TITLE PAGE

Protocol Title: An open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions.

Protocol Number: 212504

Compound Number or Name: CCI44

Study Phase: Phase 1

Short Title: BE study of Test Griseofulvin 500mg tablets versus reference and Dose Proportionality Study of test Griseofulvin 250mg and 500mg tablets under fed conditions.

Sponsor Name and Legal Registered Address:

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Manufacturer:

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Regulatory Agency Identifying Number(s): Not Applicable

Approval Date: 11-DEC-2019

SPONSOR SIGNATORY:

I, on behalf of **GlaxoSmithKline Pharmaceuticals limited.** have read, understood and approved this protocol. I hereby give our consent to conduct the study in accordance with this protocol. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the current version of the Declaration of Helsinki, the current ICH GCP, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) and CDSCO Bioequivalence study guidelines as well as relevant National Laws and Regulations.

PPD

11th Dec 2019

Sponsor's Authorized Signatory
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Date

PPD

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions.

Short Title: BE study of Test Griseofulvin 500mg tablets versus reference and Dose Proportionality Study of test Griseofulvin 250mg and 500mg tablets under fed conditions.

Rationale:

Griseofulvin is an antifungal agent used in treatment of Dermatophytosis (ringworm) caused by Microsporum spp., Trichophyton spp., Epidermophyton spp., where topical therapy is considered inappropriate or has failed[11].

Approved dose of Griseofulvin in Adults (greater than or equal to 50 kg) is 500 to 1,000 mg daily, but not less than 10 mg/kg bodyweight daily. A single daily dose is often satisfactory, but divided doses may be more effective in patients who respond poorly.

Griseofulvin is recommended 500 mg twice a day dose to manage the dermatophytosis in the current scenario[10]. Griseofulvin 1000 mg/ day dose is needed for the treatment of infections that are more difficult to eradicate, such as tinea pedis. Hence, Griseofulvin 500 mg tablet twice a day dose will be useful for patients requiring 1000 mg daily dose[12].

As mentioned above, in the current scenario, Griseofulvin 1000 mg/ day dose is needed for managing infections which are difficult to treat. Poor compliance being the major factor for increasing menace of dermatophytosis in India, It is important to have a formulation (500 mg) which can be used to overcome this challenge.

Griseofulvin 500: It is decided to launch Griseofulvin 500 mg SKU in India to manage patients with Dermatophytosis. As per the WHO guidance the Griseofulvin is Biopharmaceutical Classification System (BCS) Class 2 (“low” solubility” – “high” permeability) and not eligible for Biowaiver. Griseofulvin is single market product (formerly POLO- Product of Local Opportunity) in India. Hence BA/BE study will be conducted in India to estimate *in vivo* behavior (Pharmacokinetic characteristics) of Griseofulvin 500.

Griseofulvin 250: State regulatory authority in India has requested to submit the BE data for approval of the new Griseofulvin 250 mg formulation. In view of the same, Griseofulvin 250 mg tablet is added as an additional arm for the planned GRISEOFULVIN 500 BE study. Since the reference product (Comparator product) for GRISOVIN 250 mg is not available, dose proportionality study is planned. The dose proportionality study involving administration of only one tablet of each formulation is expected to overcome the problem of multiple peaks and incorrect AUC observed after

administration of two 250 mg tablets of the test product to match the dose of 500 mg tablet of the comparator product.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To determine whether the **Test Product (T1):** Griseofulvin Tablets, 500 mg is bioequivalent to **Reference Product (R):** Griseofulvin Tablets, 500 mg (Grisovin) in healthy participants. • To evaluate the dose proportionality across the dose range of 250 mg to 500 mg after single dose administration of **Test Product (T2):** Griseofulvin Tablets, 250 mg and **Test Product (T1):** Griseofulvin Tablets, 500 mg in healthy participants.	• C_{max}, AUC_{0-t} and AUC_{0-inf} for griseofulvin • AUC_{0-t} and C_{max}
Secondary	Secondary
• To monitor the safety and tolerability of a single oral dose of **Test Product (T1):** Griseofulvin Tablets, 500 mg; **Test Product (T2):** Griseofulvin Tablets, 250 mg and **Reference Product (R):** Griseofulvin Tablets, 500 mg (Grisovin).	• Safety and tolerability as measured by adverse events, vital signs and clinical laboratory measurements.

Overall Design:

This is an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions. This study includes a screening period (within 21 days prior to dosing of period-I) and three open-label treatment periods. Participants will be followed up 5 days after last dosing.

The whole study will be divided into three periods. For each period, eligible participants will be randomized to either T1T2R, T2RT1 or RT1T2 treatment sequence according to 1:1:1 ratio.

Disclosure Statement: This is an open label study with 3 periods and only the bio-analytical investigator will be blinded to the treatments administered to the subjects.

Number of Participants:

A maximum of 36 participants will be randomly enrolled to study treatment such that approximately 27 evaluable participants complete the study.

Treatment Groups and Duration:

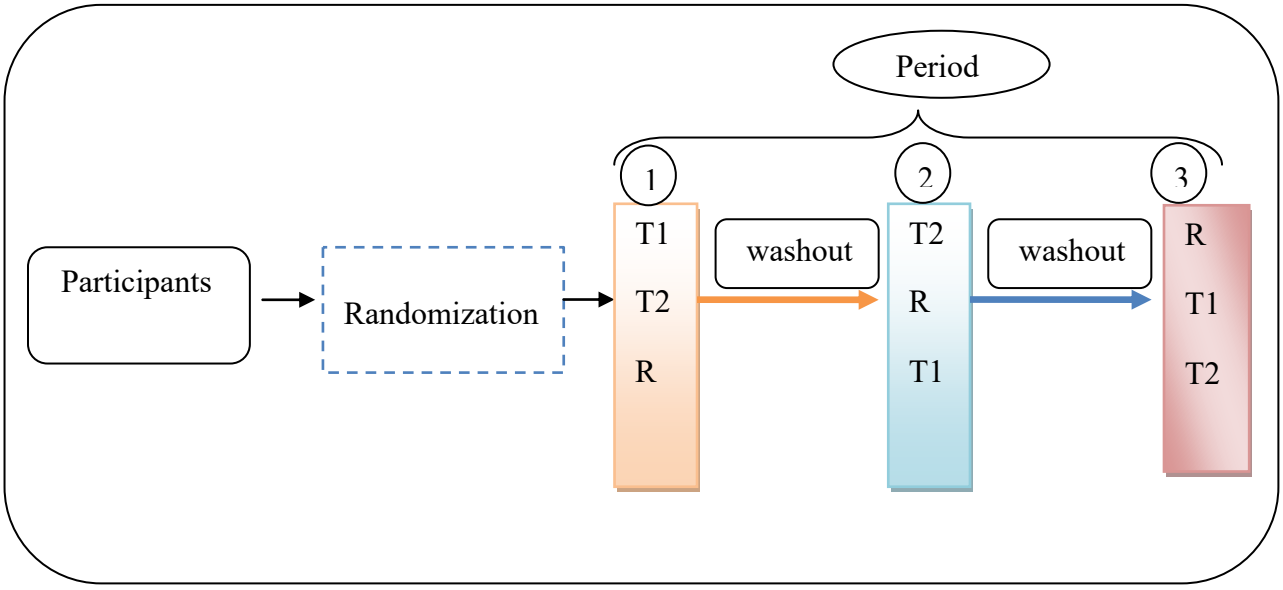
Excluding screening period, the duration of clinical phase will be approximately 20 days from Day-1 to Day 19 including a washout period of at least 7 days (not more than 14 days) for each study period.

The participants will be housed from at least 10.50 hrs before dosing until 24.00 hrs post dose in the centre for each study period. Activities beyond 24.00 hrs will be conducted on ambulatory basis.

In each period, single oral dose [Test Product (T1): 1 x 500 mg Tablet or Test Product (T2): 1 x 250 mg Tablet or Reference Product (R): 1 x 500 mg Tablet] of the study treatments will be administered to the participants as per randomization with 240 ± 2 mL of water at ambient temperature under fed condition.

