Protocol

Study ID: 221030

Official Title of Study: An Open Label, Balanced, Randomized, Two-Treatment, Four-Period, Two-Sequence, Single Oral Dose, Full Replicate Crossover, Bioequivalence Study of Albendazole Tablets IP 400 mg of Biddle Sawyer Limited (GSK group company) with Albendazole Tablets 400 mg of Glaxo SmithKline Consumer Healthcare, South Africa (PTY) Ltd in Healthy, Adult participants under Fed Condition.

NCT ID: NCT06201559

Date of Document: 04-July-2023

Clinical Study Protocol

Primary Study Intervention(s)	Albendazole Tablets IP 400 mg (**Test**) (Composition: Each uncoated tablet contains: Albendazole IP 400 mg) Name of Manufacturer: Biddle Sawyer Limited C/o GlaxoSmithKline Pharmaceuticals Limited, A-10, M.I.D.C Ambad-Pathardi Block, Nashik, Nashik - 422010.
Other Study Intervention(s)	Albendazole Tablets 400 mg (**Reference**) Manufacturer's Name: Glaxo SmithKline Consumer Healthcare, South Africa (PTY) Ltd, Epping Industrial 1, 39 Hawkins Avenue, CAPE TOWN South Africa.
Study Identifier	221030
Lambda Project No.	0110-23
Approval Date	03 Jul 2023
Title	An Open Label, Balanced, Randomized, Two-Treatment, Four-Period, Two-Sequence, Single Oral Dose, Full Replicate Crossover, Bioequivalence Study of Albendazole Tablets IP 400 mg of Biddle Sawyer Limited (GSK group company) with Albendazole Tablets 400 mg of Glaxo SmithKline Consumer Healthcare, South Africa (PTY) Ltd in Healthy, Adult Participants under Fed Condition.
Compound Number/Name	SKF-62979/ Albendazole
Brief Title	Bioequivalence study between two Albendazole 400 mg tablets in healthy adult participants under fed conditions.
Sponsor	GSK Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Oscar Della Pasqua Exec Dir Clinical Pharmacology Clinical Pharmacology Modelling and Simulation (CPMS)

Medical monitor name and contact can be found in local study contact information document

Protocol 1.0 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical and/or digital informed consent of the participant and/or the participant's legally authorized representative (LAR).
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study identifier	221030
Lambda Project No.	0110-23
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Title	An Open Label, Balanced, Randomized, Two-Treatment, Four-Period, Two-Sequence, Single Oral Dose, Full Replicate Crossover, Bioequivalence Study of Albendazole Tablets IP 400 mg of Biddle Sawyer Limited (GSK group company) with Albendazole Tablets 400 mg of Glaxo SmithKline Consumer Healthcare, South Africa (PTY) Ltd in Healthy, Adult Participants under Fed Condition.
Investigator name	Dr. Dwarkesh Oswal, MD Lambda Therapeutic Research Ltd., Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad - 382 481, Gujarat, India. Email: PPD
Signature	_____
Date of signature (DD Month YYYY)	_____

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ADE	Adverse device effect
ABE	Average bioequivalence
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve up to the last measured time point
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated to infinite time
AUC_%Extrap_obs	Percentage of AUC that is extrapolated
AxMP	Auxiliary medicinal product
BE	Bioequivalence
BMI	Body mass index
CDSCO	Central Drugs Standard Control Organization
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximal (peak) plasma concentration
COA	Certificates of analysis
COVID-19	Coronavirus Disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CPSB	Consumer Product Safety Board
CRF/eCRF	Case report form/electronic case report form

Abbreviation	Definition
CSI	Core safety information
CSR	Clinical study report
CV	Cardiovascular
CV_W	Coefficient of variation
CV%	Intra-subject variability
ECG	Electrocardiogram
ED	Early discontinuation
EoS	End-of-study
FDA	Food and Drug Administration, United States of America
FSH	Follicle stimulating hormone
FSFV	First subject first visit
GAELF	Global Alliance to Eliminate Lymphatic Filariasis
GCP	Good clinical practices
GDS	Global Data Sheet
GLM	General linear model
GMO	Genetically modified organism
GMP	Good manufacturing practice
GMR	Geometric mean ratio
HCV	Hepatitis C virus
HbsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council on Harmonisation

Abbreviation	Definition
ICMJE	International Committee of Medical Journal Editors
ICMR	Indian Council of Medical Research
IDFU	Investigational directions for use
IEC	Independent ethics committee
IM	Intramuscular
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
IND	Investigational New Drug
IRB	Institutional review board
λ_z	Slope of the (terminal) log-lin phase of the plasma concentration-time curve
LAR	Legally acceptable representative
LSLV	Last Subject Last Visit
MDA	Mass drug administration
MSR	Medical Screening Record
NIMP	Non-investigational medicinal product
NQ	Non-quantifiable
OTC	Over the counter
POAP	Pregnancy Outcome Advisory Panel
POM	Prescription only medicine
PK	Pharmacokinetic
PP	Per protocol
QTL	Quality tolerance limit
SADE	Serious adverse device effect

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SCABE	Scaled average bioequivalence
SoA	Schedule of activities
SOP	Standard operating procedure
SRT	Safety Review Team
σ_{WR}	Within-subject standard deviation
TEAE	Treatment-emergent adverse event
T_{max}	Time of peak concentration
TOC	Table of contents
TOST	Two one-sided t-test
$T_{1/2}$	Half-life
USA	United States of America
USADE	Unanticipated serious adverse device effect
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Term	Definition
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Combination product	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.
Decentralized Trial Platform	A digital engagement technology allowing for the remote delivery and access to trials for sponsors.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.

Term	Definition
	The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
NIMP/AxMP	A NIMP or AxMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Term	Definition
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: "Study intervention" and "study treatment" are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Open Label, Balanced, Randomized, Two-Treatment, Four-Period, Two-Sequence, Single Oral Dose, Full Replicate Crossover, Bioequivalence Study of Albendazole Tablets IP 400 mg of Biddle Sawyer Limited (GSK group company) with Albendazole Tablets 400 mg of Glaxo SmithKline Consumer Healthcare, South Africa (PTY) Ltd in Healthy, Adult participants under Fed Condition.

Brief Title: Bioequivalence study between two albendazole 400 mg tablets in healthy, adult participants under fed conditions.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

Overall Design: Refer to Section 4.1.

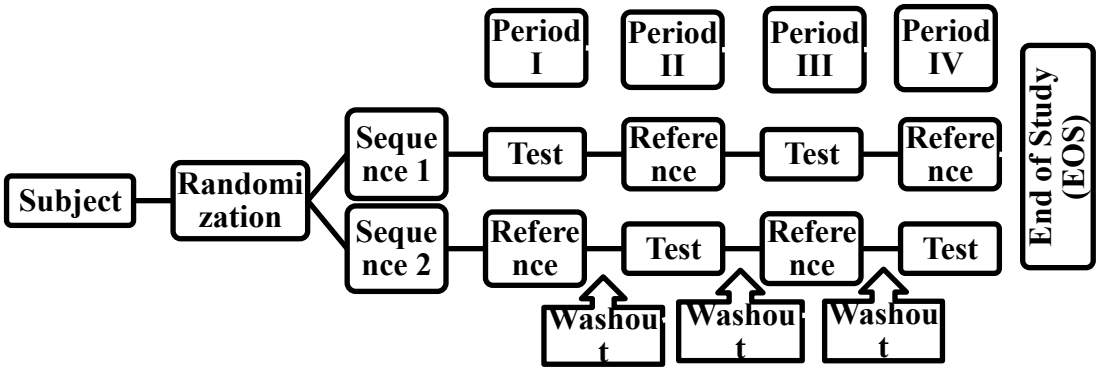
Number of Participants: Refer to Section 9.6.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Based on US FDA guidance , this study will employ 2 sequences in a 4-period cross-over design, i.e. T-R-T-R and R-T-R-T (T=test study intervention, R=reference study intervention).

Figure 1 Study design overview



1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities – Overview Across Periods

Procedure	Screening (up to 28 days before Dosing in period I)	Period I			Period II, III and IV			ED = early discontinuation / withdrawal	Reference section
Day		**-1**	**1**	**2**	**-1**	**1**	**2**		
Informed consent	● (Consent for screening)	● (Study specific consent)							[See Section 10.1.3 for details]
Inclusion and exclusion criteria		●							[See Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria]
Demography	●								[See Section 8.1.1 for more information]
Compliance Assessment		●			●				[See Section 5.3.1, Section 5.3.2 for more information]
Height and weight	●								[See Section 8.3.1 for more information]
Physical examination/ clinical examination	●	●		●	●		●		[See Section 8.3.1 for more information]
Medical history	●								[See Section 8.1.2 for more information]
Urine Drug Screening, breath alcohol Test	●	●			●				Substances: [Drugs, Alcohol, tobacco and caffeine]

Procedure	Screening (up to 28 days before Dosing in period I)	Period I			Period II, III and IV			ED = early discontinuation / withdrawal	Reference section
Day		**-1**	**1**	**2**	**-1**	**1**	**2**		
Serum Pregnancy Test (for females only)	●	●			●		*	●	[See to Section 8.3.5– pregnancy testing for instruction on timepoints]
Serology Tests [HIV, Hepatitis B and C screening]+	●								[See Section 8.3.4, Section 10.2 for more information]
Laboratory assessments +	●				●		*	●	[See Section 8.3.4, Section 10.2 for more information]
12-lead ECG	●								[See Section 8.3.3 for more information]
Chest X-ray[$]	●								[See Section 8.3.1 for more information]
Pre dose vital signs			●			●			[See Section 8.3.2 for more information]
Post dose Vital signs[%]			●			●			[See Section 8.3.2 for more information]
Check-in		●			●				
Administration of study intervention			●			●			[See Section 6.1 for more information]
Blood Collection for PK Analysis [#]			●	●		●	●		[See Section 8.5 for more information]

Procedure	Screening (up to 28 days before Dosing in period I)	Period I			Period II, III and IV			ED = early discontinuation / withdrawal	Reference section
Day		**-1**	**1**	**2**	**-1**	**1**	**2**		
AE review			●	●	●	●	●		[See Section 10.3.5, Section 8.4 for more information]
SAE review		●	●	●	●	●	●		[See Section 10.3.5, Section 8.4 for more information]
Concomitant medication review			●	●	●	●	●		[See Section 6.9 for more information]

HIV: human immunodeficiency virus, ECG: electrocardiogram, PK: pharmacokinetic, AE: adverse event, SAE: serious adverse event, (e)CRF: (electronic) case report form

● Is used to indicate a study procedure that requires databasing (either in eCRF, device, laboratory or other third-party vendor).

* End study safety assessment (i.e. at the time of check-out of period IV)

+ Clinical Laboratory tests will be performed as per Section 10.2: Clinical laboratory tests

(Meals will be provided to the participants as mentioned in the protocol)

$ Chest X-ray is valid up to 6 months including the day of first dosing.

The venous blood samples will be drawn at 0.00 (Pre-dose) and at 0.33 (0h20min), 0.67 (0h40min), 1.00 (1h00min), 1.33 (1h20min), 1.67 (1h40min), 2.00 (2h00min), 2.33 (2h20min), 2.67 (2h40min), 3.00 (3h00min), 3.33 (3h20min), 3.67 (3h40min), 4.00 (4h00min), 4.50 (4h30min), 5.00 (5h00min), 6.00 (6h00min), 8.00 (8h00min), 10.00 (10h00min), 12.00 (12h00min), 14.00 (14h00min), 18.00 (18h00min), 24.00 (24h00min) post dose in each period.

