CLINICAL PROTOCOL

A RANDOMIZED, OPEN LABEL, SINGLE CENTER, SINGLE DOSE, TWO PERIOD, TWO SEQUENCE, CROSSOVER BIOEQUIVALENCE STUDY OF PARACETAMOL IN A NEW PEDIATRIC PARACETAMOL ORAL SUSPENSION COMPARED TO A MARKETED PARACETAMOL ORAL SUSPENSION (PANADOL BABY & INFANT) IN HEALTHY ADULT SUBJECTS

Protocol Number:	215262
Quinta Study Number:	811/20
Compound/Product Name:	Paracetamol 24mg/mL Strawberry oral suspension
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	2021-000900-40
Other Regulatory Agency Identified Number:	Not applicable
Phase:	Phase I

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSKCH)** St Georges Avenue, Weybridge, KT13 0DE, United Kingdom

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	• Tests name in footnotes of ***Table 1-1 Schedule of Activities*** are made consistent with ***Table 9-1 Laboratory Tests.*** • Volume of fluids (water and soup) in ***Table 1-2 Schedule for all Study Periods*** are made consistent with ***Table 9-2 Example Standard Meal Composition.*** • Schedule of physical examination in ***Table 1-2 Schedule for all Study Periods*** is made consistent with ***Section 8 Study Period.*** • Sponsor name & legal registered address in Sponsor Information section is made consistent with contracting documents.
Amendment 2	3.0	• Added Schedule of Activities and Study Schedule tables to Section 4.1 • Added exclusion criterion to exclude subjects with anemia • Added definition of non-childbearing potential • Additional editorial changes
Amendment 3	4.0	• Increase minimum weight for inclusion to 60 kg • Section 7.1 add consideration that subjects with emesis shortly prior to administration may be withdrawn
Amendment 4	5.0	• Section 1.1 Key Subject Selection Criteria, weight for inclusion changed to 60 kg • Exclusion Criteria #10 change to reflect wording change from “more than one” to “one or more”

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

Principal Investigator Protocol Agreement Page

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

Investigator Name:	PPD
Investigator Qualifications:	M.D., Ph.D.
Investigator Signature:	
Date of Signature/Agreement:	

SPONSOR SIGNATURES

A RANDOMIZED, OPEN LABEL, SINGLE CENTER, SINGLE DOSE, TWO PERIOD, TWO SEQUENCE, CROSSOVER BIOEQUIVALENCE STUDY OF PARACETAMOL IN A NEW PEDIATRIC PARACETAMOL ORAL SUSPENSION COMPARED TO A MARKETED PARACETAMOL ORAL SUSPENSION (PANADOL BABY & INFANT) IN HEALTHY ADULT SUBJECTS

Sponsor Protocol Number: **215262**

Quinta Study Number: **811/20**

EudraCT number: **2021-000900-40**

I hereby declare that I have reviewed this study protocol and that I approve its content

PPD

PPD
Vice President, Clinical Development, GSKCH

(Sponsor's Representative)

PPD

PPD
Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor	GlaxoSmithKline Consumer Healthcare (GSKCH)
Study Title	A Randomized, Open Label, Single Center, Single dose, Two Period, Two Sequence, Crossover Bioequivalence Study of Paracetamol in a new Pediatric Paracetamol Oral Suspension Compared to a Marketed Paracetamol Oral Suspension (Panadol Baby & Infant) in Healthy Adult Subjects
Short Title	A bioequivalence study of a new paracetamol oral suspension compared to the marketed paracetamol oral suspension (Panadol Baby and Infant, abbreviated Panadol B&I).
Study Identification	EudraCT No.: 2021-000900-40 Sponsor's Protocol No.: 215262 PPD
Site	PPD
Clinical Phase	Phase I (Bioequivalence)
Study Objectives	**The primary objective is:** • To demonstrate bioequivalence of paracetamol in a new paracetamol oral suspension versus a marketed paracetamol oral suspension (Panadol B&I) **The secondary objective is:** • Assess the pharmacokinetic profile of new and marketed paracetamol oral suspension
Study Design	This is a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects, separated by one wash-out period of at least 72 hours.
Study Medication	**Test:** Name: New paracetamol oral suspension Active ingredient: Paracetamol Dosage form: Oral suspension Strength: 24 mg/ml paracetamol Dose: 42 mL (1g paracetamol) Route of administration: Oral MAH: GSKCH, Finland Manufacturer: GSKCH, Nyon, Switzerland

	Reference: Name: Marketed paracetamol oral suspension (Panadol B & I, Marketed as Panadol pro děti jahoda perorální suspenze) Active ingredient: Paracetamol Dosage form: Oral suspension Strength: 24 mg/ml paracetamol Dose: 42 mL (1g paracetamol) Route of administration: Oral Strength: 24 mg/ml paracetamol MAH: GSKCH, Czech Republic Manufacturer: Farmaclair (a contract manufacturing organization, under GSKCH), France Source market: Czech Republic
Dose	Single oral dose of Test Product (new paracetamol oral suspension) or Reference Product (Panadol B & I) will be administered to all subjects in each study period. The administration will proceed according to the randomization schedule.
Number of Subjects	Approximately 110 subjects will be screened to randomize approximately 37 healthy adult subjects to ensure at least 31 evaluable subjects complete the entire study. In addition, two (2) overnight stand-by subjects will be confined until the first dosing as a reserve for pre-dose dropouts.
Subjects Evaluated	All randomized subjects who complete the two periods and who have no major protocol deviations concerning pharmacokinetics. Subjects with baseline* paracetamol concentration > 5% of the individual C_{max} for either period will be excluded from PK population. *Baseline is defined as the last available value before dosing.
Key Subject Selection Criteria	Approximately 37 healthy adult males and female ≥ 18 and ≤ 45 years of age (on the day of Informed Consent), with body-mass index (BMI) ≥ 18.5 and ≤ 30 kg/m^2 and body weight above 60 kg (on the day of screening).
Sampling Schedule	Blood will be sampled regularly at scheduled times for 16 hours post-dose. Blood collections will be performed prior to the administration of study medication (-1.00) and 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes , and 4.00, 5, 6, 8, 10, 12, 14 and 16 hours after drug administration. Total number of blood collections in each Study Period will be 21.
Inclusion Criteria 1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.	

2. Subject is male or female

3. Subject is 18 to 45 years of age inclusive, at the signing of the informed consent.

4. A subject who is willing and able to comply with scheduled visits, treatment plan, laboratory tests, study restrictions and other study procedures.

5. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, as determined by medical evaluation, including medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests

6. A subject with a Body Mass Index (BMI) of 18.5 to 30 kg/m^2; and a total body weight >60 kg

7. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 7 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in CCI
8. Subject with two consecutive negative tests for active COVID-19, separated by > 24 hours.

9. Czech citizenship

Exclusion Criteria

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSKCH employee directly involved in the conduct of the study or a member of their immediate family.

2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days before dosing.

3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.

4. A subject who is pregnant as confirmed by a positive hCG laboratory test or intending to become pregnant over the duration of the study.

5. A subject who is breastfeeding.

6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients. This includes paracetamol and excipients in the products *e.g.* sorbitol, maltitol glycerol *etc.*

7. A subject unwilling or unable to comply with Lifestyle Considerations (Section 5.5 of protocol) described in this protocol.

8. Diagnosis of long QT syndrome or QTc > 450 msec for males and > 470 msec for females at screening.

9. A subject with evidence or history of clinically significant laboratory abnormality, hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease within the last 5 years that may increase the risk associated with study participation.

10. Any surgical or medical condition which may significantly alter the absorption, distribution, metabolism or excretion of any drug substance but not limited to any of the following:

    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling or gastric banding (note: this is not applicable for minor abdominal surgery without significant tissue resection, *e.g.,* appendectomy and herniorrhaphy)

    - History of inflammatory bowel disease

    - History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine (≥123 µmol/l) or urea (≥8.9 mmol/L) or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria);

    - History or current evidence of ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if one or more of the following lab value deviations are found: 1) AST/SGOT (≥ 1.2 ULN), ALT/SGPT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) bilirubin (≥ 1.2 ULN) or CK (≥ 3 ULN);

    - Evidence of urinary obstruction or difficulty in voiding at screening.

    - History or clinical evidence at screening of pancreatic injury or pancreatitis

11. A subject with history of regular alcohol consumption exceeding 18 g (women) or 35 g (men) of pure alcohol per day, i.e. 1 drink/day for women or 2 drinks/day for men (1 drink = 150 mL of wine or 360 mL of beer or 45 mL of hard liquor) within 6 months of screening

12. Subject reported regular consumption of > 5 cups of coffee or tea per day (or equivalent consumption of ≥ 500 mg xanthine per day using other products)

13. Positive results in any of the virology tests for HIV-Ab, HCV-Ab, HBsAg and HBc-Ab (IgG + IgM)

14. Allergy to skin disinfecting agents, tape, or latex rubber, whenever appropriate substitutions cannot be applied or in the Investigator's opinion may pose a risk to the candidate.

15. Any condition not identified in the protocol that in the opinion of the Investigator would confound the evaluation and interpretation of the study data or may put the subject at risk

16. A subject who has previously been enrolled in this study.

17. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study

18. Use of any medication (including over-the-counter medications, vitamins, herbal remedies, dietary supplements) within 2 weeks prior to admission to the unit or within less than 10 times the elimination half-life of the respective drug (whichever is longer) or is anticipated to require any concomitant medication during that period or at any time throughout the study. Allowed treatments are:

    a. systemic contraceptives and hormone replacement therapy, as long as female subject is on stable treatment for at least 3 months and continues treatment throughout the study;

    b. occasional use of ibuprofen 200 mg (up to 1200 mg daily) or equivalent analgesic

19. Subject reports consumption of any drug metabolizing enzyme (e.g. CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements (*e.g.* broccoli, Brussels sprouts, grapefruit, grapefruit juice, star fruit, St. John's Wort *etc*.) within 2 weeks prior to admission to the unit.

20. Sitting blood pressure after a minimum of 5 minutes of rest is out of the range of 90-140 mmHg for systolic BP and/or 60-90 mmHg for diastolic BP and/or heart rate out of the range of 50-100 bpm during the screening procedure.

21. Body temperature is consistently out of the range of 35.4-37.3°C at screening, at check-in or during the study.

22. Anemia, defined as level of hemoglobin in women below 120 g/L and in men below 130 g/L at screening

23. Clinically relevant chronic or acute infectious illnesses or febrile infections within 2 weeks prior to screening till admission to the unit

24. A subject with a positive urine drug screen, alcohol breath test at screening and on day of admission to the unit

25. Smokers, defined as the use of tobacco products during the 3 months prior to screening till admission to the unit or a positive urine cotinine test at screening

26. Performance of strenuous physical exercise (body building, high performance sports) from 2 weeks prior to admission to the unit

27. Donation or loss of at least 500 mL of blood within 90 days or any donation of plasma or platelets from 2 weeks prior to admission to the unit

28. Getting a tattoo, body piercing or any cosmetic treatment involving skin penetration within 90 days before the screening till admission to the unit, unless evaluated by Investigator as non-significant for inclusion in the study

29. Subject with signs and symptoms suggestive of COVID-19 (*i.e.* fever, cough, *etc.*)[1] from 2 weeks prior to screening till admission to the unit 30. Subject with known COVID-19 positive contacts in the past from 2 weeks prior to screening till admission to the unit 31. Subjects who were hospitalized for COVID-19 related reasons	
Screening	Medical history, physical examination, COVID-19 test, 12-lead ECG, clinical chemistry, urinalysis, haematology, viral serology, blood pregnancy test for females, urinary drug screen, measurement of height and weight (includes calculation of BMI), coagulation, serum FSH if applicable, vital signs measurement, body temperature, alcohol breath test, urinary cotinine test.
Total Blood Volume Taken	+ 11.5 mL for screening + 21 (samples) x 2 (study periods) x 2 mL = 84 mL + 20 (catheter purge) x 2 (study periods) x 2 mL = 80 mL + 11.5 mL at end of study visit = 187 mL of blood in total About 20 mL of blood can be additionally withdrawn if repeated laboratory tests will be required during screening or follow-up. If one or more blood collections must be repeated during the study, it may be necessary to withdraw additional amount of blood. The reason for such additional blood collections must be justified by Investigator.
Vital Signs (Blood pressure, heart rate, respiratory rate) Body temperature	Vital signs will be monitored during screening procedures, check-in, prior to dosing (-1.00) and at 2.00, 4.00, 12 and 24 hours after IMP administration in each Study Period, every day during the subjects' stay in clinical unit (including at -12:00 hour before second dose) and at exit examination. Body temperature will be measured during screening, check-in, twice a day during the subjects' stay in clinical unit, and at exit examination.
Query on AE	Query on AE will be performed during check-in and every day during hospitalization.
Exit Procedures	Physical examination, measurement of body mass, vital signs, body temperature, COVID-19 test, and the same hematology, coagulation, urinalysis and clinical chemistry tests as the screening ones except for the HBsAg, HCV, HIV tests, serum FSH, urinary drug abuse test, cotinine test and alcohol breath test and pregnancy test for women.