Data Monitoring or Other Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

Procedure	Screening (within 21 days prior to dosing of period-I)	First Period						Washout [at least 7 days (not more than 14 days) between subsequent dosing] Day 6
		Check-in Day -1	Dosing day Day 1	Checkout day Day 2	Ambulatory sample visit			
					Day 3	Day 4	Day 5	
Issue of Participant informed consent form	**X**							
Breath Alcohol test [a, c]	**X**	**X**			**X**	**X**	**X**	
Questionnaire about smoking [c]		**X**			**X**	**X**	**X**	
Weight [a]	**X**							
Height [a]	**X**							
Medical / clinical history [a]	**X**	**X**						
Vital Signs measurement [a, b, i]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Physical examination [a, b, i]	**X**	**X**		**X**				

12 Lead ECG [a]	**X**							
Serology [a]	**X**							
Haematology [a, i]	**X**							
Biochemistry [a, i]	**X**							
ALT (Alanine transaminase) test [e]		**X**						
Urinalysis [a, i]	**X**							
Serum pregnancy test for female [e]		**X**						
Urine examination for drugs of abuse [h]		**X**						
Admit to Clinical Research Center		**X**						
Meals [d]		**X**	**X**					
Study medication administration [f]			**X**					
PK Samples [g]			**X**	**X**	**X**	**X**	**X**	
Concomitant medication	→							
AE		→						
SAE		→						

Procedure	Second Period						Washout [at least 7 days (not more than 14 days) between subsequent dosing] Day 13
	Check-in Day 7	Dosing day Day 8	Checkout day Day 9	Ambulatory sample visit			
				Day 10	Day 11	Day 12	
Issue of Participant informed consent form							
Breath Alcohol test [a, c]	X			X	X	X	
Questionnaire about smoking [c]	X			X	X	X	
Weight [a]							
Height [a]							
Medical / clinical history [a]	X						
Vital Signs measurement [a, b, i]	X	X	X	X	X	X	
Physical examination [a, b, i]	X		X				

12 Lead ECG [a]							
Serology [a]							
Haematology [a, i]							
Biochemistry [a, i]							
ALT test [e]	**X**						
Urinalysis [a, i]							
Serum pregnancy test for female [e]	**X**						
Urine examination for drugs of abuse [h]	**X**						
Admit to Clinical Research Center	**X**						
Meals [d]	**X**	**X**					
Study medication administration [f]		**X**					
PK Samples [g]		**X**	**X**	**X**	**X**	**X**	
Concomitant medication	→						
AE	→						
SAE	→						

Procedure	Third Period						Post Study (Day 19) OR Early Discontinuation of Participant [M]
	Check-in Day 14	Dosing day Day 15	Checkout day Day 16	Ambulatory sample visit			
				Day 17	Day 18	Day 19	
Issue of Participant informed consent form							
Breath Alcohol test [a, c]	X			X	X	X	
Questionnaire about smoking [c]	X			X	X	X	
Weight [a]							
Height [a]							
Medical / clinical history [a]	X						
Vital Signs measurement measurement [a, b, i]	X	X	X	X	X	X	X
Physical examination measurement [a, b, i]	X		X				X

12 Lead ECG [a]							
Serology [a]							
Haematology [a, i]							**X**
Biochemistry [a, i]							**X**
ALT test [e]	**X**						
Urinalysis [a, i]							**X**
Serum pregnancy test for female [e]	**X**						**X**
Urine examination for drugs of abuse [h]	**X**						
Admit to Clinical Research Center	**X**						
Meals [d]	**X**	**X**					
Study medication administration [f]		**X**					
PK Samples [g]		**X**	**X**	**X**	**X**	**X**	
Concomitant medication	→						
AE	→						
SAE	→						

Note: Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or medical officer at any time during the course of study.

a. Breath alcohol test, demographic data (Weight, Height and BMI), medical / clinical history, physical examination including vital signs, 12-lead Electrocardiogram (ECG), Haematology, biochemistry, serology (HIV, Hepatitis B and C) and urinalysis will be performed at screening.

b. Physical examination and vital signs examination (blood pressure, pulse rate, respiration rate and body temperature) will be done at check-in and check-out of each study period.

Physical examination and vital examination can be started approximately 02.00 hours prior to the scheduled time in each study period.

Intravenous cannula site will be observed by principal investigator/co-investigator /Sub-investigator /medical officer for any swelling or thrombophlebitis.

Measurement of Vital signs (blood pressure, pulse rate, respiration rate and body temperature) will be done at pre-dose and at 01.00, 03.00, 05.00, 08.00hrs ± 45 minutes of scheduled time in each study period and at each ambulatory visits.

c. Breath alcohol test and questionnaire about smoking (history of smoking) will be carried out before check-in and before each ambulatory blood sample collection for each study period.

d.
- Standardized meal will be given during check-in night. The check-in night dinner will be served in a way to maintain at least 10.00 hours fasting before receiving high-fat and high-calories breakfast.
- On dosing day, standardized high-fat and high-calories breakfast will be given 30 minutes prior to drug administration. Participants should eat the high-fat and high-calorie breakfast completely within 25 minutes.
- Participants will be given standardized meal at around 04.00, 09.00 and 13.00 hours post-dose.

e. For all participants, ALT will be done before check-in for each study period. For female participants, serum pregnancy test (Serum (β) Beta- hCG) will be done before check-in for each study period.

f. Single oral dose of the either of two test product or reference product will be administered as per randomization with 240 ± 2 mL of water at ambient temperature under fed condition.

g. Total number of blood samples (5 mL per sample): 22 per period.
Sampling times: Pre-dose (collected within 01.00 hour prior to dosing) and at 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 10.00, 12.00, 24.00, 48.00, 72.00 and 96.00 hours post dose. The detailed description on blood sample collection is provided in section 8.5 Pharmacokinetics.
Blood samples will be collected in Na-Heparin Vacutainer.

Blood samples after 24.00 hours will be collected on ambulatory basis.

h. Urine examination for drugs of abuse test will be done on check-in Day for each study period.

i. Physical examination, measurement of blood pressure, pulse rate, respiration rate and body temperature, serum pregnancy test (Serum (β) Beta- hCG) (for female participants), Haematology, biochemistry and urinalysis will done at post study or on early discontinuation of participant.

√ indicates the occurrence, * indicates day starts from post-dose.

2. INTRODUCTION

2.1. Study Rationale

This is an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions.

GSK will manufacture new GRISOVIN 500mg as well as 250mg products with SLS enhanced new formulations for better absorption. In the view of same, a three-period cross-over design was selected so that within participant comparisons can be utilized. Three-way crossover study with Test GRISOVIN 250 mg, GRISOVIN 500 mg and Reference GRISOVIN 500 (ASPEN) is selected along with Dose normalization – where GRISOVIN 250 mg single dose is given and the results are multiplied by 2.

The Pharmacokinetic (PK) sampling and washout period are designed to ensure that PK parameters are well-estimated and pre-dose concentrations are completely negligible in subsequent periods.

Sampling time points were decided based on the pharmacokinetic parameters of Griseofulvin in past successful global BE study [15], the pharmacokinetic data available in SPC[6] and previously conducted studies by Accutest. The last sampling time point was selected as 96 hours (> 3 half-lives) considering the elimination half-life of around 9.5 hrs – 21 hours. The study is planned in fed condition as the SPC[6, 15] of griseofulvin recommends it‟s intake with food.

2.2. Background

Griseofulvin is an antifungal antibiotic which is active *in vitro* against common dermatophytes. It exerts its antifungal effect by disrupting the cell division spindle apparatus of fungal cells, thereby arresting cell division.