%Post-dose vitals will be recorded at 2, 4, 6, 12 and 24 hours post-dose in each period.

- Check-in day (Day -1)
- Dosing Day (Day 1)
- Housing Day (Day -1 to 2)
- Check-out Day (Day 2, morning)
- End Study (i.e. at the time of check-out of period IV)

Table 2 Schedule of Activities – Detailed View within Period

Procedures												
Time (h) in relation to albendazole dose	**0 (Pre-dose)**	**0.33, 0.67, 1.00, 1.33, 1.67**	**2.00**	**2.33, 2.67, 3.00, 3.33, 3.67**	**4.00**	**4.50, 5.00,**	**6.00**	**8.00, 10.00**	**12.00**	**14.00**	**18.00**	**Next day 24.00 (Discharge)**
AE/SAE assessment	←										→	
Vital signs			X		X		X		X			X
Blood collection for PK Analysis	X	X	X	X	X	X	X	X	X	X	X	X
Discharge												X

PK: pharmacokinetic, AE: adverse event, SAE: serious adverse event

2. INTRODUCTION

2.1. Study rationale

This study is being conducted to address the World Health Organization (WHO) Medicines prequalification requirements for the registration of an albendazole formulation, to be provided to the WHO global health program, manufactured at a new facility. Its primary aim is to assess the bioequivalence between the Sponsor's test study intervention and the reference study intervention after single oral dose administration in healthy adult participants under fed conditions. In addition, it compares the pharmacokinetic profile and safety between test and reference intervention. The current product being provided to WHO as part of the global health program was chosen as the comparator (reference) product. This product is comparable to the product marketed in regulated countries (Zentel, Eskazole) with respect to formulation, manufacturing process, site of manufacture, and methods with the exception of the addition of a colouring agent in the product formulation.

2.2. Background

Albendazole is a benzimidazole carbamate with antiprotozoal and anthelmintic effects against intestinal and tissue parasites. Albendazole exhibits larvicidal, ovicidal and vermicidal activity, and it is thought to exert its anthelmintic effect by inhibiting tubulin polymerization. This causes the disruption of the helminth metabolism, including energy depletion, which immobilizes and then kills the susceptible helminth.

Pharmacokinetics:

In humans, albendazole is poorly absorbed (less than 5%) following oral administration, but its absorption is greatly enhanced (approximately 5-fold) when taken with fat-rich food. After absorption, albendazole rapidly undergoes extensive first-pass metabolism in the liver resulting in several metabolites of which albendazole sulfoxide is its main metabolite.

Peak concentrations are achieved for albendazole approximately 2 hours after dose, and for albendazole sulfoxide approximately 4 hours after dose. The $T_{1/2}$ of albendazole is approximately 1.5 hours and for albendazole sulfoxide 8.5 hours.

For gastro-intestinal infections, the parent compound albendazole is considered the active moiety, whereas for systemic infections this is albendazole sulfoxide. For the purpose of determining bioequivalence, however, the WHO requires this to be shown for the albendazole parent compound.

2.3. Benefit/risk assessment

Participation in bioavailability studies yields no direct benefit to the participants. However, a charge-free study related health assessment is provided. The risks as described below are reduced considering the fact only 4 doses are to be administered at an interval of at least 7 days between dosing days of any 2 successive periods.

Table 3 Potential risks and risk mitigation strategies

The potential risks of clinical significance for albendazole tablets are derived from the prescribing information (Albendazole label). Most of these reported risks are uncommon, rare or very rare. The likelihood of these risks in a healthy population receiving a single dose is therefore expected to be low. For complete list of adverse reactions please refer the prescribing information mentioned above.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Hepatotoxicity	In 2001, GSK routine monitoring of spontaneous ADRs identified an increased number of reports of elevated liver enzymes in patients receiving low dose albendazole and reports of hepatitis and jaundice in patients receiving high dose albendazole. Higher doses of albendazole are used to treat systemic helminth infections for longer periods compared to the low dose, short treatment durations required for intestinal helminth infections in the OTC environment. A cumulative review of hepatic events was conducted to further evaluate the nature of these events and to determine whether GSK's CSI adequately reflected these adverse events. Following the review of the available data, GSK concluded that there was sufficient evidence to suspect albendazole as causing hepatic events; with low dose albendazole causing	This study will not include participants with abnormal liver function test results (transaminases). Discontinuation of study intervention in the best interest of the participant for abnormal liver tests at the investigator discretion, when liver parameter falls outside the pre-defined clinically acceptable values. If any participant has clinically significant abnormal liver function analysis during the study, in such case participant may be discontinued for specific period at the investigator discretion. The decision to continue/discontinue such participants will be based on investigator's decision.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	elevation of liver enzymes and the high dose use causing hepatitis. The CSI for POM albendazole global data sheet (GDS) was therefore updated to include these events in the Adverse Reactions section as well as appropriate warnings in the Dosing and Administration and Warnings and Precautions sections	
Exposure during pregnancy	Pre-Clinical Data in common with other benzimidazole compounds, administration of albendazole to pregnant animals can cause abnormalities of foetal development, including increased embryo resorption, soft tissue malformation and skeletal deformities. This teratogenic and embryotoxic activity has led to the recommendation that albendazole must not be prescribed to females who are pregnant. Post marketing surveillance in 2012, the GSK POAP reviewed all relevant new data in a context specific manner with a view to providing an assessment on the use of albendazole (and mebendazole another benzimidazole, which is structurally and physiologically similar to albendazole) for the treatment of intestinal	Albendazole is contraindicated in pregnancy and should not be administered during pregnancy or in women thought to be pregnant. Pregnant women will not be included. Serum Pregnancy test for female participants will be done at the time of screening, prior to check-in of each period and at the end of the study (at the time of check-out of period IV). Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative. For female participants history of menstruation and use of contraceptive methods will be evaluated by trained study physician at the time of screening.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	infections during various exposure scenarios in pregnancy. POAP considered the Weight-of-Evidence of all the reported pregnancy outcomes relative to all trimesters of pregnancy. The data reviewed included 16 publications (including meta-analyses) involving drug exposures to over 12,000 pregnant women (albendazole: N=6000; mebendazole: N=6000). Subsequent to the POAP consultation on the use of albendazole during pregnancy, the GSK CPSB decided that there was insufficient evidence to remove the contraindication regarding use during pregnancy in the OTC setting	Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention and will be withdrawn from the study.
Neurological disorders	The neurological disorders include headache and dizziness are listed in the adverse reaction section.	Considering single oral dose of albendazole with 1-week interval between the doses, headache and dizziness subsides on its own before the next period starts. If these symptoms continue during II, III and IV period admission, withdrawal of participant can be considered based on principal investigator decision and condition of participant.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate if Test Study Intervention (T): Albendazole tablets IP 400 mg, manufactured by Biddle Sawyer Limited is bioequivalent to Reference Study Intervention (R): Albendazole Tablets 400 mg, manufactured by GSK Consumer Healthcare, South Africa (PTY)	• Albendazole Cmax and AUC(0-t)
Secondary	
• To assess secondary pharmacokinetic parameters of Test Study Intervention (T): Albendazole tablets IP 400 mg relative to Reference Study Intervention (R): Albendazole tablets 400 mg.	• Albendazole AUC0-∞, Tmax, t1/2, lambda-z (λz) and AUC_%Extrap_obs. • Albendazole sulfoxide Cmax, AUC(0-t), AUC0-∞, Tmax, t1/2, lambda-z (λz) and AUC_%Extrap_obs.
• To assess the safety and tolerability of a single oral dose of the test versus the reference study intervention.	• Incidence of AE. • Absolute and change from baseline in vital signs parameters at each timepoint.

Primary estimand/coprimary estimands

The primary clinical question of interest is:

To evaluate if Test Study Intervention (T): Albendazole tablets IP 400 mg is bioequivalent to Reference Study Intervention (R) Albendazole tablets 400 mg in healthy adult participants under fed conditions.

The estimand is described by the following attributes:

- **Population**: Healthy adult participants between 18 to 45 years of age.
- **Treatment condition**: Single dose of Albendazole tablets IP 400 or Albendazole tablets 400 mg, each treatment period given under fed conditions to healthy participants.
- **Variable/endpoint**: Cmax and AUC(0-t)
- **Summary measure**:
  - Treatment ratios of geometric least square means with 90% CI, and within-subject coefficient of variation of reference study intervention (intra-subject CV in %).
- **Intercurrent events**:
  - Permanent Treatment discontinuation due to any reason (includes COVID-19 positive, AE related withdrawal etc.) – While-on treatment strategy that is, all available data up until the withdrawal of the consent will be reported.
  - Use of prohibited or rescue medication (Section 6.9) which could affect PK parameters (Cmax and AUC(0-t)) during the study – Hypothetical strategy

    Experiences emesis/vomiting before 2 times of median Tmax (i.e. 2 x 2hour = 4hour) after dose administration – Hypothetical strategy.
- **Rationale for estimand**:
  - The rationale of the while on treatment strategy is to estimate the PK parameters when participants have taken the dose/treatment condition.
  - The rationale of hypothetical strategy for prohibited/rescue medication is to minimize the potential confounding of PK data (Cmax and AUC(0-t)). It attempts to estimate treatment effects had the intercurrent event not occurred. In this scenario, if the intercurrent event occurred before 2 times median Tmax (i.e. 2 x 2hour = 4hour) after study drug administration, PK parameters (Cmax and AUC(0-t)) data would be set to be missing for that period.
  - Hypothetical strategy would be considered if emesis/vomits occur before 2 times the median Tmax (i.e. 2 x 2hour = 4hour) after study drug administration in particular period, this is because the drug would not have been absorbed into the body. In this situation, PK parameters (Cmax and AUC(0-t)) data would set to be missing for that period.

Secondary estimand(s) - PK endpoint

The secondary clinical question of interest is:

To assess secondary pharmacokinetic parameters of Test Study Investigation (T): Albendazole tablets IP 400 mg relative to Reference Study Investigation (R): Albendazole tablets 400 mg.

The estimand is described by the following attributes:

- **Population**: Healthy adult participants between 18 to 45 years of age.

- **Treatment condition**: Single dose of Albendazole tablets IP 400 mg or Albendazole tablets 400 mg, each treatment period given under fed conditions to healthy participants.
- **Variable/endpoint**:
    - **Albendazole** AUC0-∞, Tmax, t1/2, λz and AUC_%Extrap_obs.
    - **Albendazole sulfoxide** Cmax**,** AUC(0-t), AUC0-∞, Tmax, t1/2, λz and AUC_%Extrap_obs.
- **Summary measure**:

  Descriptive statistics (N, n, arithmetic mean, 95% CI of arithmetic mean, SD, median, minimum, maximum and geometric mean) will be presented for untransformed secondary PK parameters (AUC0-∞, AUC(0-t), Tmax, t1/2, λz and AUC_%Extrap_obs).
- **Intercurrent events**:
  - Same as primary endpoint

- **Rationale for estimand**:
  - The rationale of hypothetical strategy which is impacted to secondary PK parameters (AUC0-∞, AUC(0-t), Tmax, t1/2, λz and AUC_%Extrap_obs) during the study is same as primary estimands.

Secondary estimand(s) - 2(Safety)

The secondary clinical question of interest is:

To assess the safety and tolerability of a single oral dose of Test Study Intervention (T):

Albendazole tablets IP 400 mg relative to Reference Study Intervention (R): Albendazole tablets 400 mg.