[1] *as defined by WHO or local guidance*

Schedule of the Events	See Table 1-1 Schedule of Activities
Clinical Procedures during Confinement	See Table 1-2 Schedule for all Study Periods
Washout	At least 72 hours between the doses
Sample Handling	See Sample Handling Manual
Storage of Samples	Plasma samples will be stored at temperature ≤ -20°C.
Analytical Method	The Bioanalytical Laboratory of PPD will analyze plasma samples using validated method. The lower limit of quantification (LLOQ): • Paracetamol 0.25 µg/mL of plasma
Pharmacokinetic Parameters Evaluated	$AUC_{0\text{-tlast}}$, t_{max}, C_{max}, $AUC_{0\text{-inf}}$, $\%AUC_{ex}$, λ_z
Primary endpoints	• $AUC_{0\text{-tlast}}$ (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule) • t_{max} (The time of the maximum observed post-dose concentration) • C_{max} (The maximum observed post-dose concentration)
Secondary endpoints	• $AUC_{0\text{-inf}}$ (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0\text{-inf}} = AUC_{0\text{-t}} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant) • $\%AUC_{ex}$ (Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation, calculated as $(1 - [AUC_{0\text{-t}}/AUC_{0\text{-inf}}]) \times 100$) • λ_z (The terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time)
Comparison of Test and Reference Products	• The ratio of the geometric least square means between the test and reference and its 90% confidence intervals (CIs) of $AUC_{0\text{-tlast}}$ and C_{max} will be calculated. • Median differences between the test and reference and its 90% CI of t_{max} will be calculated. This study will be considered successful if bioequivalence between treatments concludes that the 90% CIs for the ratio of the means of $AUC_{0\text{-tlast}}$ and C_{max} of

	the paracetamol profiles lie completely within the range 0.8-1.25, and if there is no difference between the two treatments in terms of t_{max}.

Short Title:

A bioequivalence study of a new paracetamol oral suspension 24mg/ml compared to the marketed paracetamol oral suspension (Panadol Baby and Infant 24mg/ml) in healthy adult subjects.

Background and Rationale:

Paracetamol 24mg/ml Strawberry oral suspension is a newly developed CCI [redacted] formulation which is expected to replace the existing paracetamol 24 mg/ml oral suspension (Panadol B&I) for pediatric use. A comparative dissolution study has been performed, whose results confirmed that Panadol B&I and new paracetamol suspension have similar in vitro release characteristics. CCI [redacted]. In order to support the Marketing Authorization Application of the new oral suspension in the same indications, bioequivalence should be demonstrated with the approved paracetamol (24mg/ml) oral suspension (Panadol B&I).

Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
• To demonstrate bioequivalence of paracetamol in a new paracetamol oral suspension versus a marketed paracetamol oral suspension (Panadol B&I)	• $AUC_{0\text{-tlast}}$ (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule) • t_{max} (The time of the maximum observed post-dose concentration) • C_{max} (The maximum observed post-dose concentration)
Secondary	
• Assess the pharmacokinetic profile of new and marketed paracetamol oral suspension	• $AUC_{0\text{-inf}}$ (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0\text{-inf}} = AUC_{0\text{-t}} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant) • $\%AUC_{ex}$ (Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation, calculated as $(1 - [AUC_{0\text{-t}}/AUC_{0\text{-inf}}]) \times 100$)

	• λ_z (The terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time)
Safety	
Assess the safety profile of both products	• AEs (Adverse events), vital signs and clinical safety laboratory test results

Study Design:

This will be a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects.

Subjects will be screened for eligibility within 15 days prior to dosing. Subjects will receive each of the two study treatments in fasted state during a 6-day (5-overnight stay) residential period at the study site. Subjects will receive each treatment in a randomized order with a washout period of at least 72-hour between doses. During each treatment period, subjects will provide a pre-dose blood sample 1 hour before dosing and 20 post-dose blood samples at 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours, for bioanalytical analyses of paracetamol.

Study Products:

	Test Product	**Reference Product**
Product	New paracetamol oral suspension (24 mg/ml paracetamol)	Panadol B&I (24 mg/ml paracetamol)
Dose	42 mL (1g paracetamol)	42 mL (1g paracetamol)
Route of administration	Oral	Oral
Marketing Authorization Holder & Source market	GSKCH, Finland	GSKCH, Czech Republic (CZ)

Type and Planned Number of Subjects:

Approximately 110 subjects will be screened to randomize approximately 37 healthy adult subjects to ensure at least 31 evaluable subjects complete the entire study. In addition, two (2) overnight stand-by subjects will be confined until the first dosing as a reserve for pre-dose dropouts.

Statistical Methods:

The bioequivalence between a new paracetamol oral suspension (Test) and the marketed paracetamol oral suspension (Panadol B&I) (Reference) in fasted state will be assessed on the PK population:

- If the 90% confidence intervals (CIs) for the ratio of the means of the primary pharmacokinetic parameters, $AUC_{0\text{-}tlast}$ and C_{max} of the paracetamol profiles lie completely within the range 0.8-1.25.
- If there is no difference between the two treatments in terms of t_{max}.

An Analysis of Variance (ANOVA) model will be fitted to the log-transformed PK variables ($AUC_{0\text{- }tlast}$ and C_{max}), as the dependent variable, and treatment, period, sequence and subject nested within sequence as fixed effects. For each pairwise comparison, only the data from the two corresponding treatments will be included in the model. The presence of a statistically significant sequence effect will be noted, and its implications will be discussed. Least squares estimate of treatment effects will be calculated and a 90% confidence interval (CI) for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric least square means between the test and reference and its CI. Bioequivalence will be determined if the 90% CI for the treatment geometric least square mean ratio lies completely within the range 0.80 – 1.25.

t_{max} will be analyzed nonparametrically using Wilcoxon signed-rank test. Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on PK population.

$AUC_{0\text{-}inf}$ will be analyzed using the same ANOVA model method as for $AUC_{0\text{-}tlast}$ and $C_{max.}$

$\%AUC_{ex}$ and λz will be summarized for each treatment using descriptive statistics same as for the primary PK parameters.

1.2 Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Confinement Period[1] at Clinical Research Unit						
		Check-in	Period 1		Washout[2]	Period 2		Early Discontinuation or End of study[3]
	Day -15 to Day -2	Day -1	Day 1	Day 2		Day 4	Day 5	Day 5
Informed Consent	X							
Demographics	X							
Medical History	X							
Current/Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X
Physical examination	X		X			X		X
Height	X							
Weight	X							X
Vital signs[4]	X	X	X	X	X	X	X	X
Body temp check[5]	X	X	X	X	X	X	X	X
COVID19 test[6]	X	X						X
12-lead ECG	X							
Pregnancy test (in females)	X[7]	X[8]			X[8]			
Blood sample collection for biochemistry[9], hematology and coagulation [10]	X							X[11]
Virology	X							
Urine sample collection for urine analysis[12]	X							X
Urine illicit drug screen[13]	X	X						
Urine cotinine test	X	X						
Alcohol screen	X	X						
Inclusion/exclusion criteria	X	X[14]						
Continued eligibility[15]			X	X	X	X	X	X
Randomization		X						
Study product administration			X			X		
Blood sample collection for PK parameters[16]			X	X		X	X	
AE[17] Review	X	X	X	X	X	X	X	X
Study conclusion								X

Abbreviations: PK= Pharmacokinetic, AE= Adverse events

[1] Evening of the day prior to dosing until when end of study procedures are completed

[2] There will be a 72-hour washout scheduled between each dose administered

[3] These assessments are also to be conducted for subjects who discontinue study drug. These assessments will occur before discharge, on study Day 5

[4] Vital Signs- includes systolic and diastolic blood pressures, heart rate and respiratory rate measurement. Pre-treatment measurements (*i.e.* day 1 and day 4) of vitals will happen 1 hour before the scheduled drug administration with allowance up to +50 minutes from the scheduled time but must be measured before intravenous catheter insertion. Post treatment measurement will take place at 2.00, 4.00 and 12.00 and 24.00 hours after dosing. Additional measurements will be performed for medical reasons if necessary.

[5] Based on the actual epidemiologic situation, body temperature will be measured in all subjects in the morning and in the evening during the stay at the clinical unit.

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

- At screening visit- RT PCR test is to be done.
- At check-in and early discontinuation or end of study- Antigen test is to be done.
- At any time during residential period in study, when subjects report symptoms suggestive of COVID-19, subject will be isolated and antigen test is to be done. If test result is negative, isolate the subject in unit and conduct RT PCR. If test result is positive, conduct RT PCR test and discharge the subject for further management. Further details in Section 9.3.8: COVID-19 test.

[7] Blood pregnancy test

[8] Urine pregnancy test.

[9] Urea, Creatinine, Glucose (Fasting), Calcium, Magnesium, Sodium, Potassium, Chloride, Aspartate aminotransferase (AST), Alanine transaminase (ALT), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Alkaline phosphatase (ALP), Uric acid, Albumin, Total Protein, Creatine Kinase, Gamma-glutamyl transferase (GGT), Cholesterol and Follicle-stimulating hormone (FSH)

[10] Hemoglobin, Hematocrit, Red blood cells (RBC), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Platelets, White blood cells (WBC), Absolute counts of Neutrophils, Eosinophils, Monocytes, Basophils, Lymphocytes and prothrombin time (PT)/ international normalized ratio (INR)

[11] No FSH, HIV, HBsAg and Hepatitis C tests will be performed.

[12] pH, Glucose, Protein, Blood, Ketones, Nitrites, Urobilinogen, Bilirubin, Specific Gravity, Hemoglobin and Microscopy (RBC, WBC, squamous epithelial cells, transitional epithelial cells and casts).

[13] Amphetamine (AMP), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), ecstasy (MDMA), methamphetamine (MET), morphine (MOR), methadone (MTD), tricyclic antidepressants (TCA), and cannabinoids (THC)

[14] Only applicable to inclusion/exclusion criteria which are required to be re-confirmed before check-in as specified in section 5.2 and 5.3

[15] Continued eligibility is to be determined based on Subject Discontinuation/Withdrawal criteria (Section 7.1), as applicable on the day of assessment

[16] Pre-dose (-1 hour) and 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours post-doses

[17] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject consents to participate in the study by the completion of the Informed Consent Form (ICF).