When griseofulvin is given orally for systemic treatment of fungal infections, it enables newly-formed keratin of the skin, hair and nails to resist attack by the fungi. As the new keratin extends, the old infected keratin is shed. Griseofulvin is effective against the dermatophytes causing ringworm (tinea), including: *Microsporumcanis, T. verrucosum, T. mentagrophytes, E. floccosum and T. rubrum*[11]

Griseofulvin is not effective in infections caused by *Candida albicans* (monilia), *aspergilli, Malassezia furfur* (*Pityriasis versicolor*) and *Nocardia* species[11]

After oral dosing there is a phase of rapid absorption followed by slower prolonged absorption. Peak plasma levels (0.5 to 1.5 micrograms after a 500 mg oral dose) are achieved by 4 h and are maintained for 10 to 20 h. The absorption of griseofulvin from the gastrointestinal tract is variable and incomplete. On average, less than 50% of the oral

dose is absorbed, but fatty foods and a reduction in particle size will increase the rate and extent of the absorption[11]

In plasma griseofulvin is approximately 84% bound to plasma proteins, predominantly albumin. There is selective deposition of griseofulvin in newly-formed keratin of hair, nails and skin, which gradually moves to the surface of these appendages. 6-desmethylgriseofulvin or its glucuronide conjugate are metabolites of griseofulvin. The absorbed griseofulvin is excreted in the urine mainly as 6-desmethylgriseofulvin or its glucuronide conjugate. The terminal plasma half-life ranges from 9.5 to 21 h, there being considerable intersubject variability[11]

As per the WHO guidance[16] the Griseofulvin is Biopharmaceutical Classification System (BCS) Class 2 ("low" solubility" – "high" permeability) and not eligible for Biowaiver. Griseofulvin is single market product (formerly POLO- Product of Local Opportunity) in India. Hence BA/BE study will be conducted in India to estimate *in vivo* behavior (Pharmacokinetic characteristics) of new Griseofulvin 500 tablet compared to the current Griseofulvin 500mg. It is micronized formulation. Since there are no reference Griseofulvin 250mg tablets available, a dose proportionality comparison will be made between the new Griseofulvin 250mg and the new Griseofulvin 500mg tablet. As only a single 250mg tablet will be administered in this study, the PK parameters (AUC and C_{max}) for the Griseofulvin 250mg tablet will be multiplied by 2 prior to the statistical comparison to the Griseofulvin 500mg tablet.

2.3. Benefit/Risk Assessment

The benefit/risk assessment is positive because Griseofulvin is a marketed product approved in India by the DCGI, and by TGA in Australia, and MHRA in UK. The following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [Griseofulvin Tablets]		
Concurrent treatment with oral contraceptives	Concurrent treatment with griseofulvin may reduce the effectiveness of oral contraceptives, so additional non-hormonal contraceptive precautions should be taken during griseofulvin treatment and for a month after stopping griseofulvin.	As per inclusion criteria (Section 5.1), participants will be included if they agree to follow the contraceptive guidance described in Appendix 4.
Photosensitivity reaction	Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight.	As per the study requirement, participants will be housed in clinical facility up to 24.00 hours post dose and thereafter will be advised to avoid exposure to intense natural or artificial sunlight until completion of 5 days post last dose.
Allergic reaction	Hypersensitivity to any ingredient of the preparation	The participants will be closely monitored by medical personnel for occurrence of any allergic reaction. Appropriate medication required to treat allergic reaction will be kept ready.

Carcinogenicity and Mutagenicity	Long-term administration of griseofulvin with food has been reported to induce hepatomas in mice and thyroid tumours in rats but not in hamsters. The clinical significance of these findings in man is not known. In view of these data, griseofulvin should not be used prophylactically. [7] Griseofulvin was mentioned in the report of a cohort study designed to screen 215 drugs for carcinogenicity. Although an excess of thyroid cancer was reported among users of griseofulvin in a 9-year follow-up, no results for this drug were reported in a 15-year follow-up, implying that no significant association was observed for cancer. [17]	Being a single dose study this risk can be considered as negligible.
Use in Pregnancy (Category B3)	Griseofulvin is contraindicated in pregnancy and in women intending to become pregnant within one month following cessation of treatment. Griseofulvin is teratogenic in animals and some case reports suggest that it produces human foetal abnormalities. As griseofulvin is capable of inducing aneuploidy (abnormal segregation of chromosomes following cell division) in mammalian cells exposed to the compound *in vitro* and *in vivo*, women should not take the drug during pregnancy or become pregnant within one month following cessation of treatment.	As per inclusion criteria (Section 5.1), female participant is eligible to participate only if she is not pregnant and intending to become pregnant or breastfeeding and agreeing to use effective contraceptive measures as stated in Appendix 4 during the period of study and for at least 1 month after the last dose of study treatment.

Use in Men	Griseofulvin is capable of inducing aneuploidy (abnormal segregation of chromosomes following cell division) in mammalian cells exposed to the compound *in vitro*. In the absence of the relevant *in vivo* data, it is prudent to warn men that they should not father children within six months of treatment.	Male participants are eligible to participate if they agree to follow the instructions mentioned in point no. 9 of section 5.1 Inclusion Criteria during the treatment period and for at least six months after the last dose of study treatment.

Interaction with Other Drugs	Barbiturates may reduce the effectiveness of griseofulvin by interference with the gastrointestinal absorption of griseofulvin. The concurrent use of substances such as phenylbutazone and sedative and hypnotic drugs which induce metabolizing enzymes should be avoided as the blood level, and hence efficacy, of griseofulvin may be reduced. Griseofulvin may decrease the response to coumarin anticoagulants administered concomitantly. Dosage adjustment of the anticoagulant may be required during therapy and after griseofulvin therapy. Patients should be warned that an enhancement of the effects of alcohol by griseofulvin has been reported.	This is a single dose study in healthy Participants where in Griseofulvin will be given for PK evaluation and not for efficacy evaluation. The Participants included in the study will already be free of prescription medications or over-the-counter (OTC) products (including vitamins and minerals) within 14 days prior to administration of study treatment. Moreover, participants taking enzyme modifying drugs will not be allowed to participate. All Participants will be advised not to take any medicine during the entire period of study to avoid PK interaction. As per inclusion criteria (Section 5.1), participants with no history of significant alcoholism will be included. Participation also requires the subject‟s willingness to abstaining from any alcoholic products from 48.00 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.

2.3.2. Benefit Assessment

Participants enrolled in the study will be healthy volunteers. There will be no direct benefits gained from the participation in this study. The participant"s involvement will be contributing towards the PK and safety analysis of test griseofulvin formulations versus reference.

2.3.3. Overall Benefit: Risk Conclusion

Griseofulvin has a well-characterised safety profile since it is an approved product, been marketed for many years for chronic use. Taking into account the measures taken to minimized risk to participants participating in this study, the potential risks identified in association with the Griseofulvin Tablets are justified by the anticipated benefits that may be afforded to patients for the treatment of fungal infections.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To determine whether the **Test Product (T1):** Griseofulvin Tablets, 500 mg is bioequivalent to **Reference Product (R):** Griseofulvin Tablets, 500 mg (Grisovin) in healthy participants. • To evaluate the dose proportionality across the dose range of 250 mg to 500 mg after single dose administration of **Test Product (T2):** Griseofulvin Tablets, 250 mg and **Test Product (T1):** Griseofulvin Tablets, 500 mg in healthy participants.	• C_{max}, AUC_{0-t} and AUC_{0-inf} for griseofulvin • AUC_{0-t} and C_{max}
Secondary	Secondary
• To monitor the safety and tolerability of a single oral dose of **Test Product (T1):** Griseofulvin Tablets, 500 mg; **Test Product (T2):** Griseofulvin Tablets, 250 mg and **Reference Product (R):** Griseofulvin Tablets, 500 mg (Grisovin).	• Safety and tolerability as measured by adverse events, vital signs and clinical laboratory measurements.

4. STUDY DESIGN

4.1. Overall Design

This is an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions. This study includes a screening period (within 21 days prior to dosing of period-I) and three open-label treatment periods. Participants will be followed up 5 days after last dosing.

The whole study will be divided into three periods. For each period, eligible participants will be randomized to either T1T2R, T2RT1 or RT1T2 treatment sequence according to 1:1:1 ratio.

On Day -1
After obtaining the Informed Consent Form signed by the participants, they will be verified against the inclusion and exclusion criteria to confirm his/her eligibility to participate in the study.

Participants will be admitted into the clinical facility to complete vital signs, physical examination; eligibility for enrolment will be confirmed; and the participant‟s concomitant therapies and adverse reactions information will also be collected and recorded.

On Day 1, each enrolled participant will take a single oral dose of Test Product (T1): 1 x 500 mg Tablet or Test Product (T2): 1 x 250 mg Tablet or Reference Product (R): 1 x 500 mg Tablet once. Blood samples will be collected at a set of timepoints (refer to SoA) pre and post dosing from Day1 to Day 5 for determination of single-dose pharmacokinetics of Griseofulvin T1 or T2 or R.