The estimand is described by the following attributes:

- **Population**: Healthy adult participants between 18 to 45 years of age.
- **Treatment condition**: Single dose of Albendazole tablets IP 400 mg or Albendazole tablets 400 mg, each treatment period given under fed conditions for healthy participants.
- **Variable/endpoint**: Incidence of AE and Absolute and change from baseline in vital signs parameters at each timepoint.
- **Summary measure**:
  - Number and percentage will be presented for incidence of AE.

- Descriptive statistics (N, n, mean, SD, median, minimum and maximum) will be presented for absolute and change from baseline values of vital signs parameters at each timepoint.

- **Intercurrent events**:

  Permanent Treatment discontinuation due to any reason (includes COVID-19 positive, AE related withdrawal etc.) – Treatment policy strategy.

- **Rationale for estimand**:

  Permanent Treatment discontinuation due to any reason will be handled with a treatment policy strategy as occurrence of AE until participant are on study will be collected and reported.

4. STUDY DESIGN

4.1. Overall design

Study Design:

An Open Label, Balanced, Randomized, Two-Treatment, Four-Period, Two-Sequence, Single Oral Dose, Full Replicate Crossover, Bioequivalence Study of Albendazole Tablets IP 400 mg of Biddle Sawyer Limited (GSK group company) with Albendazole Tablets 400 mg of GSK Consumer Healthcare, South Africa (PTY) Ltd in Healthy, Adult Participants under Fed Condition.

Housing:

Participants will be housed in the clinical facility at least 11 hours before administration of the intervention and will continue to remain in the clinical facility for at least 24 hours after administration of the intervention in each period.

The participants will have to stay in the facility for 2 consecutive nights in each period.

In case of any adverse event, necessary action will be taken till the event subsides.

Wash-out Period:

There will be a washout period of at least 7 days between dosing days of any 2 consecutive periods.

Dosing:

Dose administration as described below will be done under the supervision of trained study personnel.

After an overnight fast of at least 10 hours, participants will be served high fat high calorie vegetarian breakfast 30 minutes prior to dosing, which they are required to consume within 30 minutes (Section 5.3.1). Study Intervention will be administered to the participants while in sitting position with 240 ± 2 mL of drinking water at the ambient temperature in each period. The tablets should be swallowed whole without chewing or crushing.

This activity will be followed by a thorough mouth check with torch & disposable spatula by the trained study personnel immediately after study intervention administration to assess compliance to dosing. The time of administration of the study intervention will be the time

at which the participant completes drinking 240 ± 2 mL of water and that will be captured in the respective source data forms.

4.2. Scientific rationale for study design

The manufacturing of albendazole tablets is being transferred from Cape Town, South Africa to Nashik, India. To ensure appropriate exposure after administration of the newly produced tablets from India, bioequivalence is required to be proven between the tablets from both locations. Therefore, this study evaluates the bioequivalence between the Sponsor's test study intervention (albendazole 400 mg tablets from Nashik, India) with respect to the reference study intervention (albendazole 400 mg tablets from Cape Town, South Africa) in healthy adult participants under fed condition.

Albendazole is a molecule with high intra-subject variability supported from literature[2] and in-house experience. Additionally, as per WHO product specific guidance (Notes on the Design of Bioequivalence Study: Albendazole; 29 March 2021), albendazole PK in the fed state is highly variable (up to 68% for Cmax and 62% for AUC). The WHO guideline for albendazole bioequivalence studies strongly recommends a replicate cross-over study design for albendazole bioequivalence studies, to estimate intra-subject PK variability more accurately which allows to widen the acceptance range for Cmax and AUC(0-t) ratios. Given the large variability in albendazole and albendazole sulfoxide PK, such potential larger differences in Cmax and AUC(0-t) between the proposed product and the comparator that might be accepted due to the widened acceptance range are expected to lack clinical relevance. In line with the WHO product specific guidance document, this study implements a fully replicate 4-period study design.

The PK sampling and washout period of 7 days are designed to ensure that PK parameters will be well-estimated and pre-dose concentrations are negligible in each subsequent period.

Depending on the CV% in Cmax and AUC(0-t), a joint power calculation showed that 48 evaluable participants were required to achieve a joint power of at least 90% for the two primary endpoints. Taking into account an expected dropout with fully missing data in up to 30% of participants, a total of 70 healthy adult participants will be enrolled. In case of only partially missing data in those 30%, the joint power of this study may be over 90% (Section 9.6).

4.2.1. Participant input into design

4.3. Justification for dose

The average daily dose of albendazole is 400 mg up to 2 times a day. This is taken as one 400 mg tablet up to 2 times per day with a maximum dose of 800 mg per day.

This study will be assessing the bioequivalence of a single dose of Albendazole Tablets IP 400 mg or Albendazole Tablets 400 mg in each period under fed conditions, according to a 4-period, 2-sequence full replicate crossover design bioequivalence study with a washout period of 7 days.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA (i.e. at the time of check-out of period IV).

Thus, the end of study will be the last scheduled procedure (blood collection for PK sample and safety assessment at the time of check-out of period IV) of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

a) Non-smoker, healthy, adult human participants between 18 to 45 years of age (both inclusive).

b) Having a BMI between 18.5 to 30.0 (both inclusive), calculated as weight in kg / height in m^2.

c) Not having any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and X-ray chest (postero-anterior view) recordings.

d) Able to understand and comply with the study procedures, in the opinion of the principal investigator.

e) Able to give voluntary written informed consent for participation in the study.

f) In case of female participants:

- Surgically sterilized at least 6 months prior to study participation;

  Or

  If of childbearing potential is willing to use a suitable and effective double barrier contraceptive method or intra uterine device during the study.

  And

- Serum pregnancy test must be negative.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Medical Conditions

a) Known hypersensitivity or idiosyncratic reaction to albendazole or any excipients or any related drug or any substance.

b) History or presence of any disease or condition which might compromise the haemopoietic, renal, hepatic, endocrine, pulmonary, central nervous, cardiovascular, immunological, dermatological, gastrointestinal or any other body system.

c) Any history or presence of asthma (including aspirin induced asthma) or nasal polyp or NSAIDs induced urticaria.

d) History or presence of seizure or psychiatric disorders.

5.2.2. Prior/Concomitant Therapy

a) Ingestion of a medication (prescribed medication & OTC medication, herbal remedies, cimetidine, praziquantel, dexamethasone, ritonavir, phenytoin, carbamazepine, phenobarbital) at any time in 14 days prior to dosing of period I and any vaccine (including COVID-19 vaccine) from 14 days prior to dosing of period I. In any such case participant selection will be at the discretion of the Principal Investigator.

5.2.3. Prior/Concurrent Clinical Study Experience

a) Receipt of an intervention or participation in a drug research study within a period of 90 days prior to the first dose of study intervention **.

** If intervention is received within 90 days where there is no blood loss except safety lab testing, participant can be included considering 10 half-lives duration of intervention received.

5.2.4. Diagnostic Assessments

a) A positive hepatitis screen including hepatitis B surface antigen and/or HCV antibodies.

b) A positive test result for HIV antibody (1 and/or 2).

c) The presence of clinically significant abnormal laboratory values during screening.

5.2.5. Other Exclusion Criteria

a) Difficulty in swallowing oral solid dosage form like tablet/capsule.

b) A recent history of harmful use of alcohol (less than 2 years), i.e. alcohol consumption of more than 14 standard drinks per week for men and more than 7 standard drinks per week for women (a standard drink is defined as 360 ml of beer or 150 ml of wine or 45 ml of 40% distilled spirits, such as rum, whisky, brandy etc.) or consumption of alcohol or alcoholic products within 48 hours prior to dosing of period I.

c) Smokers, or who have smoked within last 6 months prior to dosing of period I.

d) Consumption of grapefruits or grapefruit products within a period of 72 hours prior to dosing of period I.

e) Use of any recreational drugs or history of drug addiction or testing positive in pre-study drug screening.

f) A history of difficulty in donating blood.

g) Donation of blood (1 unit or 350 mL) within a period of 90 days prior to the first dose of study intervention.

h) An unusual diet, for whatever reason (e.g. low-sodium), for 4 weeks prior to dosing of Period I. In any such case participant selection will be at the discretion of the Principal Investigator.

i) Nursing mothers (females).

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

- All participants will be required to fast overnight for at least 10 hours prior to serving of high fat high calorie vegetarian breakfast, which they are required to consume completely within 30 minutes of serving the same. The kilo calories and fat content derived from the vegetarian meal menu used in this study is approximately 937.66 and 540 kcal respectively, which is comparable to the non-vegetarian high fat high calorie meal menu as recommended by USFDA (Section 10.7). Lunch will be provided 5 hours after dose administration in each period.

  The dietician/trained study person should weigh the leftover food and calculate the calories if the participant has not consumed the high fat high calorie vegetarian breakfast completely.

  A standardize meal will be served to the participants at appropriate times during their stay in the clinical facility. The contents of the meals served during each period at various time points will be identical. The participants will receive lunch at least 5 hours after dosing in each period and further meals will be served at appropriate intervals from then on, until checkout in each period. Information on the amount of meal consumed and the time taken for consuming the meal will be recorded in the source data forms. The actual time of meal distributions will also be recorded. In case meals and blood sample collection coincide, samples will be collected at schedule time only.

  Note: In case any participant has any adverse event and requires any change in diet, it will be done after consultation with the Principal Investigator. It will not be considered a protocol deviation. This will however be documented.

- No water (except 240 ± 2 mL given with study intervention administration) will be allowed from 1 hour before to 2 hour after dose administration in each period. Prior to and thereafter, water will be allowed at all times.

  Note: Non-compliance to above fasting/fed requirements and water restriction will be recorded as protocol deviation.

- All participants to abstain from grapefruit, grapefruit products for 72 hours prior to intervention administration in period I till last PK sample collection of period IV.

- All participants to abstain from an unusual diet, for whatever reason (e.g. low-sodium), for 4 weeks prior to dosing of period I and throughout the their participation in the study.

5.3.2. Caffeine, alcohol, and tobacco

- All participants to abstain from any Xanthine containing food or beverages (like tea, coffee, chocolates or cola drinks), tobacco, tobacco containing products (Gutkha, Pan/Pan masala or any other) for 24 hours prior to intervention administration in each period and throughout their stay in the clinical facility in each period.

- All participants to abstain from recreational products, alcohol or alcoholic products for 48 hours prior to study intervention administration in period I till last PK sample collection of period IV.

- Smoking for 6 months prior to dosing in period I till the completion of the study is prohibited and the participants have to abstain from the same.

5.3.3. Activity

Postural Restriction

- The study intervention will be administered to participants while in sitting posture.
- Participants will be in sitting or ambulatory posture for the first 4 hours post-dose in each period unless medically necessary due to adverse event or procedurally required or natural exigency, in such cases it would not be considered as protocol deviation. In case of adverse event appropriate position will be given to the participants.
- Thereafter, the participants will be allowed to engage only in normal activities while avoiding any strenuous physical activity.

5.3.4. Other restrictions

Not Applicable

5.4. Screen failures

Not Applicable

5.5. Criteria for temporarily delaying

Not Applicable

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study intervention(s) administered

Table 5 Study Intervention(s) Administered

Intervention Label	Test (T)	Reference (R)
Intervention Name	Albendazole tablets IP 400 mg	Albendazole 400 mg tablets
Intervention Description	Solid dosage form	Solid dosage form
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	400 mg	400 mg
Dosage Level(s)	single oral dose of 400 mg	single oral dose of 400 mg
Route of Administration	oral	oral
Use	active comparator	active comparator
IMP and NIMP/AxMP.	Study intervention	Study intervention
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study intervention will be provided in container. Each container will be	Study intervention will be provided in container. Each container will be labeled as

	labeled as required per country requirement.	required per country requirement.

While great care is taken to ensure comparability between the 2 tablets, minor differences exist (Table 6).