Table 1-2 Schedule for all Study Periods

Day	Absolute Time[1]	Relative Time	Blood sample No.	Drug Admin.	Vital Signs[2] & Temp.[3]	AE[4] Check	Others	Fluids (mL)	Standard. Food
Day -1	**Until 19:00 (Check-in)**	-12.00			Vital Signs & Temp.	AE Check	Check-in[5]	No limit	
	20:30	-10.50						200 (water)	Dinner[6]
Day 1 **Period 1**	06:00	-1.00	**1**		Vital Signs & Temp.	AE Check	i.v. catheter insertion	200[7] (water)	**No intake**
	07:00	0.00		**X**				**No intake**	
	07:05	0.08	**2**						
	07:10	0.17	**3**						
	07:20	0.33	**4**						
	07:30	0.50	**5**						
	07:40	0.67	**6**						
	07:50	0.83	**7**						
	08:00	1.00	**8**					Only water	
	08:20	1.33	**9**						
	08:30	1.50	**10**						
	09:00	2.00	**11**		Vital Signs	AE Check			
	09:30	2.50	**12**						
	10:00	3.00	**13**						
	11:00	4.00	**14**		Vital Signs	AE Check		530 (water and soup)	Lunch
	12:00	5.00	**15**					Only water	**No intake**
	13:00	6.00	**16**					Only water	**No intake**
	15:00	8.00	**17**					200 (water)	Snack
	17:00	10.00	**18**				Physical examination	Only water	**No intake**
	19:00	12.00	**19**		Vital Signs& Temp.	AE Check		200 (water)	Dinner
	21:00	14.00	**20**					Only water	**No intake**
	23:00	16.00	**21**				i.v. catheter removal	Only water	**No intake**
Day 2 **Wash-out**	07:00	24.00			Vital Signs & Temp.	AE Check		Only water	**No intake**
	8:30							Only water	Breakfast
	13:00							530 (water and soup)	Lunch

[1] Absolute time is valid for subject No. 01. The activities in consecutive subjects follow in 2-minute intervals.
[2] Vital Signs – includes systolic and diastolic blood pressures, heart rate and respiratory rate measurement.
[3] Body temperature
[4] AE – Adverse Events.
[5] Drug screening from urine, urine pregnancy test (in females), alcohol breath test, cotinine test, body temperature, protocol restrictions compliance check
[6] Consumption of dinner must be finished 30 minutes after serving.
[7] The 200 mL of water has to be consumed completely.

Day	Absolute Time[1]	Relative Time	Blood sample No.	Drug Admin.	Vital Signs[2] & Temp.[3]	AE[4] Check	Others	Fluids (mL)	Standard. Food
	17:00							Only water	Snack
	20:30				Temp.			Only water	Dinner
Day 3 **Wash-out**	07:00				Temp.			Only water	**No intake**
	8:30							Only water	Breakfast
	13:00							530 (water and soup)	Lunch
	17:00							Only water	Snack
	19:00	-12.00			Vital Signs & Temp.	AE Check		Only water	**No intake**
	20:30	-10.50						Only water	Dinner[6]
Day 4 **Period 2**	06:00	-1.00	**1**		Vital Signs & Temp.	AE Check	i.v. catheter insertion	200[7] (water)	**No intake**
	07:00	0.00		**X**				**No intake**	
	07:05	0.08	**2**						
	07:10	0.17	**3**						
	07:20	0.33	**4**						
	07:30	0.50	**5**						
	07:40	0.67	**6**						
	07:50	0.83	**7**						
	08:00	1.00	**8**					Only water	
	08:20	1.33	**9**						
	08:30	1.50	**10**						
	09:00	2.00	**11**		Vital Signs	AE Check			
	09:30	2.50	**12**						
	10:00	3.00	**13**						
	11:00	4.00	**14**		Vital Signs	AE Check		530 (water and soup)	Lunch
	12:00	5.00	**15**					Only water	**No intake**
	13:00	6.00	**16**					Only water	**No intake**
	15:00	8.00	**17**					200 (water)	Snack
	17:00	10.00	**18**				Physical examination	Only water	**No intake**
	19:00	12.00	**19**		Vital Signs & Temp.	AE Check		200 (water)	Dinner
	21:00	14.00	**20**					Only water	**No intake**
	23:00	16.00	**21**				i.v. catheter removal	Only water	**No intake**
Day 5 **Check-out**	07:00	24.00			Vital Signs & Temp.	AE Check	Check-out		

2 INTRODUCTION

2.1 Study Rationale

The reference product Panadol B&I is registered in more than 110 countries world-wide with non-prescription status (over the counter (OTC)) granted in about 80 countries. It is indicated to reduce:

A. mild-to-moderate pain including:
- tooth extraction
- toothache
- headache
- sore throat related to the inflammation of the upper respiratory tract

B. fever accompanying flu, cold, acute inflammation of the upper respiratory and infectious diseases in children, such as measles, rubella, chickenpox, scarlet fever and mumps and to reduce elevated temperatures after vaccination.

A new paracetamol oral suspension formulation has been developed by GlaxoSmithKline Consumer Healthcare (GSKCH).

In order to support the Marketing Authorization Application of the new oral suspension in the same indications, bioequivalence should be demonstrated with the approved paracetamol (24mg/ml) oral suspension (Panadol B&I). The proposed paracetamol oral suspension will have the same indications as the approved Panadol B&I.

2.2 Background

Paracetamol is one of the most commonly used non-prescription analgesic medications. Use of pediatric formulations of paracetamol is especially widespread for the management of fever and to relieve mild to moderate aches and pains due to common cold, influenza, headache, sore throat, toothaches and other indications. The safety of short-term use of paracetamol in the pediatric population is well established. Availability of the medication as a liquid formulation makes it easy to administer in children and promotes compliance.

GSKCH children's liquid paracetamol is currently marketed under the portfolio of Panadol B&I.

CCI [redacted]

CCI [redacted] A comparative

dissolution study has been performed to confirm that both products show similar in vitro release characteristics.

Paracetamol can be considered as highly permeable drug. Like BCS class I drugs, their bioavailability is unlikely to be affected by any change of small intestine transit time caused by sorbitol/ maltitol or any other critical excipients

2.3 Benefit/Risk Assessment

Complete information for this paracetamol oral suspension may be found in the single reference safety document (SRSD), which for this study is the Summary of Products Characteristics (SmPC) for Czech Republic.

2.4 Mechanism of Action/Indication

Paracetamol is an analgesic and antipyretic without anti-inflammatory effect and with good gastrointestinal tolerability. It is suitable for adults and in pediatrics. The mechanism of action is likely to be similar to that of acetylsalicylic acid and is dependent on the inhibition of prostaglandins primarily in the central nervous system.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
• To demonstrate the bioequivalence of paracetamol in a new paracetamol oral suspension versus the marketed paracetamol oral suspension (Panadol B&I)	• $AUC_{0\text{-tlast}}$ (The area under the plasma concentration versus time curve calculated from time 0 to the last measurable sampling time point, t, computed using the linear trapezoidal rule) • t_{max} (The time of the maximum observed post-dose concentration) • C_{max} (The maximum observed post-dose concentration)
Secondary	
• Assess the pharmacokinetic profile of new and the marketed paracetamol oral suspension	• $AUC_{0\text{-inf}}$ (The area under the plasma concentration versus time curve calculated from time 0 to infinity $AUC_{0\text{-inf}} = AUC_{0\text{-t}} + C(t)/\lambda_z$ where C(t) is the concentration at the last measurable sampling time point and λ_z is the terminal elimination rate constant) • $\%AUC_{ex}$ (Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation, calculated as $(1 - [AUC_{0\text{-t}}/AUC_{0\text{-inf}}]) \times 100$)

	• λ_z (The terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time)
Safety	
Assess the safety profile of both products	• AEs, vital signs and clinical safety laboratory test results

This study will be considered successful if bioequivalence between the new and the currently marketed paracetamol oral suspension concludes that the 90% CIs for the ratio of the means of the primary pharmacokinetic parameters $AUC_{0\text{-tlast}}$ and C_{max} of the paracetamol profiles lie completely within the range 0.8-1.25, and if there is no difference between the two treatments in terms of t_{max}.

4 STUDY DESIGN

4.1 Overall Design

This will be a 2-arm, single center, single dose, open-label, randomized, two-sequence, two-period crossover, bioequivalence study in healthy adult subjects. Subjects will be screened for eligibility within 15 days prior to dosing. Subjects will receive each of the two study treatments in fasted state during a 6-day (5-overnight stay) residential period at the study site. Subjects will receive both treatment regimens in a randomized order with a 72-hour washout period between each dose. During each treatment period, subjects will provide a pre-dose blood sample 1 hour before dosing and 20 post-dose blood samples at 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours, for bioanalytical analyses of paracetamol. The schedule of activities table (Table 4-1) provides an overview of the subject visits and study procedures. Table 4-2 provides an overview of the PK sampling scheme during the study.

Figure 4-1 Study design

Screening	**Period 1**	**Washout[a]**	**Period 2**	**End of study visit**
Day -15 to -2	Day -1 to 2	Day 1[b]-3	Day 4-5	Day 5

a: Washout period of at least 72 hours between the doses.
b: Begins post administration of first dose

Table 4-1 Schedule of Activities

Procedure/Assessment	Screening	Confinement Period[1] at Clinical Research Unit						
		Check-in	Period 1		Washout[2]	Period 2		Early Discontinuation or End of study[3]
	Day -15 to Day -2	Day -1	Day 1	Day 2		Day 4	Day 5	Day 5
Informed Consent	X							
Demographics	X							
Medical History	X							
Current/Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X
Physical examination	X		X			X		X
Height	X							
Weight	X							X
Vital signs[4]	X	X	X	X	X	X	X	X
Body temp check[5]	X	X	X	X	X	X	X	X
COVID19 test[6]	X	X						X
12-lead ECG	X							
Pregnancy test (in females)	X[7]	X[8]			X[8]			
Blood sample collection for biochemistry[9] hematology and coagulation [10]	X							X[11]
Virology	X							
Urine sample collection for urine analysis[12]	X							X
Urine illicit drug screen[13]	X	X						
Urine cotinine test	X	X						
Alcohol screen	X	X						
Inclusion/exclusion criteria	X	X[14]						
Continued eligibility[15]			X	X	X	X	X	X
Randomization		X						
Study product administration			X			X		
Blood sample collection for PK parameters[16]			X	X		X	X	
AE[17]Review	X	X	X	X	X	X	X	X
Study conclusion								X

[1] Evening of the day prior to dosing until when end of study procedures are completed

[2] There will be a 72-hour washout scheduled between each dose administered

[3] These assessments are also to be conducted for subjects who discontinue study drug. These assessments will occur before discharge, on study Day 5

[4] Vital Signs- includes systolic and diastolic blood pressures, heart rate and respiratory rate measurement. Pre-treatment measurements (*i.e.* day 1 and day 4) of vitals will happen 1 hour before the scheduled drug administration with allowance up to +50 minutes from the scheduled time but must be measured before intravenous catheter insertion. Post treatment measurement will take place at 2.00, 4.00 and 12.00 and 24.00 hours after dosing. Additional measurements will be performed for medical reasons if necessary.

[5] Based on the actual epidemiologic situation, body temperature will be measured in all subjects in the morning and in the evening during the stay at the clinical unit.

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

- At screening visit- RT PCR test is to be done.
- At check-in and early discontinuation or end of study- Antigen test is to be done.
- At any time during residential period in study, when subjects report symptoms suggestive of COVID-19, subject will be isolated and antigen test is to be done. If test result is negative, isolate the subject in unit and conduct RT PCR. If test result is positive, conduct RT PCR test and discharge the subject for further management. Further details in Section 9.3.8: COVID-19 test.

[7] Blood pregnancy test

[8] Urine pregnancy test.

[9]Urea, Creatinine, Glucose (Fasting), Calcium, Magnesium, Sodium, Potassium, Chloride, Aspartate aminotransferase (AST), Alanine transaminase (ALT), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Alkaline phosphatase (ALP), Uric acid, Albumin, Total Protein, Creatine Kinase, Gamma-glutamyl transferase (GGT), Cholesterol and Follicle-stimulating hormone (FSH)

[10] Hemoglobin, Hematocrit, Red blood cells (RBC), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Platelets, White blood cells (WBC), Absolute counts of Neutrophils, Eosinophils, Monocytes, Basophils, Lymphocytes and prothrombin time (PT)/ international normalized ratio (INR)

[11] No FSH, HIV, HBsAg and Hepatitis C tests will be performed.

[12] pH, Glucose, Protein, Blood, Ketones, Nitrites, Urobilinogen, Bilirubin, Specific Gravity, Hemoglobin and Microscopy (RBC, WBC, squamous epithelial cells, transitional epithelial cells and casts).

[13] Amphetamine (AMP), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), ecstasy (MDMA), methamphetamine (MET), morphine (MOR), methadone (MTD), tricyclic antidepressants (TCA), and cannabinoids (THC)

[14] Only applicable to inclusion/exclusion criteria which are required to be re-confirmed before check-in as specified in section 5.2 and 5.3

[15] Continued eligibility is to be determined based on Subject Discontinuation/Withdrawal criteria (Section 7.1), as applicable on the day of assessment

[16] Pre-dose (-1 hour) and 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours post-doses

[17] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately after a subject consent to participate in the study by the completion of the Informed Consent Form (ICF).