Following a washout of at least 7 days (not more than 14 days), participants will be crossed over in Period 2 to receive the treatment according to the assigned sequence. They will be admitted into the clinical facility to complete physical examination and confirm eligibility again on Day 7. Eligible participants will take Test Product (T1): 1 x 500 mg Tablet or Test Product (T2): 1 x 250 mg Tablet or Reference Product (R): 1 x 500 mg Tablet once on Day 8 and blood samples will be collected at a set of timepoints (refer to SoA) pre and post dosing from Day 8 to Day 12.

Following a washout of at least 7 days (not more than 14 days), participants will be crossed over in Period 3 to receive the treatment according to the assigned sequence. They will be admitted into the clinical facility to complete physical examination and confirm eligibility again on Day 14. Eligible participants will take Test Product (T1): 1 x 500 mg Tablet or Test Product (T2): 1 x 250 mg Tablet or Reference Product (R): 1 x 500 mg Tablet once on Day 15 and blood samples will be collected at a set of time points (refer to SoA) pre and post dosing from Day15 to Day 19. Post study evaluation will be done at the time of collection of last PK sample in last study period.

The analyst from bioanalytical facility will be blinded to the sequence of administration of Test and Reference product to the individual participant.

Safety data collection includes physical examinations, laboratory tests, vital signs measurements and recording of adverse events. Other clinical assessments will also be performed as appropriate. Planned time points for all safety assessments are provided in the SoA.

Participants will complete follow-up 5 days after last dosing, and complete monitoring of any adverse events.

4.2. Scientific Rationale for Study Design

This is an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate the bioequivalence of test Griseofulvin tablets, 500 mg versus reference Griseofulvin tablets, 500 mg as well as dose proportionality of test Griseofulvin tablets, 250 mg and 500 mg, in healthy, adult participants under fed conditions.

GSK will manufacture new GRISOVIN 500mg as well as 250mg products with SLS enhanced new formulations for better absorption. In the view of same, a three-period cross-over design was selected so that within participant comparisons can be utilized. Three-way crossover study with Test GRISOVIN 250 mg, GRISOVIN 500 mg and Reference GRISOVIN 500 (ASPEN) is selected along with Dose normalization – where GRISOVIN 250 mg single dose is given and the results are multiplied by 2.

The Pharmacokinetic (PK) sampling and washout period are designed to ensure that PK parameters are well-estimated and pre-dose concentrations are completely negligible in subsequent periods.

Sampling time points were decided based on the pharmacokinetic parameters of Griseofulvin in past successful global BE study [15] and the pharmacokinetic data available in SPC[6]. The last sampling time point was selected as 96 hours (> 3 half-lives) considering the elimination half-life of around 9.5 hrs – 21 hours. The study is planned in fed condition as the SPC[6, 15] of griseofulvin recommends it‟s intake with food. BE study conforms to CDSCO and/or other global regulatory guidelines.

4.3. Justification for Dose

Griseofulvin is indicated in the treatment of fungal infections of the skin, scalp, hair or nails caused by *Microsporum spp*., *Trichophyton spp*., *Epidermophyton spp*., where topical therapy is considered inappropriate or has failed.

Approved dose of Griseofulvin in adults (greater than or equal to 50 kg) is 500 to 1,000 mg daily, but not less than 10 mg/kg bodyweight daily. A single daily dose is often satisfactory, but divided doses may be more effective in patients who respond poorly. Griseofulvin is recommended with 500 mg twice a day dose to manage the dermatophytosis in the current scenario. Griseofulvin 1000 mg/ day dose is needed for the treatment of infections that are more difficult to eradicate, such as tinea pedis. Hence,

Griseofulvin 500 mg tablet twice a day dose will be useful for patients requiring 1000 mg daily dose. The test product (T1) is a tablet containing 500 mg of Griseofulvin and it will be compared with the reference product (Griseofulvin 500 mg tablet) to demonstrate bio-equivalence. The safety of Griseofulvin Tablets, 500 mg when given as a single dose, in healthy volunteers is established through different studies. As per the literature[15] a single oral dose of 500 mg results in quantifiable levels of Griseofulvin.

The test product T2 containing Griseofulvin 250 mg is indicated in patients requiring 250 mg Griseofulvin tablet twice a day (500 mg daily dose). The present study involves administration of test product T2 containing 250 mg Griseofulvin to evaluate it‟s dose proportionality with 500 mg tablet.

Both 250mg and 500mg are approved doses in India, and Australia.

The dosing of each treatment will be done under fed condition based on the recommendation given in the SPC[6, 15] to take the drug after meal, to increase the rate and extent of absorption.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including post study evaluation.

The end of the study is defined as the date of last scheduled procedure shown in the Schedule of Activities.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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:

Age

1. Participant must be 18 to 45 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by the investigator or medically qualified designee on a medical evaluation including medical baseline history, physical

examination and vital sign examination (blood pressure, pulse rate, respiration rate and body temperature).

3. Participants with clinically acceptable findings as determined by haematology, biochemistry, urinalysis, 12 lead ECG.
4. Participant‟s willingness to follow the protocol requirements especially abstaining from xanthine containing food or beverages (chocolates, tea, coffee or cola drinks) or grapefruit or grapefruit juice, any alcoholic products, the use of cigarettes and the use of tobacco products from 48.00 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample and adherence to food, fluid and posture restrictions.
5. Participants with no history of significant alcoholism (Volunteers who do not have habit of heavy drinking which is defined as regular intake of more than 2 units of alcohol per day for male and 1 unit for female {I unit= 150 ml of wine or 360 ml of beer or 45ml of 40% of alcohol}).
6. Participants with no history of drug abuse (benzodiazepines and barbiturates) for the last one month and other illegal drugs *(Appendix 2)* for the last 06 months.
7. Participants who are non-smokers and ex-smokers will be included. “Ex-smokers are someone who completely stopped smoking for at least 3 months.”

Weight

8. Body mass index (BMI) within the range 18.5-30 kg/m^2 (inclusive) and weight ≥ 50 kg.

Sex

9. Healthy Male and non-pregnant female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the treatment period and for at least six months after the last dose of study treatment:

- Refrain from donating sperm as well as agree to use contraception/barrier as detailed below
    - Agree to use a male condom and should also be advised for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant and intending to become pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP)

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the treatment period and for at least 1 month after the last dose of study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
  - A WOCBP must have a negative highly sensitive [(Appendix 2)] pregnancy test (serum as required by local regulations) within 1 day before each dose of study treatment (The participant must be excluded from participation if the serum pregnancy result is positive).
- Additional requirements for pregnancy testing during and after study treatment are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Known history of hypersensitivity to Griseofulvin.
2. Participants who have taken prescription medications or over-the-counter products (including vitamins, minerals and/or herbal supplements) within 14 days prior to administration of IMP.
3. Any medical or surgical conditions, which might significantly interfere with the functioning of gastrointestinal tract, blood–forming organs etc.

4. History of cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic, haematological, gastrointestinal, endocrine, immunological or psychiatric diseases.
5. History of malignancy (including skin cancers) or other serious diseases.
6. History of porphyria.
7. Known history of SLE (Systemic lupus erythematosus) in the exclusion criteria.

Prior/Concomitant Therapy

8. Participants consuming aspirin, oral contraceptive pills, phenobarbital, and warfarin having potential to trigger drug interactions with griseofulvin for any ailment in the previous 28 days, prior to dosing day.

Prior/Concurrent Clinical Study Experience

9. Participation in a clinical drug study or bioequivalence study 90 days prior to period I dosing of the present study.

Diagnostic assessments

10. Participants with positive HIV tests, HBsAg or Hepatitis-C tests.
11. Found positive in breath alcohol test.
12. Found positive in urine test for drug abuse.

Other Exclusions

13. Blood donation 90 days prior to period I dosing of the present study.
14. History of problem in swallowing pills.
15. Any contraindication to blood sampling i.e. keloid formation.
16. Sensitivity to heparin or heparin-induced thrombocytopenia.
17. Premenarchal female subjects

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 48.00 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.
- In each study period, all participants will be required to fast overnight for at least 10.00 hours prior to receiving high-fat and high-calorie breakfast. After dosing the participants will not be allowed food for at least 04.00 hours. Meal timings are summarized in the SoA.