Table 6 Differences between Test and Reference tablets

Parameters	Test	Reference	Conclusion
Weight target	1026 mg	1026.20 mg	Very Slight Difference in Target Weight
Weight action limit	984.96 - 1067.04 mg (1026 mg ±4%)	974.89 to 1077.51 mg ((1026 mg ±5%)	Action limit of Reference is 5% while that of Test is 4%
Weight operating limit	995.22 – 1056.78 mg (1026 mg ±3%)	1021.07 to 1031.33 mg (1026 mg ±0.5%)	Operating limit of Reference is 0.5% while that of Test is 3 %
Hardness	108 N - 210 N (11.0 to 21.4 Kg/cm^2)	≥ 110 N Target 140 N (131-153 N)	Lower Hardness Limit of Test is 108 N while for Reference is 110 N.
Thickness	6.70 to 7.30 mm	6.65 to 7.10 mm	Thickness Limits of Test is wider than that of Reference

It is the expectation that these differences will not affect absorption kinetics or bioavailability to any significant degree.

6.2. Preparation, handling, storage, and accountability

- The sponsor shall supply adequate number of dosage units of study intervention for dose administration and for retention purpose. The received study interventions will be verified for the sealed condition of packs and adequacy of label (i.e. product name, strength, number of dosage units, manufacturer, manufactured date (if available), lot number or batch number, expiry date/retest date, study number, investigator and storage condition).
- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

- Only participants enrolled in the study may receive study intervention, and only authorized clinical site staff i.e. The Pharmacy custodian or their designated study personnel will receive the study interventions with COA. The study interventions will be transferred to the pharmacy, after labelling it for project number (as applicable), product type, quantity and date of receipt, batch number or lot number, manufacturing date, expiry date/retest date, for clinical study use only & storage conditions.
- All study intervention 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.
- Note: Information related to manufactured by/for, marketed/distributed by, marketing authorization holder etc. are based on details provided by the sponsor and/or available literature at the time of protocol development. Exact details will be captured in the study interventions receipt and accountability form by the pharmacy while receiving the study interventions. The same details can be used in the clinical study report for accuracy and compliance purpose.
- The Pharmacy Custodian and Project Coordinator or their designated study personnel will dispense the required units of study interventions prior to each period. Two units of study interventions (One test study intervention and one reference study intervention) will be dispensed in addition to the required number and labelled accordingly in each period. These will be used in any situation such as dropping the study intervention's etc. The remaining units of study interventions will be kept in their original containers.
- The doses intended for administration to the participants will be transferred to the drug-dispensing containers as per randomization schedule and properly labelled for the intervention with strength, dose, product type, project number, participant number, period, 'For Clinical Trial Use Only', Lambda Therapeutic Research Ltd.
- The personnel involved in dispensing and verification of dispensed study interventions will be accountable for ensuring compliance to randomization schedule.
- The investigator, the pharmacy custodian/designate is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Unused study interventions that have not been dispensed will be retained in their original containers. Any product that had been dispensed but not used (e.g. due to the participant being unwell or dropping out from the trial etc.) will be labelled as 'Not For Use' and returned to the pharmacy and will be retained along with the other study interventions of its type.
- Retention samples: Samples of the study intervention in the original container should be retained for possible confirmatory testing in the future in compliance with the applicable national requirements or international recommendations, as appropriate. Dispensed study intervention that were not administered should also be retained. All the study interventions not used during the study will be accounted for and all unused supplies will be retained for 5 years after study completion. Once the above-mentioned time period is over, samples will be returned to the sponsor or as per sponsor's request necessary action will be taken.

6.3. Assignment to study intervention

Randomization

The order of receiving test (T) and reference (R) intervention for each participant during all the periods of the study will be determined according to a randomization schedule by Lambda. The randomization schedule will be generated using SAS® Version 9.4 or higher (SAS Institute Inc., USA) by a biostatistician.

The sequence of administration of intervention i.e. “TRTR” or “RTRT” to the participants will be determined according to the randomization schedule. (Note: T = Test study intervention and R = Reference study intervention). Equal allocation of participants in each sequence is planned.

The personnel involved in dispensing of study intervention and verification of dispensed study interventions will be accountable for ensuring compliance to randomization schedule.

6.4. Blinding, masking

Not Applicable

6.5. Study intervention compliance

Dosing activity will be followed by thorough mouth check with torch & disposable spatula by the trained study personnel immediately after study intervention administration to access compliance to dosing. The time of administration of the study intervention will be the time at which the participant completes drinking 240 ± 2 mL of water and that will be captured in the respective source data forms.

6.6. Dose modification

Not Applicable

6.7. Continued access to study intervention after the end of the study

There is no intervention following the end of the study.

6.8. Treatment of overdose

Not Applicable.

6.9. Prior and concomitant therapy

No drug (prescribed & OTC medication including herbal remedies, cimetidine, praziquantel, dexamethasone, ritonavir, phenytoin, carbamazepine, phenobarbital) other than the intervention shall be consumed by the participants from 14 days prior to dosing of period I till completion of study and any vaccine (including COVID-19 vaccine) within 14 days prior to dosing of each period. If drug therapy other than that specified in the protocol is required prior to dosing or during the study or in the wash-out period, decisions shall be taken by the Principal Investigator to continue or discontinue the Participants based on the

following:

a) The pharmacology and pharmacokinetic of the non-study medicine.

b) The likelihood of a drug–drug interaction, thereby affecting the pharmacokinetic comparison of study intervention.

c) The time and duration of administration of the non-study medicine.

All such instances will be recorded and reported in the final report.

Note: Any concomitant medication administered during the course of the trial will be documented appropriately in the source data forms.

6.9.1. Rescue medicine

Not Applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not Applicable

7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention in the best interest of the participant for abnormal liver tests at the investigator discretion, when liver parameter falls outside the pre-defined clinically acceptable values. Acceptable limits are defined in Section 10.6.

If any participant has clinically significant abnormal liver function analysis, in such case participant may be discontinued for specific period at the investigator discretion. The decision to continue/discontinue such participants will be based on investigator's decision and it will be appropriately documented in the eCRF.

7.1.2. QTc Stopping criteria

Not Applicable

7.1.3. Temporary discontinuation

Not Applicable

7.1.4. Rechallenge

Not Applicable

7.1.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.2. Participant discontinuation/withdrawal from the study

The Principal Investigator may withdraw a participant from a period or from the study for any of the following reasons:

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). (Note: If the participant does not wish to be withdrawn from particular period only or from the study permanently then participant can be allowed to continue their participation in subsequent periods as per investigator's discretion).

A participant may be withdrawn at any time at the discretion of the investigator for safety reasons, any participant found to hide important medical history, violation of this protocol (this would include pre-study directions regarding alcohol and drug use, fasting/fed or if the participant is non-compliant during the study or uncooperative with study procedures).

If it is felt in Principal Investigator's opinion that it is not in the participant's best interest to continue.

The participant suffers from significant inter-current illness or undergoes surgery during the course of the study, or the participant has any significant symptoms or signs during the course of the study.

Note: For any participant who is withdrawn from any period due to emesis (within 4 hours post-dose) or any adverse events the decision regarding participant's continuation for subsequent periods will be based on investigator's discretion.

Any participant who requires the use of an unacceptable concomitant medication (prescribed & OTC medication including herbal remedies, cimetidine, praziquantel, dexamethasone, ritonavir, phenytoin, carbamazepine, phenobarbital).

Any vaccine (including COVID-19 vaccine) within 14 days prior to dosing of each period. In any such case decisions shall be taken by the Principal Investigator to continue or discontinue the participant.

If any participant cross-participates in other drug trial or trial screening.

Found positive in serum pregnancy test (for female participants).

Any participant experiences emesis before reported 2 times median T_{max} (i.e. 2 x 2hour = 4hour) after dosing of the study intervention for a particular period, then participant will be withdrawn for that period only or from study as per investigator's discretion.

If any participant does not report to facility in any period due to own accord, then they can be allowed to continue their participation in subsequent periods as per investigator's discretion.

Any participant has consumed the high fat high calorie vegetarian breakfast less than 800 kcal, then participant will be withdrawn from a particular period or from the study as per investigator's discretion.

Any other justifiable reason, which should be adequately documented.

All instances of participant who withdraw from the study, including the date and reason for withdrawal will be documented and shall be handled as per the in-house procedure.

Any untoward effect reported by the participant who is withdrawn will be incorporated into the final study report. These participants will be followed up for their safety as per in-house SOP.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to follow-up

The participant is expected to visit the facility immediately for repeat evaluation/ follow up in case of:

- Any ongoing adverse event or abnormal laboratory parameter identified during End of Study visit.
- Any adverse event that may occur after the last intervention administration and within the duration of 10 half-lives (t1/2 of the IMP) or duration equivalent to the defined wash out period (7 days), whichever is shorter.

In either of the above 2 scenarios, the participant would be followed up till resolution/ stabilization of AE. Participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

In case the participant does not respond even after repeated communications or is not accessible, the participant should be considered as lost to follow-up and such cases will be handled as per standard operating procedures. The participant is considered to have completed the study after the last intervention administration, once the duration of 10 half-lives (t1/2 of the IMP) or duration equivalent to the defined wash out period, whichever is shorter.

8. STUDY ASSESSMENTS AND PROCEDURES

- All participants will undergo physical and clinical screening procedure within 28 days prior to the first dose administration. The participant will be selected on the inclusion and exclusion criteria mentioned in Section 5.1 and Section 5.2.

- Study procedures and their timing are summarized in the SoA in Section 1.3 Schedule of activities (SoA). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Laboratory parameters obtained during the process of screening will be evaluated as follows:

  i. Out of range values of other hematology and biochemistry parameters and urine parameters will be individually evaluated and / or repeated for their clinical significance. A participant will be enrolled into the study only if the medically qualified reviewer deems the values clinically insignificant or acceptable.

  ii. All immunology parameters are required to be negative.

  iii. Serum Pregnancy test for females will be negative

  *(**Note:** In case if any extra tests are analyzed, it will not have any impact on the trial if the parameters and the values are clinically insignificant.)*
- Include the maximum amount of blood collected from each participant over the duration of the study and if any repeat or unscheduled samples may be taken, as appropriate.
- Single oral dose of 1 tablet of either Test study intervention or Reference study intervention (each containing 400 mg of albendazole) will be administered to each participant in each period.

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth, sex, race, age, height, weight, BMI and ethnicity in the MSR.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Current medication (prescribed medication & OTC medication, herbal remedies, cimetidine, praziquantel, dexamethasone, ritonavir, phenytoin, carbamazepine, phenobarbital) and usage of any concomitant therapy or any ingestion of medicine in the previous 14 days prior to dosing of period I and any vaccine (including COVID-19 vaccine) from 14 days prior to dosing of period I.

8.2. Pharmacokinetic assessments

Planned timepoints for PK assessments:

A total of 22 blood samples, each of 3 mL will be collected from each participant in each period.

The venous blood samples for determination of albendazole and albendazole sulfoxide will be drawn at pre-dose and at 20 min, 40 min, 60 min, 80 min, 100 min, 120 min (2h00min), 2.33 (2h20min), 2.67 (2h40min), 3.00 (3h00min), 3.33 (3h20min), 3.67 (3h40min), 4.00 (4h00min), 4.50 (4h30min), 5.00 (5h00min), 6.00 (6h00min), 8.00 (8h00min), 10.00 (10h00min), 12.00 (12h00min), 14.00 (14h00min), 18.00 (18h00min) and 24.00 hours (24h00min) post dose in each period.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical/Clinical examination and clinical safety measures

- A physician will be available within the clinical facility whenever the participants are housed (from check in to checkout in each period). A consultant physician will be always available on call during the study period.
- Clinical examination of the participants including recording of vital signs (blood pressure, respiratory rate and radial pulse) and body temperature will be done at screening, after check-in, before check-out in each period.