Table 4-2 Timing Schedule for All Study Periods

Day	Absolute Time[1]	Relative Time	Blood sample No.	Drug Admin.	Vital Signs[2] & Temp.[3]	AE[4] Check	Others	Fluids (mL)	Standard. Food
Day -1	**Until 19:00 (Check-in)**	-12.00			Vital Signs & Temp.	AE Check	Check-in[5]	No limit	
	20:30	-10.50						200 (water)	Dinner[6]
Day 1 **Period 1**	06:00	-1.00	**1**		Vital Signs & Temp.	AE Check	i.v. catheter insertion	200[7] (water)	No intake
	07:00	0.00		**X**				**No intake**	
	07:05	0.08	**2**						
	07:10	0.17	**3**						
	07:20	0.33	**4**						
	07:30	0.50	**5**						
	07:40	0.67	**6**						
	07:50	0.83	**7**						
	08:00	1.00	**8**					Only water	
	08:20	1.33	**9**						
	08:30	1.50	**10**						
	09:00	2.00	**11**		Vital Signs	AE Check			
	09:30	2.50	**12**						
	10:00	3.00	**13**						
	11:00	4.00	**14**		Vital Signs	AE Check		530 (water and soup)	Lunch
	12:00	5.00	**15**					Only water	**No intake**
	13:00	6.00	**16**					Only water	**No intake**
	15:00	8.00	**17**					200 (water)	Snack
	17:00	10.00	**18**				Physical examination	Only water	**No intake**
	19:00	12.00	**19**		Vital Signs& Temp.	AE Check		200 (water)	Dinner
	21:00	14.00	**20**					Only water	**No intake**
	23:00	16.00	**21**				i.v. catheter removal	Only water	**No intake**
Day 2	07:00	24.00			Vital Signs & Temp.	AE Check		Only water	**No intake**
	8:30							Only water	Breakfast

[1] Absolute time is valid for subject No. 01. The activities in consecutive subjects follow in 2-minute intervals.
[2] Vital Signs – includes systolic and diastolic blood pressures, heart rate and respiratory rate measurement.
[3] Body temperature
[4] AE – Adverse Events.
[5] Drug screening from urine, urine pregnancy test (in females), alcohol breath test, cotinine test, body temperature, protocol restrictions compliance check
[6] Consumption of dinner must be finished 30 minutes after serving.
[7] The 200 mL of water has to be consumed completely.

Day	Absolute Time[1]	Relative Time	Blood sample No.	Drug Admin.	Vital Signs[2] & Temp.[3]	AE[4] Check	Others	Fluids (mL)	Standard. Food
Wash-out	13:00							530 (water and soup)	Lunch
	17:00							Only water	Snack
	20:30				Temp.			Only water	Dinner
Day 3 **Wash-out**	07:00				Temp.			Only water	**No intake**
	8:30							Only water	Breakfast
	13:00							530 (water and soup)	Lunch
	17:00							Only water	Snack
	19:00	-12.00			Vital Signs & Temp.	AE Check		Only water	**No intake**
	20:30	-10.50						Only water	Dinner[6]
Day 4 **Period 2**	06:00	-1.00	**1**		Vital Signs & Temp.	AE Check	i.v. catheter insertion	200[7] (water)	**No intake**
	07:00	0.00		**X**				**No intake**	
	07:05	0.08	**2**						
	07:10	0.17	**3**						
	07:20	0.33	**4**						
	07:30	0.50	**5**						
	07:40	0.67	**6**						
	07:50	0.83	**7**						
	08:00	1.00	**8**					Only water	
	08:20	1.33	**9**						
	08:30	1.50	**10**						
	09:00	2.00	**11**		Vital Signs	AE Check			
	09:30	2.50	**12**						
	10:00	3.00	**13**						
	11:00	4.00	**14**		Vital Signs	AE Check		530 (water and soup)	Lunch
	12:00	5.00	**15**					Only water	**No intake**
	13:00	6.00	**16**					Only water	**No intake**
	15:00	8.00	**17**					200 (water)	Snack
	17:00	10.00	**18**				Physical examination	Only water	**No intake**
	19:00	12.00	**19**		Vital Signs & Temp.	AE Check		200 (water)	Dinner
	21:00	14.00	**20**					Only water	**No intake**
	23:00	16.00	**21**				i.v. catheter removal	Only water	**No intake**
Day 5 **Check-out**	07:00	24.00			Vital Signs & Temp.	AE Check	Check-out		

4.2 Scientific Rationale for Study Design

Rationale for Primary Endpoints

The study design follows recommendations given by the EMA in the applicable Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr **(2010)) and the paracetamol specific bioequivalence guidelines (EMA 2017).

For establishing bioequivalence C_{max} and t_{max} and extent of absorption ($AUC_{0\text{-}tlast}$) of the active ingredient paracetamol, will be used as primary endpoints.

Rationale for Study Design

The randomized, single dose, two period, two sequence, intra-subject crossover study design is highly discriminative and hence well accepted for the direct comparison of the PK in vivo performance of two paracetamol immediate release products.

For the overall objectives of this PK-study, the open-label study design is considered acceptable and justified, because the PK variables of the study are objectively measured bio-analytical outcomes that are unlikely to be subject to investigator- or subject-induced bias. However, to facilitate objective measurement of the bioanalytical outcomes, personnel performing the bioanalytical analysis will be blinded to the randomized treatment.

Carry-over effects will be avoided by observation of an appropriate wash-out interval of at least 72 hours between treatments which covers more than 15 times of the average $t_{1/2}$ value of 4 hours. The study conditions and methodologies will be controlled and strictly standardized to keep inter- and intra-subject variability to a minimum.

Blood sampling will be done at pre-determined times for 16 hours following oral intake of the study drugs. The duration of the blood sampling period is based on the absorption and elimination rates characteristics of both components (*i.e.* average $t_{1/2}$-reported) and was designed to cover a period of at least 4-times of the average $t_{1/2}$ values ($t_{1/2}$ for paracetamol 1-4 hours).

Rationale for Study Population

Healthy adult is the population recommended for bioequivalence studies. EMA Pharmacokinetic Working Party [CCI [redacted]] recommends that, in vivo bioequivalence is almost always established in healthy subjects unless the drug carries safety concerns that make this unethical. This model, in vivo healthy subjects, is regarded adequate in most instances to detect significant formulation differences and the results will allow extrapolation to populations in which the drug is approved (the elderly, patients with renal or liver impairment etc.). The same reasoning applies also to children. This study will be performed in healthy adult subjects aged 18-45 years.

4.3 Justification for Dose

The standard single dose of paracetamol in adults is 1 g of paracetamol [Global Data Sheet v 7.0]. Both study treatments contain 24 mg/ml paracetamol; therefore, a dose of 42 ml (1 g paracetamol) will be administered in each period.

4.3.1 Medications and Treatment

No concomitant treatment is allowed during the entire period of the study (for exceptions, see exclusion criteria 18). If concomitant therapy is required for medical management of AEs

during the study, a decision for the subject's continuation will be made by the investigator, based on the time the medication was administered and, on the pharmacology, and pharmacokinetics of the study drug and the concomitant medication.

4.4 End of Study Definition

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

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Since the collection of detailed biopharmaceutic data in vulnerable children is difficult due to ethical considerations, this study plans to collect adult data with the assumption that the adult observations can be extrapolated to children. For the study healthy adult subjects aged 18-45 years will be selected.

Approximately 110 subjects will be screened to randomize approximately 37 healthy adult subjects to ensure at least 31 evaluable subjects complete the entire study. An enrolled subject will be the one who has agreed to participate in the clinical study following completion of the informed consent process and successfully met eligibility criteria to proceed beyond the screening visit as applicable for the protocol design.

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

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

5.2 Inclusion Criteria

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

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

2. Subject is male or female

3. Subject is 18 to 45 years of age inclusive, at the signing of the informed consent.

4. A subject who is willing and able to comply with scheduled visits, treatment plan, laboratory tests, study restrictions and other study procedures.

5. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, as determined by medical evaluation, including medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests

6. A subject with a Body Mass Index (BMI) of 18.5 to 30.0 kg/m^2; and a total body weight >60 kg

7. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 7 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in CCI [redacted].

8. Subject with two consecutive negative tests for active COVID-19, separated by > 24 hours.

9. Czech citizenship

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be included in the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSKCH employee directly involved in the conduct of the study or a member of their immediate family.

2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days before dosing.

3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.

4. A subject who is pregnant as confirmed by a positive hCG laboratory test or intending to become pregnant over the duration of the study.

5. A subject who is breastfeeding.

6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients. This includes paracetamol and excipients in the products *e.g.* sorbitol, maltitol glycerol *etc.*

7. A subject unwilling or unable to comply with Lifestyle Considerations (Section 5.5 of protocol) described in this protocol.

8. Diagnosis of long QT syndrome or QTc > 450 msec for males and > 470 msec for females at screening.

9. A subject with evidence or history of clinically significant laboratory abnormality, hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease within the last 5 years that may increase the risk associated with study participation.

10. Any surgical or medical condition which may significantly alter the absorption, distribution, metabolism or excretion of any drug substance but not limited to any of the following:

    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling or gastric banding (note: this is not applicable for minor abdominal surgery without significant tissue resection, *e.g.,* appendectomy and herniorrhaphy)

    - History of inflammatory bowel disease

    - History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine (≥ 123 µmol/l) or urea (≥ 8.9 mmol/L) or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria);

    - History or current evidence of ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if one or more of the following lab value deviations are found: 1) AST/SGOT (≥ 1.2 ULN), ALT/SGPT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) bilirubin (≥ 1.2 ULN) or CK (≥ 3 ULN);

    - Evidence of urinary obstruction or difficulty in voiding at screening.

    - History or clinical evidence at screening of pancreatic injury or pancreatitis

11. A subject with history of regular alcohol consumption exceeding 18 g (women) or 35 g (men) of pure alcohol per day, i.e. 1 drink/day for women or 2 drinks/day for men (1 drink = 150 mL of wine or 360 mL of beer or 45 mL of hard liquor) within 6 months of screening

12. Subject reported regular consumption of > 5 cups of coffee or tea per day (or equivalent consumption of ≥ 500 mg xanthine per day using other products)

13. Positive results in any of the virology tests for HIV-Ab, HCV-Ab, HBsAg and HBc-Ab (IgG + IgM)

14. Allergy to skin disinfecting agents, tape, or latex rubber, whenever appropriate substitutions cannot be applied or in the Investigator's opinion may pose a risk to the candidate.

15. Any condition not identified in the protocol that in the opinion of the Investigator would confound the evaluation and interpretation of the study data or may put the subject at risk

16. A subject who has previously been enrolled in this study.

17. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study

18. Use of any medication (including over-the-counter medications, vitamins, herbal remedies, dietary supplements) within 2 weeks prior to admission to the unit or within less than 10 times the elimination half-life of the respective drug (whichever is longer) or is anticipated to require any concomitant medication during that period or at any time throughout the study. Allowed treatments are:

a) systemic contraceptives and hormone replacement therapy, as long as female subject is on stable treatment for at least 3 months and continues treatment throughout the study;

b) occasional use of ibuprofen 200 mg (up to 1200 mg daily) or equivalent analgesic

19. Subject reports consumption of any drug metabolizing enzyme (e.g. CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements (*e.g.* broccoli, Brussels sprouts, grapefruit, grapefruit juice, star fruit, St. John's Wort *etc*.) within 2 weeks prior to admission to the unit

20. Sitting blood pressure after a minimum of 5 minutes of rest is out of the range of 90-140 mmHg for systolic BP and/or 60-90 mmHg for diastolic BP and/or heart rate out of the range of 50-100 bpm during the screening procedure.