- On dosing study days, after an overnight fast of 10.00 hours, all participants will be given the same high-fat and high-calorie breakfast, 30 min prior to drug administration. Participants should eat the high-fat and high-calorie breakfast completely within 25 minutes.
- No water is allowed for 01.00 hour before the start of dosing until 01.00 hour after dosing except 240 ± 2 mL of water administered to the participants for dosing of study treatments. Water is allowed ad libitum at all other times.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48.00 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.
- During each dosing session, participants will abstain from alcohol for 48.00 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed for 48.00 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.

5.3.3. Activity

- Participants will abstain from strenuous exercise from the time of their check-in activity and throughout the stay at clinical facility. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants will be advised to avoid exposure to intense natural or artificial sunlight until completion of 5 days post last dose.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY TREATMENT

Study treatment is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study treatment (s) Administered

Treatment Code	T1	T2	R
Treatment Name	Griseofulvin Tablets, 500 mg	Griseofulvin Tablets, 250 mg	Griseofulvin Tablets, 500 mg (Grisovin Aspen Pharma Pty Ltd, Australia)
Type	Test Drug	Test Drug	Reference Drug
Dose Formulation	tablet	tablet	tablet
Unit Dose Strength(s)	500 mg	250 mg	500 mg
Dosage Level(s)	1 tablet	1 tablet	1 tablet
Route of Administration	oral	oral	oral
Use	experimental	experimental	active-comparator
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Study treatment will be provided in container. Each container will be labeled as required per country requirement.	Study treatment will be provided in container. Each container will be labeled as required per country requirement.	Study treatment will be provided in container. Each container will be labeled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the CRO‟s Standard Operating Procedure.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; potential bias will be reduced by the following steps: The randomization for this study will be generated by PBS personnel using the PROC PLAN on statistical software SAS® 9.2 or a higher version at CRO. The handling of randomization will be done as per the CRO‟s Standard Operating Procedure.

The analyst from bioanalytical facility will be blinded to the sequence of administration of Test and Reference product to the individual participant.

6.4. Study treatment Compliance

- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant‟s mouth to ensure that the study treatment was ingested.
- Record of dosing for individual participant will be maintained in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, minerals and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

In case of any illness requiring unacceptable medication, Paracetamol/Acetaminophen/ Diclofenac is permitted for use any time during the study as per discretion of investigator in consultation with the Medical Monitor. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

6.6. Dose Modification

Refer to Section 4.3 for selection of each participant's dose of study.

6.7. Treatment after the End of the Study

As this is the single dose bioequivalence study to be conducted in healthy participants, no treatment at the end of study will be provided.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment in subsequent study period only if the participant is withdrawn from the study due to any adverse event, serious adverse event or non-compliance to the protocol. Drop-outs will not be replaced.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

For all participants, ALT will be done before check-in for each study period. Discontinuation of study treatment for abnormal liver tests is required when the participant shows ALT ≥ 3xULN.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- If participant is found positive for breath alcohol test in any ambulatory visit, then the ambulatory sample of that particular visit will not be collected. However, he/she may be requested to come for subsequent ambulatory samples in same study period, if continuation in the study is not expected to have any significant impact on the safety or PK outcome in the judgement of Investigator.
- The decision to withdraw the subject if suffering from vomiting/diarrhoea (3 or more consecutive watery stools) at or before two times of median T_{max} (8 hours) will be taken by the Investigator considering the nature and amount of vomitus, likely/anticipated impact on the study outcome and the participants‟ health status.
- If participant is dropped out due to personal reasons in a given period, he can be continued in subsequent periods if the PK data generated through such participation can be used for statistical analysis.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study treatment and from the study at that time.
- 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant‟s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant‟s medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant‟s routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed 367.4 mL for male participants and 371.4 mL for female participants.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

No efficacy assessment will be conducted in this Bioequivalence study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

The participants will be monitored for occurrence of adverse events and serious adverse events throughout the study. Safety evaluation will be done on the basis of outcomes of physical examination, vital signs measurement and clinical laboratory results. The activities will be performed during each study period and during post study evaluation as given in the SoA.

Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or authorized trained personnel at any time during the course of study.

Post study evaluation will be done at the time of collection of last PK sample in last study period. Physical examination and measurement of vital signs (blood pressure, pulse rate, respiration rate and body temperature) performed at the time of check-out will be considered for post-study evaluation if the timing of post study evaluation and check-out coincides.

If any participant fails to complete the study or is discontinued from the study, the post-study evaluation will be done either on the day of discontinuation or before/at the end of study. If the post study evaluation is not completed within this time frame due to any reason, the same can be attempted at later stage at the discretion of Principal Investigator.

The reason for not completing the study will be specified in the respective CRF and the clinical report.

The participants may also report spontaneously any inconvenience or AEs to the monitoring staff at any time during the study or after check-out within the total number of days not exceeding the washout period.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Demographic information will include participant registration number, initials, date of birth, race, age, gender, height, weight and Body Mass Index (BMI) of the participants.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Blood pressure, pulse rate, respiration rate and body temperature will be assessed as outlined in the SoA (see Section 1.3).

8.2.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such 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.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Ideation and Behaviour Risk Monitoring

Not Applicable.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences after obtaining informed consent but before the initiation of study treatment will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of occurrence of SAE, as indicated in Appendix 3. The investigator will submit any follow up information to the sponsor within 24 hours of occurrence.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. 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 the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Within 24 hours of SAE occurrence (both Initial and Follow up information), the Investigator should complete a soft copy of the Table 5 format of the New Drugs & Clinical Trial Rules, 2019 with details of the SAE (as required by the HA) and Forward the completed Table 5 scan copy to the Sponsor, HA and Ethics Committee.

- Within 14 calendar days of SAE occurrence, the Investigator should provide causality assessment to the HA, Ethics Committee and Head of Institution.

- Within 14 calendar days of Sponsor (GSK) awareness of SAE, the Sponsor forwards the Sponsor causality via completed Final Table 5 to the Chairman of Ethics Committee, Head of Institution and to the HA (along with other relevant documents related to submission to the HA).

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, female partners of male participants will be collected after the start of study treatment and until 6 months after the last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported within 24 hours of occurrence (please see details provided in Appendix 3).

8.4. Treatment of Overdose

For this study, any dose of Griseofulvin Tablets > 500 mg, within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose. A detailed description of overdose of Griseofulvin Tablets is provided in the Summary of Product Characteristics [6].

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until Griseofulvin can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 5 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of Griseofulvin as specified in the SoA.

An intravenous cannula will be inserted into the participant‟s arm for the collection of the blood samples before the pre-dose blood sample and up to 24.00 hrs post-dose. If difficulties occur in blood withdrawal or if the participant is not feeling comfortable with the cannula, then the cannula will be removed before 24.00 hrs post-dose and the remaining blood samples will be collected through fresh vein puncture or by recannulation. When meals, vitals and sample collections coincide, samples will be collected first followed by vitals and then meal will be served.

Before every blood sample collection, 0.2 mL of blood present in the intravenous cannula will be discarded during the use of the intravenous cannula except for the ambulatory sample. Also after every blood sample collection, 0.2 mL of heparinised saline (by mixing 1 mL of 5000 IU/5mL of heparin with 500 mL of normal saline) will be injected into the intravenous cannula.

Twenty-Two (22) blood samples will be collected in Na-Heparin vacutainers at pre-dose (collected within 01.00 hour prior to dosing), 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 06.50, 07.00, 08.00, 10.00, 12.00, 24.00, 48.00, 72.00 and 96.00 hours post dose.

Note: The actual time of blood collection (24 hour clock) will be considered for calculation of PK parameters. Duration of 2 minutes is required for the completion of procedure of blood sample collection. Hence, the reason for deviation up to 2 minutes for the blood sample collection activity need not be documented. However, the reason for delay beyond 2 minutes will be documented in the case record form and/or other document.

Blood samples after 24 hrs will be collected on ambulatory basis through direct vein puncture. The actual end-point time of collection of each blood sample will be recorded in the CRF.

Ambulatory blood sample will be collected up to 04.00 hrs from the scheduled time of blood sample collection. If the participant reports for blood sample collection beyond 04.00 hrs, the blood sample will not be collected, and the participant will be requested to come for the next ambulatory sample (if any).

