period 1, Day x	Y	Antigen	ddmmmyyyy / hh:mm	Negative
…						

Abbreviations: RT-PCR= reverse-transcription polymerase chain reaction
[a] RT-PCR or antigen
[b] Positive, negative, or indeterminate
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-9 Vital Signs (Safety Population)

Subject Number	Treatment / Sequence	Period, Visit	Date / Time of Assessment	Parameter (Unit)	Actual Value	Interpretation[a] / Is the result clinically significant? (Y/N)
xxxxx	Treatment A / AB	Period 1, Day x	ddmmmyyyy / hh:mm	Systolic BP (mmHg)	xxx.x	Normal / N
…						

Abbreviations: Y= yes; N= no
[a] Normal, abnormal, or not done
Note: Treatment A (Test)= 2X Advil PM Liqui-Gels Minis; Treatment B (Reference)= 2X Advil PM Liqui-Gels

CCI

Listing 16.2.8-10 Physical Examination (Safety Population)

Subject Number	Treatment / Sequence	Period, Visit	Assessment Type[a]	Date / Time of Assessment	Body System	Interpretation[b]	Abnormal Findings / Is the finding clinically significant? (Y/N)
xxxxx	Treatment A / AB	Period 1, Day x	Full	ddmmmyyyy / hh:mm	Head	Abnormal	xxxxxxxx / N xxxxxxxx / Y
…							

Abbreviations: Y= yes; N= no
[a] Brief or full
[b] Normal, abnormal, or not done

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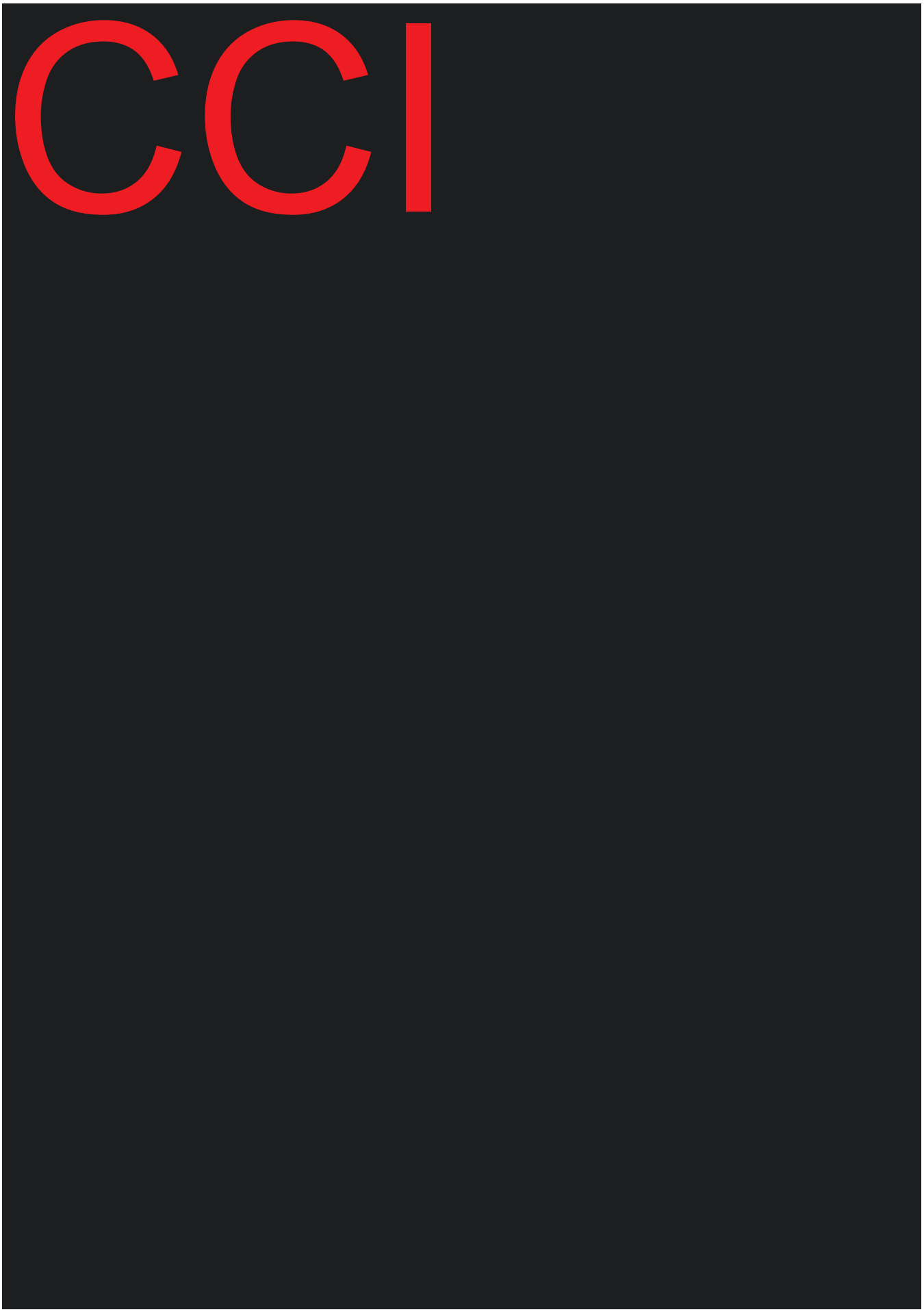
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Created by :