  Note: Clinical examination before checkout may be started 120 minutes prior to the schedule time of checkout of each participant.
- Participants should meet the criteria for enrolment in the study.
- Participants will be questioned for well-being at the time of clinical examinations and during recording of vital signs examination in each period.
- Participants will be instructed not to participate in other clinical trial or donate blood anywhere else during the study.
- Drug of abuse in urine and Breath alcohol test will be performed on check-in of each period.
- Chest X-ray (within the last 6 months) (postero-anterior view) will be carried out at the time of screening.
- Participants will be instructed not to drive or operate machines during the entire study as the study drug may cause dizziness.

8.3.2. Vital signs

- Vitals (sitting blood pressure and radial pulse) will be recorded at pre-dose (within 60 minutes before the dosing) and at 2, 4, 6, 12 and 24 hours post-dose in each period.

Note: All post-dose vitals will be performed within ± 40 minutes of the scheduled time.

8.3.3. Electrocardiograms

- 12-lead ECG will be carried out at the time of screening as outlined in the SoA (see Section 1.3).

8.3.4. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3).
- Serology tests (HIV AB (1 & 2), Anti HCV and HBsAg) will be performed at the time of screening.
- Urine parameters will be performed at the time of screening.
- Laboratory assessment for hematology and biochemistry will be performed at the time of screening.
- Laboratory assessment for hematology and biochemistry (except random glucose, sodium, potassium, chloride, alkaline phosphatase) will be performed at the end of the study (at the time of check-out of period IV).
- Laboratory assessment for liver function test (SGPT, SGOP and total bilirubin) will be performed prior to check-in of period II, III and IV.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g, SAE or AE), then the results must be recorded.

8.3.5. Pregnancy testing

- Serum Pregnancy test for female participants will be done at the time of screening, prior to check-in of each period and at the end of the study (at the time of check-out of period IV). Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- For female participants history of menstruation and use of contraceptive methods will be evaluated by trained study physician at the time of screening.
- Refer to Section 8.4.5 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Safety Measures for Volunteers during Covid-19 pandemic

Regulatory authorities have recognized that COVID-19 pandemic may impact the conduct of clinical trials of medical products. Thus, in order to assure safety of trial participants, and to ensure compliance with protocol and regulatory guidance and to minimize risk to trial integrity during COVID-19 pandemic, certain additional safety measures shall be taken into consideration. These safety measures are described in the Safety Policy for COVID-19 Pandemic situation (Document Number: SP/IND/001 or as applicable). The participants will be informed about additional safety measures through respective Annexure of Safety Policy and consenting for the same will be taken.

8.3.7. Study stopping rules/holding rules, safety monitoring AND/OR Committee

Not Applicable

8.4. Adverse Events (AEs) serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the end of period IV at the time points specified in the SoA.

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a participant consents to participate in the study.

All adverse events, including both observed or voluntarily reported problems; complaints, signs or symptoms occurring after the first dose administration shall be recorded on the relevant page "Adverse Event/Medical Event Record Form" of eCRF irrespective of its association with the ongoing study medication. Prior to first dose administration in each participant, the event will be considered as a medical event and the aforementioned form will be completed by encircling “Medical Event” in the title.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of occurrence as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor as Follow up report within 24 hours of awareness.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section [8.4.1].

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant/LAR(s) is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.4.4. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See [Section 8.4.1] for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 8.4.
- An investigator who receives an safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the package insert and will notify the Institutional Review Board (IRB) / Institutional Ethics Committee (IEC), if appropriate according to local requirements.

Table 7 Timeframes for submitting SAE, pregnancy and other events reports to GSK, Ethics Committee and CDSCO

Type of event	Responsible	Initial reports		Follow-up of relevant information on a previous report	
		Time frame	Documents	Time frame	Documents
SAEs	Investigator	**24 hours of SAE Occurence*** ‡	Completed Table 5 format of the New Drugs & Clinical Trial Rules, 2019 to be sent to CDSCO via SUGAM portal and to GSK PV mailbox: india.pharmacovigilance@gsk.com and to the Chairman of the respective Ethics Committee	24 hours of awareness of follow up information *	Upload the Follow up Table 5 in SUGAM (via eVartalap) and send to the Sponsor (GSK PV mailbox) and EC

Type of event	Responsible	Initial reports		Follow-up of relevant information on a previous report	
		Time frame	Documents	Time frame	Documents
SAEs	Investigator	Within 14 calendar days of SAE occurrence	Due Analysis Report (Investigator Causality Assessment) to be submitted to CDSCO via SUGAM and notify Head of Institution (HOI) and EC via email/letter and notify GSK via sending email to PV mailbox mentioned above. In case of any delay, the reason for delay will need to be provided in SUGAM and the Sponsor. Note: In case of technical issue of SUGAM portal, notify to CDSCO via email dci@nic.in	Within 14 calendar days of SAE awareness	Update the Due Analysis report via SUGAM and notify HOI and EC via email/letter and notify GSK via sending email to PV mailbox mentioned above. Note: In case of technical issue of SUGAM portal, notify to CDSCO via email dci@nic.in
Pregnancies	Investigator	Within 24 hours of learning	Pregnancy Notification Form to be sent to WW.GSKAEReportingAPAC@gsk.co	Within 24 hours of awareness	Pregnancy Follow up Notification Form to be sent to WW.GSKAEReportingAPAC@gsk.co

Type of event	Responsible	Initial reports		Follow-up of relevant information on a previous report	
		Time frame	Documents	Time frame	Documents
		of pregnancy	m with a copy to india.pharmacovigilance@gsk.com	*	m with a copy to india.pharmacovigilance@gsk.com

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

CDSCO=Central Drugs Standard Control Organization, , EC= Ethics Committee, PV= pharmacovigilance, SAE= serious adverse event.

8.4.5. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention and will be withdrawn from the study but may continue other study procedures at the discretion of the investigator.

Handling and reporting of pregnancy during the clinical study will be done as per in-house SOP.

8.4.6. Cardiovascular (CV) and death events

CV and death events will be handled as per Section 8.4 and Section 10.3.

8.4.7. Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not Applicable

8.4.8. Contact information for reporting SAEs, Pregnancies

Table 8 Contact information for reporting SAEs, pregnancies

Study contact for questions regarding SAEs and pregnancies, Contact CRO/GSK's local and/or medical contacts	Sponsor SAE/Pregnancy reporting Contact Information: Email: india.pharmacovigilance@gsk.com Phone: +91-8657549542

8.5. Pharmacokinetics

Assessment of Pharmacokinetic Parameters:

Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed on the available concentration data of all the participants.

Criteria for exclusion of pharmacokinetic parameters of particular participants from statistical analysis will be as below:

Participants who were discontinued/withdrawn and do not have evaluable data for at least 1 treatment and 1 reference drug period will be excluded.

Three consecutive missing (M) / Non-Reportable (NR) samples in elimination phase may significantly influence the AUC_{0-t} and elimination phase dependent parameters (AUC0-∞, AUC0-t, t1/2, λz, AUC_%Extrap_obs). Inclusion of such parameters in the statistical analysis may mislead the final outcome. Hence, AUC(0-t) and elimination phase dependent parameters (AUC0-∞, AUC(0-t), t1/2, λz, AUC_%Extrap_obs) will be excluded.

The concentration–time profiles of subjects who exhibit pre-dose concentrations higher than 5% of the corresponding Cmax of that period will be excluded from the statistical analysis [Note: a statistical sensitivity analysis including the same will be provided for information purpose].

Participants without measurable concentrations or who have only very low plasma concentrations relative to that of the product in question, will be excluded from the pharmacokinetic and statistical analyses. A participant is considered to have very low plasma concentrations if their AUC is less than 5% of the geometric mean AUC of the product in question, calculated without inclusion of data from the outlying participant [Note: statistical analysis with including the same will be provided for information purpose].

Pharmacokinetic Parameters

The following pharmacokinetic parameters will be computed for albendazole and albendazole sulfoxide using non-compartmental model of Phoenix® WinNonlin® Version 8.3 or higher (Certara L.P.) for each period:

Primary PK Parameters:		
Cmax	:	Maximum measured plasma concentration.
AUC(0-t)	:	Area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
Secondary PK Parameters		
AUC0-∞	:	Area under the plasma concentration versus time curve from time zero to time infinity. Where AUC0-∞ = AUC(0-t) + Ct/λz, Ct is the last measurable concentration and λz is the terminal rate constant.
Tmax	:	Time of the maximum measured plasma concentration.
λz	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last 3 non-zero plasma concentration values.
t1/2	:	The terminal half-life will be calculated as 0.693/λz.
AUC_%Extrap_obs	:	The residual area in percentage will be determined by the formula, [(AUC0-∞ - AUC0-t)/AUC0-∞] x 100.

For all the above computations, actual time points of the sample collection will be used.

Non-quantifiable (NQ) data, such as concentrations below the quantification limit may be excluded or omitted, depending on where they are located in time, see Section 9.4.2.5.

No value of λz, AUC0-∞, AUC_%Extrap_obs and t1/2 will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Procedure of blood sampling and its collection

Blood samples will be collected through an indwelling intravenous cannula (Venflon) placed in a forearm vein of the participants. The pre-dose blood sample will be collected within a period of 60 minutes before dosing. Post dose in-house blood samples will be collected within ± 2 minutes from scheduled time. The actual time of collection of each blood sample will be recorded immediately after blood collection. For precaution purpose, the blood samples will be kept in an ice-cold water bath during collection.

Cannula will be removed after collection of 24.000 hours blood sample.

All Blood samples not collected within this time frame from scheduled time will be documented as sampling deviations.

Intravenous indwelling cannula will be kept in situ as long as possible by injecting 0.5 mL of normal saline solution to maintain the cannula patent (to prevent cannula from clogging) for collection of all the blood samples up to 24.000 hours post dose in each period. In such cases blood samples will be collected after discarding the first 0.5 mL of normal saline containing blood from the tubing. The blood samples will be collected and transferred into pre-labelled (mentioning Project number, Participant number, Period, Sample ID No./ Bar code ID and Sampling time point) sample collection tube containing K2EDTA as an anticoagulant. Immediately after each tube of blood is drawn, it should be inverted gently several times to ensure the mixing of tube contents (i.e., anticoagulant). The sample collection tubes will be placed in an ice-cold water bath until centrifugation for precaution purpose.

Alternatively, if the cannula is blocked or there is difficulty in withdrawing blood through the cannula, blood samples may be withdrawn by a fresh vein puncture using a disposable sterile syringe and a needle at each time of collection. Blood sample for serum pregnancy test for females prior to check in of each period and blood sample for laboratory assessment of liver function test prior to check-in of period II, III, IV will be collected through a fresh vein puncture.

For each participant, the total volume of blood loss should not be exceeding **334 mL** for male participants and **342 mL** for female participants calculated as follows:

			Male Participants	**Female Participants**
+	Blood volume for the samples for 4 periods (84 post-dose samples of 3 mL each and 4 pre-dose samples of 3 mL each).	:	264 mL	264 mL
+	Discarded normal saline blood for 4 periods (88 samples of 0.5 ml each)	:	44 mL	44 mL
+	Blood withdrawn for screening prior to study	:	Up to 11 mL	Up to 11 mL

			Male Participants	Female Participants
+	Serum β-HCG tests (On check-in day of each period for female participants	:	---	8 mL
+	Laboratory assessment for liver function test prior to check-in of period II, III and IV	:	6 mL	6 mL
+	Blood withdrawn for post-study safety assessment	:	Up to 9 mL	Up to 9 mL
Total Blood Loss for each participant		:	**334 mL**	**342 mL**

Note: In addition to above up to additional of 20.0 mL blood sample will be collected if required, for hemolyzed sample, clotted sample, sample loss, any safety assessment deemed necessary at screening, prior to check-in of any period & during the study, required as per method requirement or any other reason.