21. Body temperature is consistently out of the range of 35.4-37.3°C at screening, at check-in or during the study.

22. Anemia, defined as level of hemoglobin in women below 120 g/L and in men below 130 g/L at screening.

23. Clinically relevant chronic or acute infectious illnesses or febrile infections within 2 weeks prior to screening till admission to the unit

24. A subject with a positive urine drug screen, alcohol breath test at screening and on day of admission to the unit

25. Smokers, defined as the use of tobacco products during the 3 months prior to screening till admission to the unit or a positive urine cotinine test at screening

26. Performance of strenuous physical exercise (body building, high performance sports) from 2 weeks prior to admission to the unit

27. Donation or loss of at least 500 mL of blood within 90 days or any donation of plasma or platelets from 2 weeks prior to admission to the unit

28. Getting a tattoo, body piercing or any cosmetic treatment involving skin penetration within 90 days before the screening till admission to the unit, unless evaluated by Investigator as non-significant for inclusion in the study

29. Subject with signs and symptoms suggestive of COVID-19 (*i.e*. fever, cough, *etc*.)[1] from 2 weeks prior to screening till admission to the unit

30. Subject with known COVID-19 positive contacts in the past from 2 weeks prior to screening till admission to the unit

31. Subjects who were hospitalized for COVID-19 related reasons

[1] *as defined by WHO or local guidance*

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. Subjects will be allocated to receive two test regimens in a specific order determined by a randomization schedule.

5.5 Lifestyle Considerations

Subjects will be required to reside at the study site from admission on Day -1 until the morning of Day 5 after the end of Study visit procedures have been performed. Following lifestyle restrictions will apply to all study participants:

- Meals intake during the study will also be standardized (only water will be allowed unrestricted at certain times).
- Subjects will receive standardized food and beverages throughout the study.

5.5.1 Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose PK sample. Water is permitted until 1 hour prior to investigational product administration. Water may be consumed without restriction beginning 1 hour after dosing.
- Liquid intake during the study will also be standardized (only water will be allowed unrestricted at certain times).
- Lunch will be provided approximately 4 hours after dosing.
- An evening snack may be permitted approximately 8 hours after dosing.
- Dinner will be provided approximately 12 hours after dosing.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (e.g. Seville oranges, pomelos, papaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits) from 14 days prior to the first dose of investigational product until collection of the final pharmacokinetic blood sample.
- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

5.5.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 72 hours prior to the start of dosing and continue abstaining from alcohol until completion of study. Subjects may undergo an alcohol breath test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products (i.e. tea, coffee, chocolate, cola), chewing gums, other xanthine or CO_2 containing food and beverages for 24 hours prior to the start of dosing until completion of study.

- Subjects will abstain from the use of tobacco- or nicotine-containing products including nicotine patches and other delivery devices such as electronic cigarettes or vaporizers) during confinement at the clinical site.

5.5.3 Activity

To standardize gastric emptying, subjects will sit upright on the edge of their beds for 20 minutes after dosing. Thereafter, they will be asked to lie on their right sides for the remainder of the first hour post-administration. Except for bladder voiding, blood sampling and ingestion of food and beverages as indicated, subjects will remain recumbent until 5 hours after administration of study medication, after which no restrictions concerning posture or movement will apply. Posture control procedures will be documented

5.5.4 Contraception

All female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for 7 days after the last dose of investigational product.

A female subject will be considered of non-childbearing potential if they satisfy at least one of the following criteria:

1. Achieved menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause
2. Have undergone a documented hysterectomy and/or bilateral oophorectomy
3. Have medically confirmed ovarian failure

The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and **document such conversation**. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (*i.e.,* have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (*e.g.* calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive (CCI [redacted])

4. Injectable progestogen (CCI [redacted])
5. Contraceptive vaginal ring (CCI [redacted])
6. Percutaneous contraceptive patches (CCI [redacted])
7. Bilateral tubal ligation at least six weeks before taking study treatment
8. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject (CCI [redacted]. The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5.6 Screen Failures

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

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact number in the ICF. The document will provide, as a minimum, protocol identifiers, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

Assessment of medical history, and prior medication/treatment, physical examination, safety evaluation and adverse events reporting needs to be performed by qualified medical physician.

6 STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, study intervention is defined as any investigational intervention(s), marketed

product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

The selection of Panadol B&I (reference product) will be based on assay content to ensure that this test product does not differ by more than 5% from that of the batch used as reference product according to the European Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **(2010)).

6.1 Study Product Supplies

The following study products will be manufactured according to Good Manufacturing Practice and will be supplied by the Clinical Supplies Department, GSKCH:

Table 6-1 Investigational/Study Product Supplies

	Test Product	Reference Product
Product Name	Paracetamol Suspension, Strawberry flavor, color-free (24 mg/ml paracetamol)	Panadol B&I (Marketed as Panadol pro děti jahoda perorální suspenze), Strawberry flavor, color-free suspension (24 mg/ml paracetamol)
Pack Design	Glass bottle with a syringe	Glass bottle with a syringe
Dispensing Details	To be administered orally via a syringe	To be administered orally via a syringe
Product Master Formulation Code (MFC)	CCI [redacted]	Czech Republic marketed product MA number: CCI [redacted]
Manufacturer	GSKCH, Nyon, Switzerland	Farmaclair (a Contract Manufacturing Organization under GSKCH), France
Marketing Authorization holder	GSKCH, Finland	GSK, Czech Republic
Source Market	NA	Czech Republic
Dose	42 ml (1 g paracetamol)	42 ml (1 g paracetamol)
Route of Administration	Oral	Oral
Usage Instructions	Volume of 42ml to be administered orally via a syringe	Volume of 42ml to be administered orally via a syringe
Return Requirements	All used/unused samples to be returned	All used/unused samples to be returned

Detail instructions for dosing will be described in dosage and administration instructions. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSKCH during the study in time for study close out visit.

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Pregnancy Test kits	Site	Commercial pack	Use as per study schedule	Disposal to be managed by the site	Disposal to be managed by the site
Alcohol breath analyzer	Site	Commercial pack	Use as per study schedule	Disposal to be managed by the site	Disposal to be managed by the site
Oral Dosing Syringes	GSKCH	Commercial pack	Use as per study schedule	Destroy at site using site disposal procedures	Return as per instructions provided by GSKCH
Dosing cups	GSKCH	Commercial pack	Use as per study schedule	Destroy at site using site disposal procedures	Return as per instructions provided by GSKCH

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

6.1.1 Dosage Form and Packaging

The test product and the reference products will be supplied to the clinical site as packaged bottles. Each bottle will have a clinical study label affixed.

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

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

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

6.1.2 Preparation and Dispensing

Paracetamol and Panadol B& I suspensions will be prepared and/or dispensed by qualified site personnel according to the dosage and administration instruction.

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSKCH vendor ([CCI]), prior to the start of the study, using validated software.

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

6.2 Administration

A physician or an appropriate member of the study site personnel, will administer study formulations, a second suitably qualified person will witness this. The appropriate volume of each study treatment will be administered orally via a single use syringe. Detail instructions for dosing will be described in dosage and administration instructions.

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

6.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

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

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

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

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

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

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol. Overdose is not likely to occur in this study. Limited quantities of the study product(s) will be supplied, and closely monitored by the site for each subject.

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

6.3 Investigational/Study Product Storage

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

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

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

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

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

6.4 Investigational/Study Product Accountability

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

All study drug received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability records according to PPD appropriate SOP.

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

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

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of GSKCH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers), will be returned for destruction to the GSKCH Clinical Supplies or appropriate GSK approved vendor. Used sundry items will be destroyed at the site, per Table 6-2, and should not be returned. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSKCH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

Randomization

Subjects who sign the informed consent form (ICF), meet eligibility criteria, and check into the study clinic on Day -1 will be randomly assigned to 1 of the 2 treatment sequences: (1) Test/Reference; and (2) Reference/Test.

A randomization list will be generated by an PPD randomization statistician*, who is independent from the study team, prior to the start of study for implementation at study site. Randomization must be followed exactly as generated, and eligible subjects will be assigned sequentially (i.e., based on Screening order).

The responsibility of this statistician is limited to generation and maintenance of randomization related materials.

The randomization list will be saved in a secure access-restricted folder on PPD network drive. Only the randomization statistician and another senior reviewer (another independent statistician) will have access to this folder. Only after database lock and receipt of the unblinding request for the study (to be signed by GSK and PPD, will the randomization statistician will release the randomization files for use by study team in generation of TLFs.

GSKCH Clinical Supplies will be provided with randomization schedule prior to study initiation to allow the packaging of study products individually for each subject and their verification. Study products will be individually packed and labelled for each subject and period according to the Randomization Schedule by responsible persons delegated by GSKCH.

Returned study products should not be re-dispensed to any subject.

Blinding

Study will be open label, but laboratory analysis will be blinded. Analysts of bioanalytical laboratory will have no access to randomization schedule, and, samples will be sent to analytical laboratory with blinded code to ensure that staff at analytical lab are not aware of treatment status of the subjects. Also, study personnel who will be involved in data analysis are to remain blinded to treatment codes until the database lock.

6.6 Breaking the Blind

Not applicable given the open label study design.

6.7 Compliance

Study products will be administered under the supervision of investigator site personnel. The designated dosing personnel must check the mouth to ensure that the suspension has been swallowed. A record of the administration of study treatments (time and date of preparation of study drug, study drug ingestion start and stop time and date, including dates for intervention delays) will be kept using the Dosing Accountability Log and the CRF, any comments on the performance of this procedure should be recorded on the CRF. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject will continue in the study.

6.8 Concomitant Medication/Treatment(s)

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

Medication/treatments taken within 30 days prior to signing the informed consent form and before first dose of study product will be documented as a prior medication/treatment. Medications/treatments taken after first dose of study product will be documented as concomitant medication/treatments.

Subjects will abstain from all concomitant treatments, except for contraceptives and those used for the treatment of adverse events.

6.9 Rescue Medication

Not applicable as study subjects are healthy and thus there is no disease condition symptoms to be controlled.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL.

7.1 Subject Discontinuation/Withdrawal

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

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

At subject's discretion

- Withdrawal of informed consent
- Subject lost to follow-up

At investigator's discretion

- Protocol violation that may impact the subject's safety

- If the subject is no longer able to participate for other clinically relevant medical reasons (*e.g.* difficult blood drawing, surgery, adverse event)
- Serious adverse event
- Pregnancy
- Emesis shortly/immediately before administration of investigational product (assessed on case by case basis)
- Emesis within 103 minutes[1] post dosing
- Diarrhea within 10 hours post dosing
- Positive test for COVID-19, conducted during the study, at times deemed necessary by Investigator
- Body temperature consistently < 35.4 and/or ≥ 37.3°C (three consecutive measurements assessed at least 15 minutes apart in a single day)
- If the subject requires treatment with any medication which is known or suspected that it can interfere with the study drugs pharmacokinetics or analytical methodology
- There is evidence that the subject fails to comply with the study protocol directives (non-attendance at study assessments, non-compliance with the treatment schedule, non-adherence to dietary rules or other restrictions which may influence on pharmacokinetic study results). Discontinuation of the subject depends on Investigator's judgement and decision
- Any other condition occurs which in the opinion of the Investigator no longer justifies or permits a safe participation of the subject.

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. Subjects who withdraw or are withdrawn from the study after dosing will not be replaced. Subjects withdrawn for safety reasons or following a vomiting episode will be asked to remain at the clinic until the Investigator(s) agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped.

In the event of a premature withdrawal after dosing, the subject will be requested to complete a safety assessment at the time of discontinuation (or as soon as possible after the time of discontinuation) CCI [redacted]

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs).

[1] This equals twice the reference's t_{max}; observed in GSK study A2210378

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

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

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

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. An overview of study activities is provided in Table 4-1 and Table 4-2.

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

The site may contact subjects prior to study visit as part of pre-screening activities and follow up of AEs as detailed in Section 8.4: Follow up Visits Further details will be included in the Informed Consent Form (ICF). Subjects will be invited for antigen test at least 16 hours before check-in. Subjects will be then confined from at least 12 hours before dosing until after the second 24-hour post-dose blood collection. There will be a washout of at least 72 hours between drug administration.

Participation of each subject in this study should last approximately 1 month (from the time of ICF signature to the end of the clinical part of the study).

8.1 Screening

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

Subjects will be screened within 15 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed:

8.1.1 Informed Consent

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

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSKCH.

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

The time the subject signed the informed consent form will be captured as this is the point at which all Adverse Events will be captured from. The date and time of consent will be captured in the CRF.