Approximate blood loss during the study:

		Males	**Females**
Total PK blood samples (66 x 5 mL)	**:**	330 mL	330 mL
Pre study screening	**:**	Upto 10 mL	Upto10 mL
Post study evaluation	**:**	Upto 10 mL	Upto 10 mL
Discarded heparinised blood (57 x 0.2 mL)	**:**	11.4 mL	11.4 mL
*For ALT test (before check-in for each	**:**	6 mL	6 mL

study period)			
Serum β-hCG (3 x 2 mL)	:	-	6 mL
Approximate blood loss	:	**367.4 mL**	**371.4 mL**

*Samples for ALT will be collected in PlainTube/ Plain Gel Tube

Blood withdrawal beyond this specified blood volume in the study will be considered as an incidental blood loss.

The incidental blood loss may occur due to following reasons.

1. For performing pending laboratory tests if study participant are primarily screened for other study not having such investigations.
2. For performing pending laboratory tests on the day of check-in for period I if such investigations are not performed on the day of screening due to any reason.
3. For repeating PK sample due to any reason after check-in in the study if required in the opinion of the investigator (example: loss of blood sample due to spillage or breaking of sample container etc).

It is expected that incidental blood loss due to above mentioned reasons will not exceed a blood loss up to 20 ml.

The participants will be compensated as per the compensation policy of CRO.

If additional blood sample is taken for safety evaluation anytime after check in for first period, no compensation will be provided for such blood loss.

Instructions for the collection and handling of biological samples will be specified in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of Griseofulvin. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of Griseofulvin plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

Name and address details of Bio-Analytical Investigator:
Set# 01 (PK aliquot) will be shipped to:
Name: Dr. PPD, Ph.D. (Analytical Chemistry)
Address: Analytical Facility:
Accutest Research Laboratories (I) Pvt. Ltd.,
A-31/77, MIDC, T.T.C. Industrial Area, Khairane, Navi Mumbai – 400 709,
Maharashtra, INDIA.
Tel: PPD
Fax:
Email : PPD

Set# 02 (back-up aliquot) will be forwarded to the same analytical laboratory only after confirmation of receipt of Set# 01 by the analytical laboratory, if necessary.

A validated LC-MS/MS analytical methodology will be used for the determination of Griseofulvin from the human plasma samples. Validation of the methodology will be carried out in accordance with applicable guidelines and the applicable SOP of analytical facility of Accutest Research Laboratories (I) Pvt. Ltd which are designed in accordance with the regulatory guidelines such as USFDA, EMEA, DCGI etc.

The following parameters (as applicable for BE demonstration and for dose proportionality) will be calculated for each participant-formulation combination using the non-compartmental model by using statistical package SAS® 9.2 or higher version:

All concentration values below the limit of quantification (BLQ) will be set to zero for the estimation of pharmacokinetic parameters.

If the pre-dose value is >5 percent of C_{max}, the respective period of that subject will be dropped from all PK evaluations and statistical evaluations

The pharmacokinetic samples of subjects dropped out or withdrawn due to vomiting / diarrhoea or any other reason will not be analyzed for the respective study period. The samples of subjects completing at least 2 periods of the study will be subjected to statistical analysis.

Depending upon availability of data, the subject will be either included in bioequivalence evaluation or dose proportionality evaluation.

Primary parameters

C_{max}	Maximum observed drug concentration during the study.
AUC_{0-t}	Area under the plasma concentration - time curve measured to the last quantifiable concentration, using the linear trapezoidal rule.
AUC_{0-inf}	AUC_{0-t} plus additional area extrapolated to infinity, calculated using the formula $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.

Secondary parameters

T_{max}	Time to observe maximum drug concentration. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.
AUC_{0-t} /AUC_{0-inf}	Ratio of AUC_{0-t} and AUC_{0-inf}
Residual area	Extrapolated area (AUC_{0-inf} - AUC_{0-t})/ AUC_{0-inf}

K_{el}	Apparent first – order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve, using the method of least square regression.
$t_{1/2}$	Terminal half-life as determined by quotient $0.693/K_{el}$
Vd	Fluid volume that would require to contain the whole drug in the body at the same conc. found in the plasma is given by formula, Dose / (K_{el} x AUC_{0-inf})
CL	Clearance of a given individual in the measure of his body capacity to eliminate a drug and is given by formula Dose / AUC_{0-inf}

The pharmacokinetic parameters will not be calculated in case of inconclusive concentration time profile (e.g. lack of sufficient measurable concentrations).

No value of K_{el}, Residual area, AUC_{0-t}/AUC_{0-inf}, AUC_{0-inf}, Vd, CL and $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Name and address details of Biostatistician (For PK analysis):
Name: Mr. PPD, M.Sc. (Statistics)/ Ms. PPD (B. Com, SAS Programmer)
Address: Statistical Facility:
Accutest Research Laboratories (I) Pvt. Ltd.,
A-77, MIDC, T.T.C. Industrial Area,
Khairane, Navi Mumbai – 400 709,
Maharashtra, INDIA.
Tel: PPD
Fax: PPD
Email:
PPD

All the procedures of PK analysis will be carried out in accordance with applicable guidelines and the applicable SOP of statistical facility of Accutest Research Laboratories (I) Pvt. Ltd.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Not Applicable.

8.10. [Health Economics] OR [Medical Resource Utilization and Health Economics]

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Null Hypothesis Testing
For BE Demonstration (T1 vs. R)
Null hypothesis H0 and alternative hypothesis H1 can be written in multiplicative form:
H0: $m_{test\ 1} / m_{ref} < L$ or $m_{test\ 1} / m_{ref} > U$
H1: $L \leq m_{test\ 1} / m_{ref} \leq U$

Where L (Lower Limit) = 80.00% and U (Upper Limit) = 125.00%,
$m_{test\ 1=}$ geometric least-squares means for test product (Griseofulvin 500mg tablets)
$m_{ref\ =}$ geometric least-squares means for reference product (Griseofulvin tablets, 500 mg (Grisovin))

The type I error will be set to α = 5% and therefore 90% (two-tails) confidence intervals will be provided together with indication whether the null hypothesis of non-equivalence for appropriate parameter can be rejected.

For For dose proportionality (T2 vs. T1)
Null hypothesis H0 and alternative hypothesis H1 can be written in multiplicative form:
H0: $m_{test\ 2} / m_{test\ 1} < L$ or $m_{test\ 2} / m_{test\ 1} > U$
H1: $L \leq m_{test\ 2} / m_{test\ 1} \leq U$

Where L=80.00% and U=125.00%,
$m_{test\ 1=}$ geometric least-squares means for test product (Griseofulvin 500 mg tablets)
$m_{test\ 2\ =}$ geometric least-squares means for reference product (Griseofulvin 250 mg tablets)

The type I error will be set to α = 5% and therefore 90% (two-tails) confidence intervals will be provided together with indication whether the null hypothesis of non-equivalence for appropriate parameter can be rejected.

Step 1: For BE Demonstration (T1 vs. R):

PROC MIXED procedure will be used for analysis of variance and the estimation of least square mean differences (Test (T1) - Reference (R)) of the test (T1) and reference formulations on the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. The corresponding standard errors of the differences will also be computed. Based on these parameters, the 90% confidence intervals will be constructed for the least square mean differences of log-transformed parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. The antilog (or exponential) of the limits obtained from the log-transformed data will give the 90% confidence interval for the ratio of geometric means of test (T1) and reference (R) products.

If the 90% confidence interval of geometric mean ratio of C_{max}, AUC_{0-t} and AUC_{0-inf} between test (T1) and reference (R) products falls within the range of 80.00% to 125.00% for Griseofulvin, the null hypothesis will be rejected. In this case the test product (T1) will be concluded as bioequivalent to the reference product R.

If bioequivalence is demonstrated between the Test product (T1) and reference product (R), the following step II will be followed.

Step 2: For dose proportionality (T2 vs. T1):
Dose normalization will be done for test product T2 for AUC_{0-t} and C_{max} parameter by multiplying with the correction factor 2.

PROC MIXED procedure will be used for analysis of variance and the estimation of least square mean differences (Test (T2) - Test (T1)) of the test (T2) and test (T1) products on the log-transformed pharmacokinetic parameter AUC_{0-t} and C_{max}. The corresponding standard errors of the differences will also be computed. Based on these parameters, the 90% confidence intervals will be constructed for the least square mean differences of log-transformed parameter AUC_{0-t} and C_{max}. The antilog (or exponential) of the limits obtained from the log-transformed data will give the 90% confidence interval for the ratio of geometric means of test (T2) and test (T1) products.