Sampling Schedule

A total of 22 blood samples each of 3 mL, will be collected from each participant in each period.

The venous blood samples will be withdrawn at the following times. All actual sample times will be recorded in addition to their planned time.

Table 9 PK sampling schedule

Day	Time points (Hours)	Proposed clock time	Blood volume (mL)	Analytes to measure	
				Albendazole	Albendazole Sulfoxide
1	Pre-dose (0.00)	Within 60 minutes prior to dosing	3.0 mL	√	√
	0.33	0h20min	3.0 mL	√	√
	0.67	0h40min	3.0 mL	√	√
	1.00	1h00min	3.0 mL	√	√
	1.33	1h20min	3.0 mL	√	√
	1.67	1h40min	3.0 mL	√	√
	2.00	2h00min	3.0 mL	√	√
	2.33	2h20min	3.0 mL	√	√
	2.67	2h40min	3.0 mL	√	√

Day	Time points (Hours)	Proposed clock time	Blood volume (mL)	Analytes to measure	
				Albendazole	Albendazole Sulfoxide
	3.00	3h00min	3.0 mL	√	√
	3.33	3h20min	3.0 mL	√	√
	3.67	3h40min	3.0 mL	√	√
	4.00	4h00min	3.0 mL	√	√
	4.50	4h30min	3.0 mL	√	√
	5.00	5h00min	3.0 mL	√	√
	6.00	6h00min	3.0 mL	√	√
	8.00	8h00min	3.0 mL	√	√
	10.00	10h00min	3.0 mL	√	√
	12.00	12h00min	3.0 mL	√	√
	14.00	14h00min	3.0 mL	√	√
2	18.00	18h00min	3.0 mL	√	√
	24.00	24h00min	3.0 mL	√	√

Day 1: Day of study intervention administration in each period.
Day 2: Subsequent day after study intervention administration in each period.

Sample Analysis for Pharmacokinetic / Safety analysis

Plasma Separation

The blood samples will be centrifuged at 3000 ± 100 rcf for 5 minutes below 10 °C to separate plasma. For precaution purpose the blood samples will be kept in an ice-cold water bath before centrifugation and during separation.

The separated plasma will be transferred to pre-labelled polypropylene tube in 2 aliquots (around 0.5 mL in first aliquot and rest of the volume in second aliquot).

All the samples will be stored upright in a box containing adequate amount of dry ice or in a freezer at a temperature -55 °C or below at clinical site until transferred to bio-analytical site.
The samples will be transferred from clinical site to bio-analytical site by keeping them in a box containing adequate amount of dry ice and stored in a bio-analytical freezer at -55 °C or below until completion of analysis at Lambda Therapeutic Research Ltd., Ahmedabad.

Initially first aliquot samples will be transferred to bio-analytical site and once the samples received at bio-analytical site, the second aliquot will be transferred from clinical site separately.

Bioanalytical Procedures

Plasma samples of participants will be assayed for albendazole and albendazole sulfoxide

using single liquid-chromatography with tandem mass spectrometry (LC-MS/MS) method, which is validated according to the international guidelines.

Bioanalytical study plan will be prepared before study sample analysis.

The analysis of participant samples will be done using a calibration curve with quality control samples. The details for the preparation of the calibration curve and quality control samples, analytical run organization and the analytical run acceptance criteria as discussed in the respective in-house SOP will be followed during analysis.

The analysts will not have access to the randomization schedule.

All the collected samples will be analyzed except if any participant dropped out after dosing and no post dose samples are collected then pre-dose sample of that period of such participant would not be analyzed.

The criteria for repeat analysis, as defined in the respective in-house SOP, will be followed.

Incurred sample reproducibility will be performed to confirm the reliability of the study data. Sample selection will be based on the below table and the procedure and acceptance of the results will be as per the in-house SOP. The results will be presented in the bioanalytical report.

Sample Size		No. of ISR samples
Total sample size up to 1000 sample	:	10 % of total samples
Total sample size >1000 sample	:	100 samples (10 % of 1000 samples) + 5 % of (Total samples – 1000 samples)

Any missing samples will be reported as `M' and any non-reportable concentration values which may arise due to insufficient quantity for repeat analysis or due to any other reason as per in-house SOP will be reported as 'NR'.

Primary (first) aliquot used for study sample analysis will be discarded after completion of analysis.

8.6. Pharmacodynamics

Not Applicable

8.7. Genetics

Not Applicable

8.8. Biomarkers

Not Applicable

8.9. Immunogenicity assessments

Not Applicable

9. STATISTICAL CONSIDERATIONS

A SAP will be prepared which will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

According to WHO product specific guidance (Notes on the Design of Bioequivalence Study: Albendazole; 29 March 2021), albendazole pharmacokinetics in the fed state is highly variable (up to 68% for Cmax and 62% for AUC). Therefore, this study was designed as a replicate cross-over study, to estimate variability more accurately and, if indicated, to widen the acceptance range for Cmax and AUC(0-t) (World Health Organisation, 2021). Considering the same, full replicate study has been planned in line with WHO product specific guidance document and reference-scaled average bioequivalence approach will be used for hypothesis testing.

The null hypothesis to be tested is:

$$H_0: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \geq \theta$$

Versus alternative hypothesis

$$H_1: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} < \theta$$

Where: μ_T and μ_R are the means of ln-transformed PK parameters (Cmax and/or AUC) obtained from the BE study for the test and reference products, respectively.

σ_{WR} is the within-subject standard deviation of the log-transformed values of PK parameter of the reference study intervention.

Testing will be performed at a level of 0.05 and θ is the scaled average BE limit.

The test drug must pass for primary endpoint PK parameters (Cmax and AUC(0-t)) to demonstrate BE to the reference drug. Let σ_{W0} be the regulatory constant (based on 0.80-1.25 geometric mean ratio restriction criteria) and assumed to be 0.294.

a. The 90% confidence interval of GMR of T/R must be contained within [U, L] = exp [±k·s_{WR}], which is scale acceptance limit based on k(θS),

   Where k = ln(1.25)/σ_{W0} which is approx. 0.760

   U is the upper limit of the acceptance range, L is the lower limit of the acceptance range,

s_{WR} is the within-subject standard deviation of the log-transformed values of PK parameter of the reference study intervention

b. Point estimate of GMR of T/R should be between 80.00 –125.00%.

For the parameters Cmax and AUC(0-t), if the intra-subject CV_W of for the reference study intervention is less than or equal to 0.30 upon trial completion for any of these treatment group, conventional average BE approach with TOST procedure with α=0.05 for each one-sided test will be used to test $0.8 \leq GMR \leq 1.25$. This is equivalent to requiring that a 90% interval for the true ratio of test to reference geometric means falls entirely within the range of 80.00 to 125.00%. If the intra-subject coefficient of variation (CV_W) of for the reference study intervention is greater than 0.30 upon trial completion, a reference-scaled average bioequivalence approach will be used[5].

If the intra-subject variability for Cmax and AUC(0-t) following replicate administrations of the comparator product is > 30%. If this is the case the acceptance criteria for Cmax and AUC(0-t) will be widened to a maximum of 69.84–143.19%.

9.2. Multiplicity Adjustment

No multiplicity adjustment is required for this bioequivalence study.

9.3. Analysis sets

Analysis Sets	Description
Randomized	All participants assigned to study treatment
Safety set	The safety set will include all randomized participants who receive at least 1 dose of study medication. The safety population will be used for all analyses of safety data.
PK set	All participants in the Safety set who had at least 1 measurable PK assessment (for the purpose of the PK analysis, only those participants in this dataset who have evaluable data for one test and one reference period will be used).

9.4. Statistical Analysis

9.4.1. General considerations

The pharmacokinetic parameters will be analyzed to evaluate the differences between the test and reference study interventions by applying referenced scaled average bioequivalence approach.

All the statistical analysis will be performed using SAS® Version 9.4 or higher (SAS Institute Inc., USA).

The participants having pharmacokinetic parameters available for 2 reference treatments will be included for calculation of intra-subject variability of reference study intervention.

Descriptive statistics & average bioequivalence analysis will be performed on the

participants having pharmacokinetic parameters available for at least on test and 1 reference arm.

9.4.2. Primary Endpoint(s)/Estimand(s) Analysis

9.4.2.1. Descriptive statistics

Statistical analysis for primary endpoints will include descriptive statistics for the following pharmacokinetic parameters:

Cmax and AUC(0-t)

Descriptive statistics (N, n, arithmetic mean, 95% CI of arithmetic mean, geometric mean, 95% CI of geometric mean, SD, median, minimum and maximum) will be presented for primary PK parameters.

Average values of Test Study Intervention-T and Reference Study Intervention-R for PK parameters for each participant will be calculated and reported. Descriptive statistics will be calculated and reported for the same data.

Individual values of PK parameters for Test Study Intervention-T (first administration), Test Study Intervention-T (second administration), Reference Study Intervention-R (first administration) and Reference Study Intervention-R (second administration) for each participant will be calculated and reported. Descriptive statistics will be calculated and reported for the same data.

PK parameters will be analyzed to evaluate the differences between the test and reference products by applying SCABE following EMA guidelines in investigation of bioequivalence regarding highly variable drug product (% of CVw >30), otherwise ABE will be applied.

Analysis of Variance (ANOVA) will be used on ln-transformed pharmacokinetic parameters Cmax and AUC(0-t) for albendazole or albendazole sulfoxide. The ANOVA model will include participants, period and formulation as fixed effects.

Each analysis of variance will include calculation of ratio of geometric least-squares means and the standard error associated with these ratios. The above statistical analyses will be done using PROC GLM of SAS® procedure. Significance level of 5% (alpha =0.05) will be used for the model.

More technical and detailed description of the statistical analyses will be described in SAP of this study. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoints.

9.4.2.2. 90% Confidence Interval

90% confidence intervals for the ratio of geometric least squares means between drug formulations will be calculated for ln-transformed data of Cmax and AUC(0-t) for albendazole and albendazole sulfoxide.

9.4.2.3. Ratio analysis

Ratio of geometric least squares means of test and reference formulations will be computed and reported for ln-transformed pharmacokinetic parameters Cmax and AUC(0-t) for albendazole and albendazole sulfoxide.

9.4.2.4. Intra-subject variability

Intra-subject variability of reference study intervention-R will be computed and reported for ln-transformed pharmacokinetic parameters Cmax and AUC(0-t) for albendazole and albendazole sulfoxide.

The existence of outlier subjects that inflate the intra-subject variability will be assessed. In case of such outliers, results will be reported with and without those outliers

9.4.2.5. Missing and non-reportable values

If 1 or more NQ values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration.

If a single NQ value occurs between measurable concentrations in a profile, the NQ should be omitted (set to missing) in the derivation of pharmacokinetic parameters and statistical analysis.

If 2 or more NQ values occur in succession between measurable concentrations, the values in question will be set to missing. For the derivation of pharmacokinetic parameters, these NQs will be omitted. The NQ values will be set to 0 and the trapezoidal rule will be applied to all the observed data.

NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and statistical analysis.
Any missing samples (M) concentration value will be disregarded in pharmacokinetic and statistical analysis.