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

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

8.1.2 Demographics

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

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Medical History

The Investigator, or medically qualified designee, will take a medical history from each subject. Details of relevant medical and surgical history (in the last 1 year), including allergies or drug sensitivity, will be documented in the CRF.

8.1.4 Prior Medication/Treatment

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days prior to signing the informed consent form, will be documented in the CRF.

8.1.5 Physical Examination

Physical examination will be performed, and findings will be documented in the CRF.

8.1.6 Height and Weight

Height and weight measurements will be recorded in the CRF.

8.1.7 Vital Signs

Vital signs will be assessed, and readings will be documented in the CRF.

8.1.8 Body Temperature

Body temperature will be checked, and readings will be documented in the CRF.

8.1.9 Screening Procedures

Nasopharyngeal swab sample will be collected for COVID19 test once for screening. The second test will be done on the day of check-in (Day -1). Date and time of sample collection and test results (positive or negative) will be documented in the CRF.

12-lead ECG assessment will be performed, and findings; normal or abnormal (with details), and clinical significance will be documented in the CRF.

Blood sample will be collected for blood pregnancy test, Biochemistry, Hematology and coagulation. Date and time of sample collection will be documented in the CRF.

Blood sample will be collected for Virology. Date and time of sample collection will be documented in the CRF.

Urine sample will be collected for analysis. Date and time of sample collection will be documented in the CRF.

Urine sample will be collected for illicit drug screen. Date and time of sample collection and test's outcome (positive or negative) for each drug will be documented in the CRF.

Urine sample will be collected to perform cotinine test. Date and time of sample collection and test's outcome (positive or negative) will be documented in the CRF.

Alcohol screen with breath analysis will be performed. Date and time of sample collection and test's outcome (positive or negative) will be documented in the CRF.

8.1.10 Inclusion/Exclusion Criteria

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

8.1.11 Subject Eligibility

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

To prepare for study participation, subjects will be instructed in the Informed Consent Form and information for volunteers, Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.2 Study Period

8.2.1 Day -1

During check-in, the subject receives an unremovable bracelet with Study number, Subject Number and Period Number. Subjects must wear the bracelet until the last blood collection in the second Study Period.

Randomization of subjects to either of test or control arms will be performed

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Body temperature will be checked, and readings will be documented in the CRF.

Nasopharyngeal swab sample will be collected for COVID19 antigen test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.

Urine Pregnancy test will be done with female subjects. Date and time of test and test's outcome (positive or negative) will be documented in the CRF.

Urine sample will be collected for illicit drug screen. Date and time of sample collection and test's outcome (positive or negative) for each drug will be documented in the CRF.

Urine sample will be collected to perform cotinine test. Date and time of sample collection and test's outcome (positive or negative) will be documented in the CRF.

Alcohol screen with breath analysis will be performed. Date and time of sample collection and test's outcome (positive or negative) will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

The admission procedure must be completed before dinner is served. The dinner should be consumed within 30 minutes after being served in order to keep the fasting period for at least 10 hours prior to dosing.

Thirty-seven (37) subjects and two (2) over-night standby subjects will be confined. The standby subjects follow all Day -1 and Day 1 study procedures until the first study product administration. Catheter insertion and pre-dose blood sample are not applicable for standby subjects if not necessary.

8.2.2 Day 1

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Physical examination will be performed, and findings will be documented in the CRF.

Vital signs will be assessed, and readings will be documented in the CRF.

Body temperature will be checked, and finding is to be documented in the CRF

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF.

Standby subjects can replace a subject who are not randomized on Day 1, otherwise he/she is discharged.

Study product (test and control) will be administered as per the study groups to which subjects are randomized for period 1. A record of the administration of study treatments (intervention start and stop dates, including dates for intervention delays and/or dose reductions) will be kept using the Dosing Accountability Log and the CRF, any comments on the performance of this procedure should be recorded on the CRF.

Blood sample collection for PK parameters will be done as per the schedule outlined in the Table 4-2. Actual times of PK-blood sampling will be recorded in CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

8.2.3 Day 2

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Vital signs will be assessed, and readings will be documented in the CRF.

Body temperature will be checked, and finding is to be documented in the CRF.

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF.

Blood sample collection for PK parameters will be done as per the schedule outlined in the Table 4-2. Actual times of PK-blood sampling will be recorded in CRF.

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

8.2.4 Washout

There will be a 72-hour washout scheduled between each dose administered.

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Vital signs will be assessed, and readings will be documented in the CRF.

Body temperature will be checked, and finding is to be documented in the CRF.

Urine Pregnancy test will be done. Date and time of test along with test's outcome (positive or negative) will be documented in the CRF.

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF.

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

The dinner should be consumed within 30 minutes after being served in order to keep the fasting period for at least 10 hours prior to dosing.

8.2.5 Day 4

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Physical examination will be performed, and findings will be documented in the CRF.

Vital signs will be assessed, and readings will be documented in the CRF.

Body temperature will be checked, and reading will be documented in the CRF.

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF.

Study product (test and control) will be administered as per the study groups to which subjects are randomized in period 2 of study *i.e.* post crossover. A record of the administration of study treatments (intervention start and stop dates, including dates for intervention delays and/or dose reductions) will be kept using the Dosing Accountability Log and the CRF, any comments on the performance of this procedure should be recorded on the CRF.

Blood sample collection for PK parameters will be done as per the schedule outlined in the Table 4-2. Actual times of PK-blood sampling will be recorded in CRF.

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

8.2.6 Day 5

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF. Blood sample collection for PK parameters will be done as per the schedule outlined in the Table 4-2. Actual times of PK-blood sampling will be recorded in CRF.

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

8.3 End of Study /Day 5

The exit examination procedure will be done before check-out from the clinic in case of subjects withdrawn from the study, within 72 hours after withdrawal, if possible.

Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Physical examination will be performed, and findings will be documented in the CRF.

Vital signs will be assessed, and readings will be documented in the CRF.

Body temperature will be checked, and reading will be documented in the CRF.

Nasopharyngeal swab sample will be collected for COVID19 antigen test. Date and time of sample collection and test results (positive or negative) will be documented in the CRF.

Continued eligibility criteria will be checked. If a subject is not found eligible for further continuation in the study, reason should be documented in the CRF.

Blood sample will be collected for Biochemistry, Hematology and coagulation. Date and time of sample collection will be documented in the CRF.

Urine sample will be collected for analysis. Date and time of sample collection will be documented in the CRF.

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

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

8.4 Follow-up Visit

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

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment.

In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Section 8: Study Procedures of this protocol

9.2 Efficacy Assessments

Not applicable.

9.3 Safety and Other Assessment

Over the course of the study, subjects will be monitored by PPD clinical staff. Other Health-related events/Adverse events will be collected by PPD . Any result outside normal ranges will be evaluated by Investigator. The assessments may be repeated for safety reasons if abnormal results are observed at the initial reading.

At screening phase, Safety Monitoring includes collection and assessment of medical and medication histories, physical examination including body height and weight, 12-lead ECG, vital signs, body temperature, haematology, clinical chemistry, serum FSH if applicable, coagulation, urinalysis and pregnancy test.

During confinement phase, Safety Monitoring includes collection and assessment of vital signs. At Clinical Unit, the subjects will be wearing wireless pager for activation of the emergency alarm system. One physician and one nurse will be present at Clinical Unit during whole confinement phase as a minimum.

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Section 8: Study Procedures.

9.3.1 Laboratory Tests

The following laboratory tests/analytical measures will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Section 8: Study Procedures.

Table 9-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Neutrophils (Absolute count) Eosinophils (Absolute count) Monocytes (Absolute count) Basophils (Absolute count) Lymphocytes (Absolute count) PT/INR	Urea Creatinine Glucose (fasting) Calcium Magnesium Sodium Potassium Chloride AST ALT Direct Bilirubin Indirect Bilirubin Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase GGT Cholesterol Serum FSH[a]	pH Glucose Protein Blood Ketones Nitrites Urobilinogen Urine Bilirubin Specific gravity Hemoglobin Microscopy (RBC, WBC, squamous epithelial cells, transitional epithelial cells and casts)	Urine drug screen[b] Urine cotinine screen Serum pregnancy test[c]

Definitions: RBC= Red blood cell; MCV= Mean corpuscular volume; MCH= Mean corpuscular hemoglobin; MCHC= Mean corpuscular hemoglobin concentration; ; WBC= White blood cells; ; HIV= Human immunodeficiency virus; AST= transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/ international normalized ratio; GGT= Gamma-glutamyl transpeptidase.

a FSH done at Screening Period only in females who have been amenorrhoeic for 1 year.

b Minimum requirement for drug testing includes cocaine, THC, morphine, benzodiazepines, amphetamines, barbiturates, tricyclic antidepressants, methamphetamine, methadone and ecstasy; to be done at screening and Day - 1

c Female subjects of childbearing potential will be tested for serum human chorionic gonadotropin (hCG) as applicable-see section 9.3.2

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

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

Any remaining serum/plasma from samples collected for clinical safety labs at baseline and at all times post-dosing must be retained and stored for the duration of the study.

All Human Biological Samples (HBS) will be refrigerated (or kept cold in a cooler with a frozen ice pack) until transported to the laboratory for analysis. The cooler will be securely sealed with tape and sent to the Laboratory, preferably on the same day as collection.

All HBS to be stored till it is properly disposed of at the end of its retention period (*i.e.* till study report is issued), or useful life (*i.e.* till expiry of stability), or upon receipt of a request to destroy the HBS due to withdrawal of consent. No sample will be retained beyond 1 year from last participant last visit.

9.3.2 Pregnancy Testing

For female subjects of childbearing potential, a blood pregnancy test, will be performed during screening. Urine pregnancy test will be performed on Day -1 and Day 3. Female with a positive urine pregnancy test should not be dosed until a serum ß-hCG is negative.

A sample of urine will be collected into a universal container and a pregnancy test will be performed using urinary pregnancy kit.

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

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

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

9.3.3 Physical Examination

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, vascular and neurological systems.

Participants with findings outside the normal range, observed during screening, should be excluded from the study based on investigator's discretion. Any untoward findings identified on physical exams conducted after the administration of the first dose of investigational product will be captured as an AE, if those findings meet the definition of an AE.

9.3.4 Height, Weight and BMI

Height will be measured using a portable stadio-meter, with the subject standing bare-foot, to the nearest 0.1 cm. An average of 3 measurements will be recorded.

Weight will be measured in standard clothing on standardized weighing scale to the nearest 0.1 kg. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

BMI will be calculated according to PPD SOP

9.3.5 Blood Pressure and Pulse Rate

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

Supine blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after a minimum 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. In case of coincidence of one or more clinical procedures, and unless deemed by the Investigator necessary otherwise, the order of procedures is: Blood Sampling > Vital Signs Reading > AE Checks > water intake and/or food intake.

Systolic and diastolic blood pressures (BP, mmHg) and heart rate (HR, bpm) will be monitored during screening procedure, check in, prior to dosing (-1.00) and 2.00, 4.00 and 12.00 and 24.00 hours after dosing, every day during the subjects' stay in clinical unit and at exit examination. Additional measurements will be performed for medical reasons if necessary.

Pre-dose vital signs (-1.00 hour) will be measured with allowance up to +50 minutes from the scheduled time but must be measured before intravenous catheter insertion. After the drug administration, the vital signs will be measured after blood samples drawing with allowance up to +15 minutes from the scheduled time.

The Investigator should be notified immediately, if BP (systolic/diastolic) is outside the range of 90-140/60-90 mmHg or HR out of range 50-100 bpm during check-in on day -1, prior to dosing (-1.00 hour) and 2.00, 4.00, 12.00 and 24.00 hours after dosing in each period. The Investigator should assess clinical significance of each deviation from above described range of BP or HR.

9.3.6 Respiratory Rate

Respiratory rate will be measured as a part of vital signs, along with blood pressure and heart rate assessment. It will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

9.3.7 Body Temperature

Body temperature will be measured during screening procedures, check in, in the morning and in the evening during the subjects' stay at the clinical unit, and at exit examination and additionally based on Investigator's judgement.

Abnormal values ranges are < 35.4 and/or ≥ 37.3°C.