PPD	PPD	PPD
Printed Name, Title	Signature	Date (DD-Mmm-YYYY)

Reviewed by:

PPD	PPD	PPD
Printed Name, Title	Signature	Date (DD-Mmm-YYYY)

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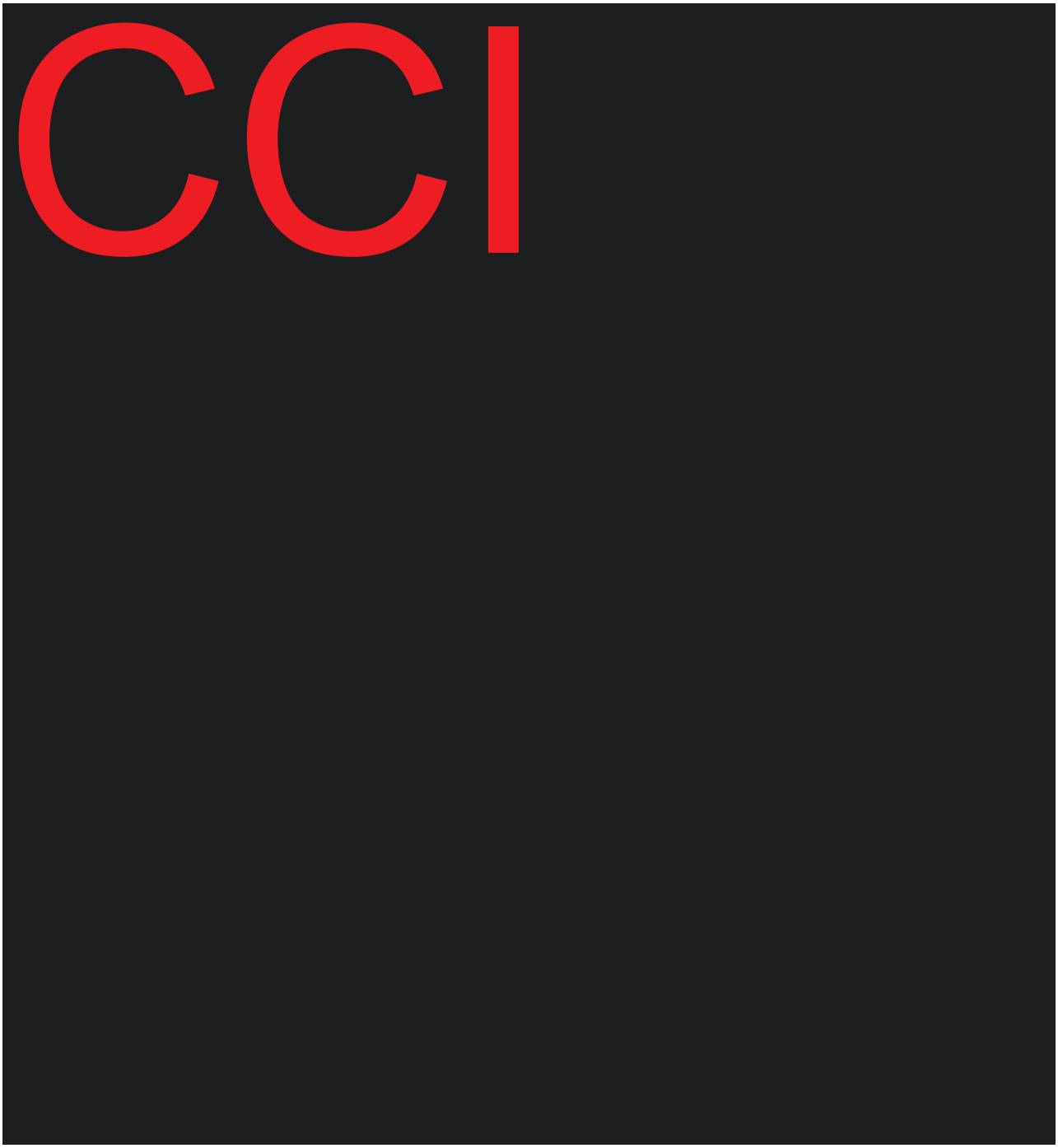
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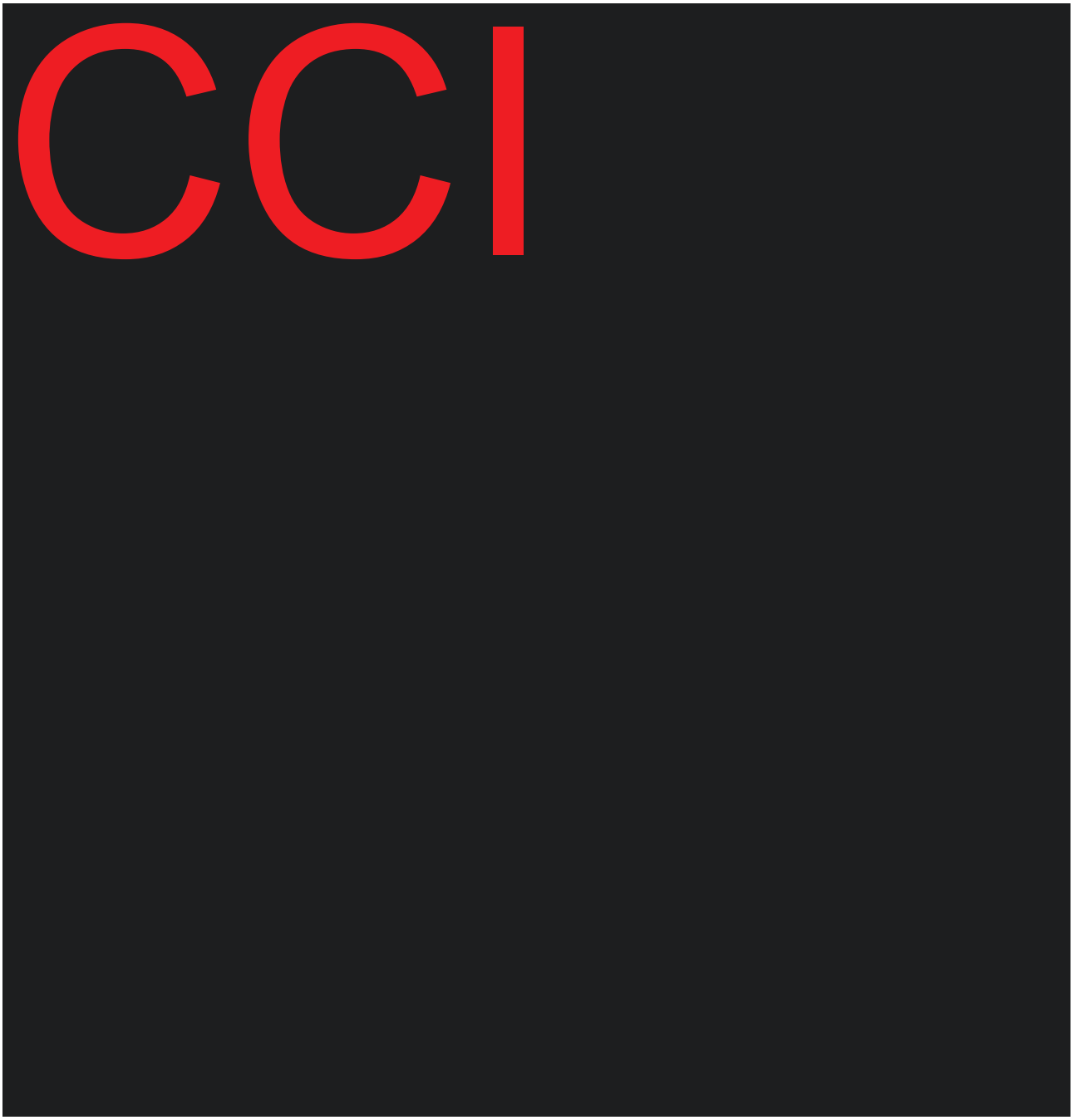
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