9.4.2.6. Intercurrent event and handling of missing data

The data will be affected by occurrence of the intercurrent event and only data available while the patient is receiving the treatment will be used under while-on treatment policy strategy. Participant level missing data will not be imputed, and available data will be used in the analysis.

In the case of emesis/vomiting or use of prohibited/rescue medication, the data for that period will not be used for the analysis of PK parameters relating to the primary endpoint using hypothetical strategy.

9.4.2.7. Bioequivalence Criteria

Based on the statistical results of 90% confidence interval for the ratio of the geometric least square means for both ln-transformed pharmacokinetic parameters Cmax and AUC(0-t), conclusion will be drawn for Test Study Intervention-T vs. Reference Study Intervention-R for albendazole with following considerations.

For Cmax and AUC(0-t):

1. If within-reference intra-subject CV of ln-transformed Cmax and/or AUC(0-t) ≤ 30% then bioequivalence of the test study intervention with that of the reference study intervention will be concluded, if the 90% confidence interval falls within the acceptance range of 80.00–125.00% for ln-transformed pharmacokinetic parameter Cmax and AUC(0-t).
2. If within-reference intra-subject CV of ln-transformed Cmax and/or AUC(0-t) > 30% then Cmax and/or AUC(0-t) limit will be widened using scaled-average-bioequivalence. Under scaled-average-bioequivalence, [U,L] = exp [$\pm k \cdot s_{WR}$] where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and S_{WR} is the within-subject standard deviation of the ln transformed values of Cmax and/or AUC(0-t) of the reference study intervention.
3. If within-reference intra-subject CV of ln-transformed Cmax and/or AUC(0-t) ≥ 50% then Cmax and/or AUC(0-t) bioequivalence limits will be widened to a maximum of 69.84 – 143.19%.

   Bioequivalence of the test study intervention with that of the reference study intervention will be concluded for Cmax and/or AUC(0-t), if both of the following conditions are satisfied:

   - The 90% confidence interval for ln-transformed data of Cmax and/or AUC(0-t) falls within the newly widen range [U, L] = exp [$\pm k \cdot s_{WR}$], which is based upon the within-subject variability observed for Cmax.
   - The geometric least square mean ratio (GMR) of test to reference for Cmax and/or AUC(0-t) falls within the acceptance range of 80.00–125.00%.

Data of metabolite albendazole sulfoxide will be provided as supportive information only.

9.4.3. Secondary Endpoint(s)/Estimand(s) Analysis

Statistical analysis for secondary endpoints will include descriptive statistics for the following pharmacokinetic parameters:

Albendazole: AUC0-∞, Tmax, t1/2, λz and AUC_%Extrap_obs

Albendazole sulfoxide: AUC0-∞, AUC0-t, Cmax, Tmax, t1/2, λz and AUC_%Extrap_obs.

Descriptive statistics (N, n, arithmetic mean, 95% CI of arithmetic mean, SD, median, minimum, maximum and geometric mean with 95% CI) will be presented for untransformed secondary PK parameters.

Average values of Test Study Intervention-T and Reference Study Intervention-R for PK parameters for each participant will be calculated and reported. Descriptive statistics will be calculated and reported for the same data.

Individual values of PK parameters for Test Study Intervention-T (first administration), Test Study Intervention-T (second administration), Reference Study Intervention-R (first administration) and Reference Study Intervention-R (second administration) for each participant will be calculated and reported. Descriptive statistics will be calculated and reported for the same data.

In case of treatment discontinuation due to any reason, only the data available before the occurrence of intercurrent event will be used to estimate secondary PK parameters using while-on-treatment policy strategy.

If any participant experience emesis/vomiting or if a prohibited/rescue medication is used by any participant, the participant's data for that period will not be used for the analysis of secondary endpoints related to PK using hypothetical strategy.

Treatment policy strategy will be used to analyze the secondary endpoints related to safety to make use of all available data for a participant.

9.4.4. Safety Analysis

Safety data will be presented in tabular and/or listing format and summarized descriptively.

Number and percentage will be presented for incidence of AE.

Descriptive statistics (N, n, mean, SD, median, minimum and maximum) will be presented for absolute and change from baseline values of vital signs parameters at each timepoint.

Comprehensive description for statistical analyses of safety endpoints will be described in the SAP.

9.5. Interim analyses

Not Applicable

9.6. Sample size determination

Based on the WHO guideline for albendazole, the maximum intra-subject variability observed for primary pharmacokinetic parameters Cmax and AUC(0-t) could be up to ~

68% and 62% respectively. For this sample size calculation, a product difference of up to 10% (i.e. T/R ratio as 90.0-111.1%) has been assumed.

The sample size was determined using R software considering the following assumptions:

a. T/R ratio = 90.0-111.1%
b. Intra-Subject CV (%) ~ 68% (Cmax) and 62% (AUC(0-t)), or 48% (both)
c. Significance Level = 5%

Correlation between Cmax and AUC(0-t) was calculated to be very high, based on an in-house albendazole study (GSK study O7921353). The exact Cmax and AUC(0-t) covariance matrix was calculated from this historical study (Table 10) and used to simulate realistic Cmax and AUC(0-t) values based on multivariate normal distributions. These values were then used to perform joint power calculation on the basis of inclusion of 70 participants with varying levels of missing data. To determine the power, success rates were based on 1000 replicates of the study design.

Table 10 Covariance matrix used for Cmax and AUC(0-t) in power calculations

	AUC(0-t)	Cmax
AUC_{0-t}	0.814	0.685
Cmax	0.685	0.747

Table 11 Joint power calculation results (N=1000) across various scenarios of missing data

Scenario	Joint Power (CV% = 48% for both Cmax and AUC(0-t))	Joint Power (CV% = 68% and 62% for AUC(0-t) and Cmax respectively)
48 participants have complete data for Cmax and AUC(0-t) for all 4 periods and 22 Participants data is completely missing	90.3%	93.7%
48 participants have complete data for Cmax and AUC(0-t) for all 4 periods, 10 participants have 2 period data and 12 participants data is completely missing	93.4%	95.8%
48 participants have complete data for Cmax and AUC(0-t) for all 4	91.5%	94.9%

periods, 6 participants have data for 2 periods and 16 remaining participants have no data at all		

Based on these results, and the aforementioned covariance matrix, at least 48 participants would be required to power a study to 90% to establish bioequivalence under the assumptions highlighted above. Based on experience, ~30% dropouts and/or withdrawals (due to unavoidable reasons like medical ground, adverse events, own accord, etc.) should be considered, requiring a target inclusion of 70 participants for this study. In-house data showed the variance of Cmax and AUC to be closer to 48%, implying that the above sample size calculation takes into account the worst-case scenario, and may in fact provide a power of >95%.

Sufficient number of volunteers will be asked to report on the day of check-in of period I in order to ensure that at least **70 participants** will be enrolled in the beginning of the study. Subsequent dropouts after dosing in period I will not be replaced.

Note: Additional participants if available, may be checked-in on the day of check in of period I to compensate for any dropout prior to dosing of period I. These participants will be dosed if there are dropouts prior to dosing in period I. If there are no dropouts, these participants will be checked-out without being dosed after completion of dosing in period I.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Clinical facility, Bioanalytical, Pharmacokinetic, Biostatistics and programming, Quality Assurance and Clinical laboratory Services:

Lambda Therapeutic Research Ltd.,

Lambda House, Plot No. 38, Survey No. 388,

Near Silver Oak Club, S. G. Highway, Gota,

Ahmedabad - 382481, Gujarat, India.

Tel. No.: +91-79-40202020

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10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (Brazil, October 2013) and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines: [ICH E6(R2) 'Guideline for Good Clinical Practice' (2016)]
  - Applicable laws and regulations including current version of the [New Drugs & Clinical Trial Rules, 2019 of CDSCO, Ministry of health and family welfare, Government of India], [Ethical guidelines for biomedical research on human participants, ICMR ((2017)]
- Any significant change in the study procedure or study design will only be effected upon mutual agreement between the Sponsor and Lambda, and after obtaining a favorable opinion from the Ethics Committee.
- All such changes will be documented in the amended version of the protocol and a summary of changes with reference to the previous version will be generated. The protocol amendments, ICF and other relevant documents must be submitted to an IRB/IEC as soon as possible by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- In cases where there is an immediate safety hazard to the participants, the amended protocol will be effective immediately and approval of the IEC/IRB will be obtained as soon as possible.
- Protocols and amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- This Protocol and the corresponding ICF used to obtain consent of study participants will be reviewed by the IEC/ IRB and the study will commence only after a written approval is obtained from the IEC/ IRB.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Not Applicable.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits and information regarding the study intervention to the participants/ LAR(s) and answer all questions regarding the study at the time of ICF presentation. This will be done through an oral presentation regarding the purpose, procedures to be carried out, potential hazards and rights of the participants, in their local language. Participants will be encouraged to ask questions and clarify their doubts regarding any aspect of the study.
- Potential participants/ LAR(s) must be informed that their participation is voluntary. They or their LARs will be required to physically sign/ put a thumb impression on a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Participants will be required to sign / put a thumb impression on the informed consent form summarizing the discussion prior to check-in for the study. Signature of the LAR/Impartial witness (if applicable) will be taken on the informed consent form in case the Participant is not able to sign on the informed consent form. Participants who fail to understand the informed consent procedure and/or are unable to communicate with the study personnel will not be enrolled.
- The physical informed consent will be obtained before the participant gets enrolled in the study and the date of the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- The Participants will give their consent for participation in the trial by signing /putting a thumb impression on ICF, which will also be signed by the LAR/Impartial witness (if applicable) and Lambda's person conducting the ICF presentation, principal investigator or designate.
- A photocopy of ICF with the signature or thumb impression must be provided to the participant or their LAR, while the original will be retained at Lambda Therapeutic Research Ltd.

10.1.4. Recruitment strategy

Upon receiving of regulatory approval, ethics committee approval, study intervention availability at clinical site and tentative dates of clinical planning, our participant recruitment team will initiate calling the participants telephonically for screening to enroll enough participants in the study as per sample size defined in protocol.