9.3.8 COVID-19 Test

Nasopharyngeal swab will be collected to test for COVID-19 using RT PCR or antigen test, at times specified in the Section 8: Study procedures. Two consecutive negative tests for active COVID-19 separated by > 24 hours are required for inclusion in the study. The second test will be done on the day of check-in (Day -1).

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

- At screening visit - RT PCR test is to be done.
- At check-in and early discontinuation or end of study - Antigen test is to be done.
- At any time during residential period in study, when subject report symptoms suggestive of COVID-19, subject will be isolated in the unit and antigen test will be done.
    - If antigen test result is negative, RT PCR test will be conducted, and subject will be isolated in the unit. If the RT PCR test result is negative, decision on further study participation will be as per investigator's discretion based on subject's medical condition. If RT PCR test result is positive, subject will be withdrawn from the study as per protocol Section 7.1: Subject Discontinuation/Withdrawal and discharged for further management of the disease.
    - If antigen test result is positive, RT PCR test will be conducted and without waiting for test results, subject will be withdrawn from the study as per protocol Section 7.1: Subject Discontinuation/Withdrawal and discharged for further management of the disease.

COVID-19 history should be completed for each potential participant maximally 4 days before the participant enters the centre.

The staff and the study participants will adhere to SUKL´s latest recommendation and to PPD measures to ensure the safety of the study participants during the COVID-19 pandemic (e.g. wearing masks, ensuring social distancing and increasing the disinfection schedule, as well as checking the body temperature).

9.3.9 Electrocardiogram

A standard 12 lead ECG will be performed for screening purposes only. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. A single ECG tracing will be labeled with the study number, subject initials, subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities will be recorded on the relevant medical history/Current medical conditions eCRF page.

The Fridericia QTC correction formula will be used.

Subjects should be in a quiet environment and not speak during the resting period or measurement. Generally, ECGs should not be collected within 3 hours after food or beverage consumption.

9.3.10 Virology

Virus serology will be performed at times specified in the Section 8: Study Procedures for HBs Ag, anti-HBc (IgG + IgM), anti-HCV Ab, HIV 1 and HIV 2 antibodies. Serology will be performed by using the same sample drawn for chemistry; therefore, no additional blood needs to be drawn for serology. In case of a positive finding in virus serology screen, the subject must be excluded from trial participation.

9.3.11 Urine illicit drug screen

Urine will be collected at times specified in the Section 8: Study Procedures. In case of a positive finding for any substance class, the subject must be discontinued from the trial (or excluded from trial participation in case of positive findings at the screening visit).

9.3.12 Urine cotinine level

Urine cotinine level will be measured at times specified in the Section 8: Study Procedures. In case of positive urine cotinine test, the subject must be excluded from trial participation.

9.3.13 Alcohol test

An alcohol breath tests will be conducted at times specified in the Section 8: Study Procedures. In case of a positive finding in the alcohol breath test, the subject must be discontinued from the trial.

9.4 Standard Meals

During confinement in Study Periods all subjects will be provided with standard meals at scheduled times (see Table 1-2). The composition of the standard meals follows the restrictions mentioned in Section 5.5: Lifestyle Considerations and will be identical for all study periods. An example of the standardized meal composition is shown in **Table 9-1 Example Standard Meal Composition.**

Table 9-2 Example Standard Meal Composition

Day -1	
Dinner	Wholegrain roll 2pcs, Butter 10g, Ham salami 100g, Banana, water 200ml
Day 1 and Day 4	
Lunch	Chicken broth with meat and noodles (330ml), Potato dumplings stuffed with smoked meat, with cabbage, Water 200ml
Snack	Croissant, banana, water 200ml
Dinner	Wholemeal roll 3pcs, Lučina 120g, Apple, Water 200ml
Day 2	
Breakfast	Roll 2pcs, Butter 10g, Jam 20g, Water 200ml
Lunch	Pea soup scrubs (330ml + 10g), Gypsy pork ribs with rice (100g meat, 200g sauce, 200g rice), Water 200ml
Snack	Croissant, banana, water 200ml
Dinner	Bread 2pl., Butter 10g, Ham 100g, Tomato 100g, Water 200ml
Day 3	
Breakfast	Roll 2pcs, Butter 10g, Jam 20g, Water 200ml
Lunch	Beef soup with meat and rice (330ml), Beef goulash with dumplings (100g meat + 200ml sauce + 160g dumplings), Water 200ml
Snack	Corny BIG cranberry, Apple1pc, Water 200ml
Dinner	Goulash soup (330ml), Roll 2pcs, Water 200ml

9.5 Pharmacokinetics (PK)

9.5.1 Plasma for Analysis of Paracetamol

In morning of dosing days of both study periods a dead-volume intravenous catheter will be inserted into a forearm vein (starting at 06:00 o'clock) by skilled nurses under Investigator's supervision. Catheter insertion is not applicable for stand-by subjects if not necessary. Blood samples will be obtained by the catheter for the first 16 hours post-dose. The blood samples may be collected by direct venipuncture in case that subject refuses the insertion of the catheter or if the catheter is blocked and/or needs replacement.

During all study periods, blood samples (2mL in each sampling) for pharmacokinetic analysis will be collected into appropriately labeled tubes at times specified in the Section 8: Study Procedures.

Total number of blood collections in each study period will be 21. Blood samples will be taken at Pre-dose (1 hour before dosing) , and 5, 10, 20, 30, 40, 50, 60, 80, 90, 120, 150, 180 minutes, 4, 5, 6, 8, 10, 12, 14, 16 hours post-doses.

Actual times of PK-blood sampling will be recorded immediately after each blood sampling. The actual sample times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. Sampling time deviations ≥ ±2 minutes will be repotted during the first 6 hours after drug administration. Sampling time deviations ≥ ± 15 minutes will be reported for all remaining sampling intervals. During each sampling, venous blood samples (2 ml) will be withdrawn by a suitable trained member of the study staff, either from an indwelling cannula or venipuncture

situated in a forearm vein. In order to avoid clotting, the catheter will be rinsed with approximately 2 mL of a heparinized saline solution (500 IU heparin in 100 mL 0.9 % w/v NaCl solution) after each blood sample collection. Prior to each blood sample collection from the catheter, the content of the catheter, i.e. heparin lock solution and approximately 2 mL of blood will be aspirated and discarded. Further details regarding the collection, processing, storage and shipping of the blood samples should be described in the Sample Handling Manual.

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

Bioanalytic of paracetamol in plasma samples will be performed by a specific and highly sensitive LC-MS/MS methodology in a laboratory with GLP certification. The analyses of plasma samples will follow the principles of GLP [OECD Principles of GLP] and GCP [ICH Topic E6] whenever applicable Method validation will have to be conducted in full compliance with the respective guidance document: (EMA Guideline on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). The targeted LLOQ of the method is 0.25 µg/mL. Reference and internal standards will be supplied by PPD. The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

9.5.2 Sample Handling

Bioanalytical Laboratory of PPD will issue Sample Handling Manual with instructions for processing of samples.

Over the course of storage, the temperature will be constantly monitored and recorded in accordance with PPD SOP. Tube labels contain the information on Subject Number, Period Number (A = period 1, B = period 2). Sample Number and PPD Study Number.

Example: 11A16/811 means 16th sample of the first Period of subject No. 11, PPD

9.6 Blood Volume

The total blood sampling volume for each subject in this study is H 187 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at the discretion of the investigator or GSKCH.

Table 9-2 Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times				Total Volume (mL)
		Screening	Study Period 1	Study Period 2	End of Study visit	
Safety Labs	11.5	1	0	0	1	23
PK	2	0	21	21	0	84

Sample Type	Sample Volume (mL)	Number of Sampling Times				Total Volume (mL)
		Screening	Study Period 1	Study Period 2	End of Study visit	
Catheter purge	2	0	20	20	0	80
TOTAL						187

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

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

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product

Events Meeting the AE Definition:

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

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

The Adverse event reporting period begins when the subject first signs informed consent and continues until 7 days following last administration of the study product (or last procedure. All AEs should be recorded in the CRF in a timely manner. Serious AEs MUST be recorded and reported to the Sponsor or designee in the eSAE CRF page immediately (within a maximum of 24 hours). The investigator will submit any updated SAE data to GSK within 24 hours of it being informed.

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

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

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

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

10.4 Reporting Procedures

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

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

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

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

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

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

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSKCH in lieu of completion of the AE CRF page/eSAE form.

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

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

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

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be reported using concise medical terminology on the CRF as well as on the electronic form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an eSAE form should be completed, as fully as possible.

It is essential to enter the following information:

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

The following are desirable and are of particular relevance for investigator and GSKCH assessment of the eSAE report:

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

The eSAE form, completed as fully as possible, must be sent to CRO **immediately and under no circumstance should this exceed 24 hours** of awareness.

SAE Contact Information:

PPD , PPD

CRO will then email the eSAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance at GSKCH PPD), with copy to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager will be responsible for forwarding the eSAE form to other GSKCH personnel as appropriate.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

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

10.5.2 Assessment of Causality-

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the eSAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, of the products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the eSAE data to GSKCH.** The investigator may change his/her opinion of causality in light of follow-up information and send an eSAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSKCH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the eSAE form (subject to the classification of the AE).

The investigator will submit any updated eSAE data to GSKCH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly (within 24 hours) notify CRO PPD CRO will then email to GSKCH by emailing the information to the GSKCH Clinical Operations Safety Reporting email box PPD). The GSKCH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD

The investigator will submit any updated eSAE data to GSKCH within the designated reporting time frames.

At any time during residential period in study, when subject report symptoms suggestive of COVID-19, subject will be isolated in the unit and antigen test will be done.

- If antigen test result is negative, RT PCR test will be conducted, and subject will be isolated in the unit. If the RT PCR test result is negative, decision on further study participation will be as per investigator's discretion basis subject's medical condition. If RT PCR test result is positive, subject will be withdrawn from the study as per

protocol Section 7.1: Subject Discontinuation/Withdrawal and discharged for further management of the disease.

- If antigen test result is positive, RT PCR test will be conducted and without waiting for test results, subject will be withdrawn from the study as per protocol Section 7.1: Subject Discontinuation/Withdrawal and discharged for further management of the disease.

10.7 Withdrawal Due to an Adverse Event

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

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

10.8 Regulatory Reporting Requirements for SAEs

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

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

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

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

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

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 7 days after the last administration of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to CRO PPD) within 24 hours of learning of the subject becoming pregnant. CRO will then email to the GSKCH Clinical Operations Safety Reporting email box PPD) within 24 hours of learning of the subject becoming pregnant. The GSKCH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD). Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSKCH Clinical Operations Safety Reporting email box and the GSKCH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD). Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

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

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

The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The investigator will record pregnancy information on the appropriate form and submit it to CRO within 24 hours of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to CRO. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

CRO will scan and email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSKCH PPD with copy to the appropriate GSKCH Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

11 DATA MANAGEMENT

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

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

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

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

The clinical data will be collected on paper source documents or in other suitable way (Subjects Cards, see Section 11.5 and/or Source Data Forms, see Section 11.6) in line with the respective SOPs by PPD and subsequently transcribed, where necessary, onto the CRFs by the clinical research staff of the Clinical Site. The source data/documents will be

retained by the Clinical Site in line with requirements listed in Section 8 of the ICH consolidated guideline on (GCP) R2 [ICH GCP E6 R2].

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, CCI [redacted]

11.2.1 Data Queries

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

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

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

11.3 Processing Patient Reported Outcomes

Not applicable.

11.4 External Data

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

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

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

11.5 Subject Cards

Subject Cards are personal medical records. An individual Subject Card for each subject is kept at Clinical Unit of PPD . Subject Card could contain study specific information on screening examinations. Also, they contain other individual records on procedures/investigations required by Investigator on ad hoc basis for medical reasons, unless recorded in Subject Data Forms. The records are sorted out study-by-study within the Subject Card. Subject Cards are kept at Clinical Unit of PPD .