Null hypothesis will be rejected if the 90% confidence interval of geometric mean ratio of AUC_{0-t} and C_{max} between test (T2) and test (T1) products falls within the range of 80.00% to 125.00% for Griseofulvin.

9.2. Sample Size Determination

*Intra subject variability of 21% was chosen as clinically meaningful estimate based on the Sensitivity analysis on the variability estimates of 17% performed using 95th percentile approach. [8]

A sample size of 27 participants (adjusted for 9 subjects per sequence) without dropouts will be appropriate to provide 90% power for 90% confidence interval for the ratio of

Test to Reference for log-transformed C_{max} and AUC to lie within the acceptance region of bioequivalence 80% to 125%. This estimate is based on the ratio of Test product and Reference product is 0.95 and intra subject variability of 21% of Griseofulvin.

A sample size of 36 subjects are proposed for this 3-way cross-over study considering the dropouts and withdrawal of participants.

9.3. Populations for Analyses

Three (3) populations sets are defined for analysis purposes.

Safety Analysis Set

The safety population will include all randomized participants who receive at least one dose of study medication. The safety population will be used for all analyses of safety data. Individual pharmacokinetic parameters and its descriptive statistics will be presented.

BE Analysis Set

The data of subjects completing at least 2 periods with 500mg test and 500mg reference treatments of the study will be subjected to statistical analysis.

Dose Proportionality Analysis Set

The data of subjects completing at least 2 periods with 500mg test and 250mg test treatments will be subjected to dose proportionality analysis.

The following populations are defined:

Population	Description
Enrolled	All participants who signed the ICF
Randomized	All participants assigned to study treatment.
BE Analysis Set	The data of subjects, completing at least 2 periods with 500mg test and 500mg reference treatments of the study will be subjected to statistical analysis.
Safety Analysis Set	The safety population will include all randomized participants who receive at least one dose of study medication. The safety population will be used for all analyses of safety data. Individual pharmacokinetic parameters and its descriptive statistics will be presented
Dose Proportionality	The data of subjects completing at least 2 periods with 500mg

Analysis Set	test and 250mg test treatments will be subjected to dose proportionality analysis

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to study initiation and it 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.

9.4.1. Analysis of Variance

Step 1: For BE Demonstration (T1 vs. R):

ANOVA will be performed using PROC MIXED on log-transformed pharmacokinetics parameters C_{max}, AUC_{0-t} and AUC_{0-inf} at α level of 0.05.

The analysis of variance model will include sequences, period and treatment as fixed factors and participants nested within sequence as random factor [i.e. Model LC_{max} or $LAUC_{0-t}$ or $LAUC_{0-inf}$ = sequence period treatment (fixed factors) and random: Participant (Sequence) (random factor)].

A separate ANOVA model will be used to analyze each of the parameters. All main effects will be tested against the residual error (mean square error) from the ANOVA model as the error term.

Each analysis of variance will also include calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

Step 2: For dose proportionality (T2 vs. T1):

ANOVA will be performed using PROC MIXED on log-transformed pharmacokinetics parameter AUC_{0-t} and C_{max} at the α level of 0.05.

The analysis of variance model will include sequences, period and treatment as fixed factors and participants nested within sequence as random factor [i.e. Model $LAUC_{0-t}$ or LC_{max} = sequence period treatment (fixed factors) and random: Participant (Sequence) (random factor)].

A separate ANOVA model will be used to analyze each of the parameters. All main effects will be tested against the residual error (mean square error) from the ANOVA model as the error term.

Each analysis of variance will also include calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

9.4.2. Confidence Interval

Consistent with the two one-sided test for bioequivalence, 90% confidence intervals will be constructed for the difference (Test (T1) – Reference (R) or Test (T2) - Test (T1)) of least square means of the log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for BE demonstration and of the log-transformed AUC_{0-t} and C_{max} for dose proportionality. The antilog (or exponential) of these limits will give the 90% confidence interval for the ratio of geometric least square means of the test (T1) and reference (R) formulations or test (T2) and test (1) formulations.

9.4.3. Acceptance Criteria for Bioequivalence

Bioequivalence will be concluded if:
The 90% confidence interval of geometric mean ratio of log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} between test (T1) and reference (R) products fall within the range of 80.00% to 125.00% for Griseofulvin.

Dose proportionality will be concluded if:
The 90% confidence interval of geometric mean ratio of log-transformed AUC_{0-t} and C_{max} between test (T2) and test (T1) products falls within the range of 80.00% to 125.00% for Griseofulvin.

9.4.4. Accountability Procedure

9.4.4.1. Treatment of Missing Values

Missing sample values (MSV) or non-reportable values (NRV), of the plasma concentration data, will be represented as MSV and NRV in the plasma concentration tables and reasons for their missing will be documented. Any BLQ value occurring between two measurable concentration values will also be treated as missing sample (MS). These missing values will be treated as „missing values“ for Pharmacokinetic and statistical analysis. All the procedures will be performed in accordance with current version of SOP for „Calculation of Pharmacokinetic Parameters“.

For participants with missing or non-reportable concentrations for three or more of the last samples, only the C_{max} and T_{max} will be presented and included in the statistical analysis. Other PK parameters will not be reported.

Data from the participants with missing concentrations values (missed blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these participants will be excluded from the final analysis.

9.4.4.2. Missing samples

Missing samples can be due to withdrawal of participant and accidental spillage of samples as mentioned in current version of SOP for „Missing Sample".

9.4.4.3. Treatment of outliers

Before the results of the bioequivalence analysis are summarized into confidence intervals, the available untransformed C_{max}, AUC_{0-t} and AUC_{0-inf} data for BE demonstration and AUC_{0-t} and C_{max} data for dose proportionality will be tested for possible outliers based on studentized residuals. Participants identified as outliers will be removed regardless of whether results meet the standard

Values that meet both of the following criteria will be considered outliers:

• Studentized residual value larger than 3; and

• Observation outside of the range [Q1 – 3 x IQR; Q3 + 3 x IQR], where Q1, Q3 and IQR are respectively the 1st quartile, the 3rd quartile and the inter-quartile range of the distribution of all observations (i.e. regardless of the formulation).

Data from participants who meet both criteria for C_{max}, AUC_{0-t} and AUC_{0-inf} data for BE demonstration and AUC_{0-t} and C_{max} data for dose proportionality will be excluded from the statistical analysis for the outlying period.

No more than 5% of the participants may be considered outliers. If greater than 5% of the participants are considered outliers, no data will be removed from the statistical analysis.

A valid clinical or physiological reason will be explored for such an outlier, if found, and will be reported if identified by the Principal Investigator of the study (in accordance with current SOP of statistical outlier).

However, to avoid the biasness in the results, the statistical analysis will be performed on both the data sets i.e. including as well as excluding the outliers if the outlier is justified clinically as well.

9.4.5. Treatment of Time Point Deviation

Sampling time deviations will be considered during the calculation of pharmacokinetic parameters. However, graphical summary for mean data will be presented using nominal sampling times. Graphical summaries for individual subjects will be presented using actual sampling times.

9.4.6. Safety Analyses

All safety analyses will be made on the Safety Population. Safety data will be presented in tabular and/or graphical format and summarized descriptively.

9.5. Interim Analyses

Not Applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - 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/EC
  - Notifying the IRB/IEC of SAE 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

[Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant‟s legally authorized representative.