10.1.5. Data protection

- Participants will be assigned a unique identifier by study personnel. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant/LAR must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant /LAR that their data will be used as described in the informed consent.
- The participant/LAR must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to

statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- eCRF will be designed as per Lambda in-house SOP IND/CDM/0001-X (Clinical Data Management involvement for in-house studies).
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the [state location(s)] to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the [monitoring plan] [contracts].
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the

written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source documents

- All clinical raw data generated during conduct of the study will be directly entered in the respective electronic source forms / eCRF. Electronic software (BizNET, IMPTrack etc.) will be used for capturing the data generated during conduct of the study as per in-house SOPs. The study specific activity such as study intervention administration, sample collection, meal distributions, vitals and clinical examination etc. will be directly entered into electronic source forms/eCRF. However, the activity like such as participant's consent, duty delegations records etc. will be available in paper copy (wet ink signature).
- All source data and transcribed data forms will be compiled by the study personnel assisting in the study and will be checked wherever applicable for completeness. Further, information of Type and location of data generated for study will be traceable from Trial Master File.
- All bio-analytical raw data of sample processing and associated data such as solution preparation, role allocation etc. will be directly entered in the respective source data forms. The data acquisition system software will be used for the quantitative determination and Biolyte software will be used for review of generated data as per in-house SOPs. All data related to the project will be in the custody of the designated study personnel until transferred to archives.
- Once the concentration data is received from bio-analytical department through Biolyte software, data will be combined with randomization schedule and actual sampling time point, as applicable. Handling of the concentration data and pharmacokinetic and statistical analysis will be done as per in-house SOPs. All pharmacokinetic and statistical analysis will be performed on network drive. Archival of the pharmacokinetic and statistical data will be done as per defined archival procedure.
- A paper source/forms (if required to be used due to temporary non-functioning of software or no provision to document in software) will be maintained and filed with project specific binders as per in-house SOPs.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF 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.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in

the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

The Lambda Therapeutic Research Ltd. for safety reasons and the sponsor reserves the right to discontinue the study at any time. The sponsor and the IEC/ IRB will be immediately informed in case the study is terminated by Lambda. Reasons for this termination will be provided to the participants. The study may be terminated by the IEC\IRB if there are major violations of ethical considerations or due to any serious adverse event**.**

10.1.11. Publication policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical laboratory tests

Table 12 Protocol-required safety laboratory tests

PARAMETERS		Visits*			
Hematology		1	2	3	4
1	Hemoglobin [Hb]	X			X
2	RBC count	X			X
3	HCT	X			X
4	MCV	X			X
5	MCH	X			X
6	MCHC	X			X
7	RDW CV	X			X
8	Platelet count	X			X
9	WBC (total)	X			X
10	Neutrophils %	X			X
11	Lymphocytes %	X			X
12	Eosinophils %	X			X
13	Monocytes %	X			X
14	Basophils %	X			X
15	Neutrophils abs	X			X
16	Eosinophils abs	X			X

Urine Parameters				**1**	**2**	**3**	**4**
1	Specific Gravity	6	pH	X			
2	Leucocytes	7	Protein	X			

PARAMETERS		Visits*			
Biochemistry		**1**	**2**	**3**	**4**
1	Random Glucose	X			
2	Bilirubin Total	X		X	X
3	Total Protein	X			X
4	Albumin	X			X
5	Serum Globulin	X			X
6	A/G ratio	X			X
7	SGOT (AST)	X		X	X
8	SGPT (ALT)	X		X	X
9	Creatinine	X			X
10	Blood Urea Nitrogen	X			X
11	Sodium	X			
12	Potassium	X			
13	Chloride	X			
14	Alkaline phosphatase	X			

Microbiology & Serology		**1**	**2**	**3**	**4**
1	HIV AB (1 & 2)	X			
2	Anti HCV	X			
3	HBsAg	X			

3	Bilirubin	8	Ketones	X			
4	Urobilinogen	9	Glucose	X			
5	Erythrocytes	10	Nitrite	X			
11	Microscopic examination#			X			

Drug of abuse/alcohol test		**1**	**2**	**3**	**4**
1	Drugs of abuse in urine+	X	X		
2	Breath alcohol test	X	X		

Hormonal Assay		**1**	**2**	**3**	**4**
1	β-HCG (For females)	X	X		X

***Visits**: **1)** Screening | **2)** Prior to check-in of each period | **3)** Prior to check-in period II, III and IV | **4)** End Study (at the time of check-out of period IV).

As applicable

+ Morphine, Cannabinoids, Amphetamines, Barbiturates, Benzodiazepines, Cocaine

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • 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 intervention.

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 signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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. • Significant failure of an expected pharmacologic or biological action. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).
- 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. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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 AE. 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.

d. 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e.	**Is a congenital anomaly/birth defect in the offspring of a study participant**
f.	**Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, ectopic pregnancy)**

10.3.3. Definition of CV events

Not Applicable

10.3.4. Definition of TEAE

Not Applicable

10.3.5. Recording, assessment and follow-up of AE, SAE and pregnancies

10.3.5.1. AE and SAE recording

The following will be recorded during the conduct of the study:

a) Clinical Examination and recording of vital signs at regular intervals.

b) Concomitant therapy.

c) Adverse event monitoring and reporting.

Handling of adverse events:

Participants will be monitored throughout the study period for adverse events. Participants will be instructed to bring to the notice of the nurse or the doctor or study personnel (e.g. Custodian), any adverse event that may occur during their stay at the clinical facility.

Participants will also be specifically asked about any adverse events throughout the study period during the recording of vital signs. A physician will be available round the clock during the time of Participants stay/housing at the clinical facility. All adverse events will be treated by the attending physician at the clinical facility, or in a nearby reputed hospital. All adverse events will be followed up wherever possible until resolution or until the investigator believes there will be no further change. This may involve additional visits.

All adverse events, including both observed or voluntarily reported problems; complaints, signs or symptoms occurring after the first dose administration shall be recorded on the relevant page "Adverse Event/Medical Event Record Form" of eCRF irrespective of its association with the ongoing study medication. Prior to first dose administration in each participant, the event will be considered as a medical event and the aforementioned form will be completed by encircling “Medical Event” in the title.

Each adverse event shall be evaluated for duration, severity, seriousness and unexpectedness, action taken, date and time of resolution and association with the study treatment. The study may be suspended or terminated depending on the seriousness of the adverse events.

The IEC/IRB, regulatory bodies and the Sponsor shall be informed regarding the same as per local regulatory requirements.

Handling of Serious Adverse Event:

In case of Serious Adverse Events, the Sponsor or Sponsor's representative, licensing authority and IEC/IRB will be informed by any available mode of communication within 24 hours of their occurrence or as soon as the initial treatment is provided. In case, the Investigator fails to report any serious adverse event within the stipulated period, they shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event. The report of serious adverse event, after due analysis shall be forwarded by principal investigator to sponsor, Licensing Authority, as referred in as referred in clause (ix)-Section 35 of Part-B of Chapter-V of New Drugs & Clinical Trial Rules, 2019, Chairman of IEC/IRB (and the Head of the institution where the trial has been conducted, if applicable) within fourteen days of the occurrence of the serious adverse event.

10.3.5.2. Assessment of intensity

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

- **Mild:**
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:**
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:**
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.5.3. Assessment of causality

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e.

	an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
Unrelated	• The adverse event is clearly NOT related to the investigational medicinal product • A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

10.3.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious AEs recorded during the study as:

- Recovered/resolved

- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.5.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

After the initial AE/SAE /pregnancy] or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until 12 months after end of the studyor until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 12 months after the end of the study or until the participant is lost to follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

10.3.5.6. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.5.7. Reporting of SAEs and pregnancies

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

SAE Reporting to Sponsor via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- **Premenarchal: Tanner stage 1 (prepubertal)**

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Not Applicable

10.5. Appendix 5: Liver safety: suggested actions and follow-up assessments

Laboratory assessment for liver function test will be performed at the time of screening and prior to check-in of period II, III and IV.

10.6. Appendix 6: Clinically acceptable values

Parameters	Male	Female	Unit
HEMATOLOGY			
Hemoglobin (Hb)	≥ 12.5 to ≤16.5	≥ 11.5 to ≤14.7	g/dL
RBC Count	≥ 4.1 X 10^6 to ≤ 6.3 X 10^6	≥ 3.6X 10^6 to ≤ 5.5 X 10^6	/ µL
HCT	≥ 37 to ≤ 52	≥ 32 to ≤ 48	%
MCV	68 - 111	61 - 115	fL
MCH	20 - 40	19 - 40	pg
MCHC	27 - 40	27 - 40	g/dL
RDW CV	09 - 22	09 - 23	%
Platelet Count	≥ 150 X 10^3	≥ 150 X 10^3	/ µL
WBC (Total)	4.2 - 11.5 X 10^3	4.2 - 11.5 X 10^3	/ µL
Neutrophils%	30 - 90	30 - 90	%
Neutrophils (abs)	1.5 - 9	1.5 - 9	10^3 / µL
Lymphocytes%	12 - 50	12 - 50	%
Eosinophils%	0 - 18	0 - 18	%
Eosinophils (abs)	0.015 – 1.8	0.015 – 1.8	10^3 / µL
Monocytes %	01 - 13	01 - 13	%
Basophils %	0 - 03	0 - 03	%

Parameters	Male	Female	Unit
BIOCHEMISTRY			
Random Glucose	≤ 200	≤200	mg/dL
Bilirubin Total	≤ 1.5 mg/dL	≤ 1.5 mg/dL	mg/dL
Total Protein	6.2 - 9.5	6.2 - 9.5	g/dL
Albumin	3.4 - 5.8	3.4 - 5.8	g/dL
Globulin	2.2 - 4.8	2.2 - 4.8	g/dL
A/G ratio	1.0 - 2.5	1.0 - 2.5	
SGOT (AST)	≤ 73.0	≤ 46.0	U/L
SGPT (ALT)	≤ 82.0	≤ 56.0	U/L
Creatinine	≤ 1.1 mg/dL	≤ 0.9 mg/dL	mg/dL
Blood Urea	≤ 40	≤ 40	mg/dL
Sodium	129 - 150	129 - 150	mmol/L
Potassium	3.5 - 5.7	3.5 - 5.7	mmol/L
Chloride	92 - 113	92 - 113	mmol/L
Alkaline Phosphatase	< 1.5 times upper limit of normal	< 1.5 times upper limit of normal	U/L
Blood Urea Nitrogen	≤ 22	≤ 22	mg/dL
URINE ANALYSIS			
Specific Gravity	01 - 1.03	01 - 1.03	

Parameters	Male	Female	Unit
PH	4.5 - 08	4.5 - 08	
Glucose	Absent	Absent	
Protein	Absent	Absent	
Bilirubin	Absent	Absent	
Ketones	Absent	Absent	
Urobilinogen	Absent	Absent	
Erythrocytes	Up to 2+	Up to 3+	
Leucocytes	Up to 2+	Up to 3+	
Nitrite	Absent	Absent	
Epithelial	Occasional	Occasional	/ HPF
Pus Cells	Up to 8	Up to 10	/ HPF
Red Cells	Up to 8	Up to 10	/ HPF
Cast	Absent	Absent	
Crystal	Absent	Absent	
Trichomonas	Absent	Absent	
Yeast	Absent	Absent	
Bacteria	Absent	Absent	
Amorphous	Absent	Absent	

10.7. Appendix 7: High fat high calorie vegetarian breakfast menu

Food Items	***Servings***	***Ingredients***	***Qty. Of Ingredients***	**Calorie** (Kcal)	**CHO** (gms)	**Fats** (gms)	**Proteins** (gms)
Toast	1 no	Bread	1 Slice	61.25	12.98	0.18	1.95
		Butter	10 gms	72.90	0.00	8.10	0.00
*Chana Chat	60 gms	Chana	20 gms	72.00	12.18	1.06	3.42
		Onions	5 gms	2.95	0.63	0.01	0.09
		Peanuts	10 gms	56.7	2.61	4.01	2.53
		Oil	2 ml	18.00	0.00	2.00	0.00
Vegetable Cutlets (Approx 130 gms)	1 serving / 2 nos	Potatoes	50 gms	48.50	11.30	0.05	0.80
		Cheese	40 gms	139.20	2.52	10.04	9.64
		Onions	5 gms	2.95	0.63	0.01	0.09
		Bread	¼ Slice	15.31	3.24	0.04	0.49
		Oil	10 ml	90.00	0.00	10.00	0.00
		Paneer	50 gms	146.00	3.95	11.50	6.70
Milk	1 serving	Milk	200 ml	192.00	10.00	13.00	8.60
		Sugar	5 gms	19.90	4.97	0.00	0.01
TOTAL				**937.66**	**65.01**	**60.00**	**34.32**
NUTRIENT CALORIES					**260.04**	**540.00**	**137.28**
NUTRIENT CALORIES AS % TOTAL					**27.73 %**	**57.59 %**	**14.64%**

*Soaked and boiled Chana will be 40 gms, Soaked and boiled Peanuts will be 15 gms.

Salt, Black pepper, Chat Masala, Green Chillies, Coriander and Tomato Ketchup may be as taste enhancers

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