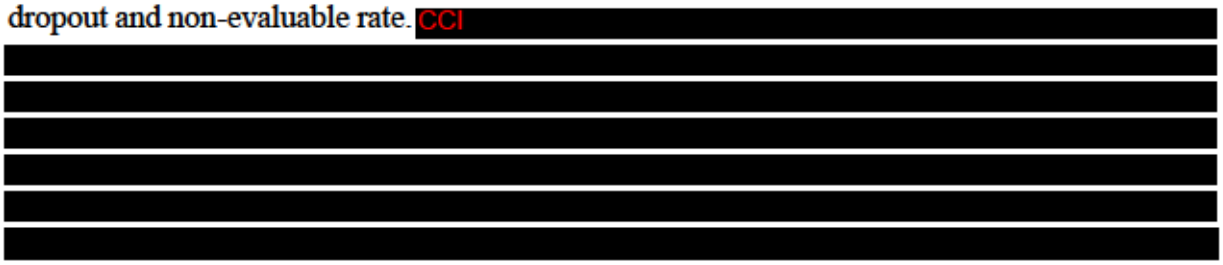
11.6 Subject Data Forms

Subject Data Forms (SDFs) are completed during the study and they are source documents. These documents are common for all study subjects. Completed SDFs are kept at PPD . and copies of these documents (with blinded subjects' personal data) will be provided to the Sponsor in the Clinical Report.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Approximately 110 subjects will be screened to randomize approximately 37 healthy adult subjects to ensure at least 31 evaluable subjects complete the entire study, assuming a 15% dropout and non-evaluable rate. CCI



CCI

12.2 Populations for Analysis

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

The PK population is defined as all randomized subjects who complete the two periods and who have no major protocol deviations concerning pharmacokinetics. Subjects with baseline* paracetamol concentration > 5% of the individual Cmax for either period will be excluded from PK population.

If significant number of subjects/periods are excluded from PK population due to baseline* paracetamol concentration > 5% of the individual Cmax, a sensitivity analysis will be conducted including all subjects even those with the affected data.

*Baseline is defined as the last available value before dosing.

12.3 Statistical Analyses

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

12.3.1 Primary Analysis(es)

The primary pharmacokinetics Analysis Variables:

• $AUC_{0\text{-}tlast}$ -area under the plasma concentration-time curve from zero to the last measurable sampling time point, t, computed using the linear trapezoidal rule.

• C_{max}-maximum plasma concentration

• t_{max}-time to maximum plasma concentration

PK parameters will be derived using actual sampling times after database lock and unblinding.

Criteria for assessing bioequivalence:

The bioequivalence between a new paracetamol oral suspension (Test) and the marketed paracetamol oral suspension (Panadol B&I) (Reference) in fasted state will be assessed:

- If the 90% CIs for the ratio of the means of the primary pharmacokinetic parameters, $AUC_{0\text{-}tlast}$ and C_{max} of the paracetamol profiles lie completely within the range 0.8-1.25.
- If there is no difference between the two treatments in terms of t_{max}.

The null and alternative hypotheses to be tested in the primary analyses are:

$AUC_{0\text{-}tlast}$ and C_{max}

H_0: The (geometric) mean $AUC_{0\text{-}tlast}$ (likewise C_{max}) of a new paracetamol oral suspension (Test) is less than 80.0% or greater than 125.0% of that of Panadol B& I (Reference).

H_1: The (geometric) mean $AUC_{0-tlast}$ (likewise C_{max}) of a new paracetamol oral suspension (Test) is between 80.0% and 125.0% of that of Panadol B&I (Reference).
t_{max}

H_0: There is no difference between a new paracetamol oral suspension (Test) and Panadol B&I (Reference).

H_1: There is a difference between a new paracetamol oral suspension (Test) and Panadol B&I (Reference).

An Analysis of Variance (ANOVA) model will be fit to the log-transformed PK parameters ($AUC_{0-tlast}$ and C_{max}), as the dependent variable, and treatment, period, sequence and subject nested within sequence as fixed effects. For each pairwise comparison, only the data from the two, corresponding treatments will be included in the model. The presence of a statistically significant sequence effect will be noted, and its implications will be discussed. Least squares estimates of treatment effects will be calculated and a 90% CI for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric least square means between the test and reference and its CI. Bioequivalence will be determined if the 90% CI for the treatment geometric least square mean ratio lies completely within the range 0.80 – 1.25.

t_{max} will be analyzed nonparametrically using Wilcoxon signed-rank test. Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on the PK population.

Individual plasma concentrations of paracetamol will be summarized descriptively by treatment and each time point for the PK population and will be listed for the safety population. Mean plasma concentration vs. nominal time profiles by treatment will be graphed for the PK population. Individual plasma concentration vs. actual time profiles by treatment and individual plasma concentrations vs. actual time profiles by subject will be graphed for the safety population. All concentration-time profiles will be shown on both original and semi-logarithmic scales.

All PK parameters will be summarized for each treatment by descriptive statistics (for t_{max} and $\%AUC_{ex}$, N, arithmetic mean, standard deviation, first and third quartiles, median, minimum, and maximum; for the rest of PK parameters, N, arithmetic mean, standard deviation, geometric mean, coefficient of variation of geometric mean, median, minimum, and maximum) for the PK population.

A listing containing individual statistics for each PK parameter will be provided for the safety population.

12.3.2 Secondary Analysis(es)

The secondary pharmacokinetics Analysis Variables:

• AUC_{0-inf}-area under the plasma concentration time curve from zero and extrapolated to infinity time.

• $\%AUC_{ex}$-Percentage of AUC_{0-inf} obtained by extrapolation, calculated as $(1 - [AUC_{0-t}/AUC_{0-inf}]) \times 100)$

• λz -The terminal elimination rate constant computed as the slope of the regression line of ln (C(t)) on time. The regression should generally involve at least 3 consecutive measurable concentrations that decrease over time.

$AUC_{0\text{-}inf}$ will be analyzed using the same ANOVA model method as for $AUC_{0\text{-}tlast}$ and C_{max}.

$\%AUC_{ex}$ and λz will be summarized for each treatment using descriptive statistics same as for the primary PK parameters.

12.3.3 Safety Analysis(es)

Safety variables will be summarized for the safety population.

Adverse Event:

Treatment Emergent adverse events (TEAEs), i.e. AEs that are emergent or that worsen after the first study product (test or reference) administration, will be summarized by presenting, for each treatment, the number and percentage of subjects having any AE, any AE in each MedDRA System Organ Class (SOC) and having each individual AE. The subset of AEs suspected of a relationship to study drug will be presented similarly. All treatment-emergent AEs will also be tabulated by severity. Any other information collected (e.g. action taken, duration, outcome) will be listed. Each AE will be attributed to the treatment taken most recently before the onset of the AE. Adverse events due to COVID-19 will be listed and tabulated separately.

Vital signs:

Vital signs including temperature will be summarized by time-point and treatment. Summary statistics will include mean, standard deviation, minimum, median, and maximum. No inferential statistics will be presented. Data will be listed with abnormal values flagged.

Physical examination:

Physical Examination data will be listed with abnormal values flagged.

Laboratory tests:

Safety Laboratory data will be listed with abnormal values flagged.

Note: Laboratory data at the screening is considered source and will not be listed unless otherwise noted.

Criteria for assessing safety:

Vital signs, clinical safety laboratory tests and monitoring of adverse events will be used to assess the safety and tolerability of the study products.

12.3.4 Exclusion of Data from Analysis

Subjects who deviate from the protocol will be identified and excluded from analyses as agreed by the biostatistician and clinical scientist or designee. *Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

* Exclusion of subjects with baseline > 5% of the C_{max} will be determined after database lock and unblinding.

12.3.5 Demographic and Baseline Characteristics

The Safety population will be used for demographic and baseline characteristics. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic, and baseline characteristics. Medical history will be listed.

12.3.6 Study Drug/Product Compliance and Use of Other Therapies

12.3.6.1 Study Drug/Product Compliance

The number of subjects exposed to each treatment will be tabulated for the safety population. Treatment deviations for individual subjects will be listed and summarized. Cases of partial exposure, including subjects vomiting of the treatment within 103 minutes post dosing, and subjects with baseline > 5% of the C_{max} will also be summarized. Other medications and other concomitant non-drug therapies will be listed for the safety population.

12.3.6.2 Prior and Concomitant Medications

Prior medications, concomitant medications, and other concomitant non-drug therapies will be listed for the safety population.

12.3.6.3 Other Therapy/Rescue Medication (if applicable)

Not applicable

12.3.7 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data. Missing plasma concentrations values or those below the lower limit of quantification (BLOQ) will be indicated in the data listings.

12.3.8 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

13.2 Quality Assurance

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

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

The investigator(s) will notify GSKCH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSKCH or its agents to prepare the study site for the inspection and will allow GSKCH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSKCH or its agent. Before response submission to the regulatory authority, the investigator will provide GSKCH or its agents with an opportunity to review and comment on responses to any such findings.

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016),

guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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

13.3.3 Subject Information and Consent

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

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

Note that the use of initials should be avoided.

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

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, GSKCH should be informed immediately.

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSKCH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes,

names and addresses. Documents not for submission to GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

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

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

13.7 Conditions for Terminating the Study

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

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

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

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

14 Facilities

The study will be performed by PPD PPD . QUINTA-ANALYTICA s.r.o. acts in this study as Clinical Site, Bioanalytical Laboratory and CRO. PPD , M.D., PhD., is the Principal Investigator.

Clinical laboratory tests (haematology, coagulation, viral serology, clinical chemistry, urinalysis, pregnancy test) will be carried out by the Clinical Safety laboratory AeskuLab k. s., PPD

The PCR testing for COVID-19, will be carried out by synlab czech s.r.o., PPD

15 Competent Authority and Ethics Committee

Final Study Protocol, Informed Consent Form and Information for Subjects and other relevant documents will be reviewed by Competent Authority – State Institute for Drug Control (SÚKL), PPD and also by Ethics Committee (EC) of IKEM and TN, PPD before study initiation. The Study will not begin until SÚKL and EC favorable written approvals for the above-mentioned study documents and/or their substantial amendments in line with ICH GCP (R2) [6] have been obtained.

If any changes introduced to the protocol or new information relating to the scientific documents in support of the trial are substantial, i.e.:

- the safety or physical or mental integrity of the subjects
- the scientific value of the trial
- the conduct or management of the trial
- the quality or safety of any study products used in the trial

Those changes are the subject of an Amendment to the Clinical Study and SÚKL and EC must review the Amendment and approve it before study initiation or continuation.

If the changes in Study Protocol involve only logistical or administrative aspects of the study (e.g. change of monitor(s), telephone number(s)), written approvals are necessary from Sponsor, but not from the EC and the SÚKL before their implementation.

Documentation of SÚKL and EC approvals must be received by the Sponsor as soon as available before the study commencement. The medication can be released by the Sponsor once scanned copies of both EC and SÚKL approvals are received by the Sponsor.

16 Insurance

The Sponsor will contract a clinical study insurance policy in compliance with all applicable laws, rules, and regulations. Subjects will be insured against possible harmful consequences of the clinical study. Sponsor will indemnify any subject included in the clinical study for any damage to the health if the damage is either associated with the study drug itself or with the clinical study.

PPD shall indemnify any subject for any claim of concerning any damage to the health of the subject other than damage related to the study drug itself or to the clinical study for example malpractice.

17 REFERENCES

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CCI [redacted]

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18 APPENDICIES

18.1 ABBREVIATIONS

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

Table 18-1 Abbreviations

Abbreviation	Term
λ_z	The terminal elimination rate constant
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase

Abbreviation	Term
AUC	area under the curve
AUC_{24}	area under the concentration−time curve from time 0 to 24 hours
AUC_{0-10}	area under the plasma concentration time curve from zero to 10 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
AUC0-t_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BA	bioavailability
BDR	blinded data review
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CDS	core data sheet
CI	confidence interval
CL_r	renal clearance
C_{max}	peak or maximum observed concentration
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FRP	Females of Reproduction Potential
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBS	Human Biological Samples
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonization
ID	identification
EC	Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IUS	Intrauterine system

Abbreviation	Term
K_2EDTA	dipotassium ethylene diamine tetra acetic acid
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
N/A	not applicable
PD	pharmacodynamics
PG	pharmacogenomics
PI	principal investigator
PI	Personal information
PK	pharmacokinetics
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
SAE	serious adverse event
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	summary of product characteristics
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
$T_{1/2}$	terminal half-life
THC	tetrahydrocannabinol
t_{max}	time to reach maximum concentration
US	United States
USPI	United States package insert
WBC	white blood cell

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