GSK (alone or working with others) may use participant‟s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about Griseofulvin Tablets or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the Griseofulvin Tablets approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. 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.
- The participant must be informed that his/her 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her 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.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- 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 Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer 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.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator‟s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory of CRO.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing serum (Serum (β) Beta- hCG) should be conducted before check-in for each study period during treatment
- Pregnancy testing serum should be conducted at the end of relevant systemic exposure.
- Additional serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 1 Protocol-Required Safety Laboratory Assessments

Test Description	**Reference range**	**Clinically Acceptable Limit**
HEMATOLOGY		
Haemoglobin	12.5 - 18.0 g/dL - Male 11.5 – 16.0 g/dL - Female[#]	12.3 – 18.0 g/dL – Male 11.0 – 16.0 g/dL – Female[#]
Erythrocyte Count	4.5 - 5.9 million/cmm - Male 4.0 - 5.1 million/cmm - Female[#]	4.0 – 7.1 million/cmm - Male 3.6 - 5.6 million/cmm - Female[#]
PCV (Packed Cell Volume)	41.5 - 50.4% - Male 35.9 - 44.6% - Female[#]	To be correlated with hemoglobin value
MCV (Mean Corpuscular Volume)	80 - 96 μm^3	
MCH (Mean Corpuscular Haemoglobin)	27.5 - 33.2 pg	
MCHC (Mean Corpuscular Haemoglobin-Concentration)	33.4 - 35.5g/dL	
WBC Count	4400 - 11000 /cmm	3960-12100 /cmm

(Contd…)

Test Description	**Reference range**	**Clinically Acceptable Limit**
Differential Count		
Neutrophils	40 - 80 %	36 - 88 %
Eosinophils	0 - 7 %	upto 14 %
Test Description	**Reference range**	**Clinically Acceptable Limit**
Basophils	0 - 2 %	0 - 2 %
Lymphocytes	20 - 40 %	18 - 44 %
Monocytes	2 - 10 %	2 - 10 %
Platelet Count	150 - 450 x 1000/cmm	135 - 495 x 1000/cmm
BIOCHEMISTRY		
Blood urea	Upto 50 mg/dL	Upto 55 mg/dL
Blood Glucose (Random)	70 to 130 mg/dL	63 to 140 mg/dL
Blood Urea Nitrogen	Upto 23.3 mg/dL	Upto 25.0 mg/dL
Serum Creatinine	0.7 - 1.2 mg/dL - Male 0.5 - 0.9 mg/dL - Female#	0.6 - 1.3 mg/dL - Male 0.4 - 1.0 mg/dL - Female#
Serum Bilirubin – Total	0.0 to 1.0 mg/dL	0.0 - 1.47 mg/dL
Serum Bilirubin – Direct	0.0 to 0.2 mg/dL	0.0 - 0.3 mg/dL
Serum Bilirubin – Indirect	0.1 to 1.0 mg/dL	0.0 – 1.5 mg/dL
SGOT (ASAT)	Upto 38 U/L - Male Upto 32 U/L - Female#	Upto 70 U/L - Male Upto 50 U/L - Female#
SGPT (ALAT/ALT)	Upto 41 U/L - Male Upto 31 U/L - Female#	Upto 72 U/L - Male Upto 50 U/L - Female#
S.Alkaline Phosphatase	40 to 129 U/L - Male 35 to 104 U/L - Female#	36 to 141 U/L - Male 35 to 120 U/L - Female#

(Contd…)

Test Description	**Reference range**	**Clinically Acceptable Limit**
Infectious Disease Screening		
HIV-1 & HIV-2 Antibodies	Reactive / Non-Reactive	Non-Reactive
Hepatitis B	Reactive / Non-Reactive	Non-Reactive
HCV Antibodies	Reactive / Non-Reactive	Non-Reactive
Test Description	**Reference range**	**Clinically Acceptable Limit**
Serum (β) Beta- hCG Test #		
Serum (β) Beta- hCG (Human Chorionic Gonadotropin) level (For Female)	Positive / Negative	Negative
Urinalysis		
Physical Examination:		
Colour	---	---
Reaction (pH)	5.0 to 9.0	---
Specific gravity	1.000 to 1.030	---
Transparency	---	---
Volume	---	---
Chemical Examination:		
Protein	Negative	Trace (+)
Glucose	Negative	Trace (+)
Ketone bodies	Negative	Trace (+)
Occult blood	Negative	Trace (+)
Urobilinogen	0.2 to 1.0 Ehrlich unit/dL	0.2 to 1.0 Ehrlich unit/dL
Bilirubin (Bile salt / bile pigment)	Negative	Trace (+)

(Contd…)

Test Description	**Reference range**	**Clinically Acceptable Limit**
Microscopic Examination		
Leucocytes	0-10 /hpf	0-10 /hpf
Red Blood Cells	0-10 /hpf	0-10 /hpf
Epithelial Cells	0-10 /hpf	0-10 /hpf
Casts	Absent	(+)
Crystals	Absent	(+)
Bacteria	Absent	Absent

Urine Examination For Drug of Abuse	
Test Description	**Reference range**
Benzodiazepines	Negative = Below 300 ng/mL
Marijuana	Negative = Below 50 ng/mL
Barbiturates	Negative = Below 300 ng/mL
Cocaine	Negative = Below 300 ng/mL
Morphine	Negative = Below 300 ng/mL
Amphetamine	Negative = Below 1000 ng/mL

*Urine microscopy will be done only if dipstick found positive for protein/leukocytes/blood.

If applicable.

Note:

1. If laboratory values are within normal range, it will be classified as Normal (N).
2. If laboratory values are outside normal range, but within acceptable range, it will be classified as Not Clinically Significant (NCS).

3. If any parameter is outside acceptable range without any associated clinical sign/symptom(s), it will be considered as Not Clinically Significant (NCS) at the discretion of medical personnel.
4. If any parameter is outside acceptable range and associated with clinical sign/symptom(s), it will be considered as Clinically Significant (CS) and will be documented as an AE accordingly.
5. If a value reflects or is indicative of any organ dysfunction (through a marked abnormal laboratory parameter), it will be considered as Clinically Significant (CS) and will be documented as an AE even in the absence of subject‟s clinical sign/symptom(s) and will be documented accordingly.
6. Reference may change as per manufacturer‟s kit reference. [18]

10.3. Appendix 3: Adverse Events: 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 treatment, whether or not considered related to the study treatment. • 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 treatment.

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 conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- 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.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician‟s office or outpatient setting. Complications that occur during hospitalization are 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.

Results in persistent or significant disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may

not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant‟s medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as „serious“ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Other measures to evaluate AE and SAE may be utilized (e.g. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator‟s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data** completed in the SAE Sections of the paper CRF (for entry in the GSK Argus Safety database) and the Table 5 format to GSK (for submission to the HA) within 24 hours of occurrence of the event. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report (completed in the SAE sections of the paper CRF and the Table 5 format) with the updated causality assessment to GSK within 24 hours of awareness of the new information.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK 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 GSK with a copy of any post-mortem findings including histopathology, within 24 hours of awareness of this information.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated / additional information on the SAE reported to GSK as a follow up report within 24 hours of awareness of the additional information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF
• Forward completed SAE sections of the paper CRF along with the Table 5 format via Email: PPD as a preferred method to transmit this information to the GSK LOC PV team.

Table 2: Reporting of SAEs with timelines

Responsible	Type of Report	Forward to	Timelines
Investigator	Completed SAE Report (Initial / Follow up) in SAE sections of the paper CRF. Note: In case of a death case, the Investigator should forward scanned copy of the completed paper CRF to the Sponsor instead of only the SAE pages of the paper CRF.	Sponsor for entry into the Argus Safety database	Within 24 hours of SAE occurrence
Investigator	Completed Table 5 format of the New Drugs & Clinical Trial Rules, 2019	Indian Health Authorities (HA) and Ethics Committee	Within 24 hours of SAE occurrence
Investigator	Causality assessment	Indian HA, Ethics Committee and Head of Institution	Within 14 calendar days of SAE occurrence
Sponsor	Final Table 5 along with the Sponsor causality	Chairman of Ethics Committee and Head of Institution	Within 14 calendar days of GSK awareness of SAE)

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 mIU/mL) is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner additionally following contraceptive barrier methods such as condoms
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant‟s female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive Griseofulvin Tablets.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner‟s pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.

- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will be withdrawn from the study

10.5. Appendix 5: Country-specific requirements

This study will be conducted in compliance with the protocol approved by the Ethical Committee (EC) and according to the current version of the Declaration of Helsinki, the current ICH GCP, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) and CDSCO Bioequivalence study guidelines as well National Laws and Regulations, all relevant SOPs required for the conduct of this study.

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviations

AE(s)	Adverse Event(s)
ANOVA	Analysis of Variance
ALAT	Alanine (Amino)Transaminase
ALT	Alanine aminotransferase
ARL	Accutest Research Laboratories (I) Pvt. Ltd.
AUC_{0-t}	Area Under The Concentration Versus Time Curve Up To The Last Measurable Time Point
AUC_{0-inf}	Area Under The Concentration Versus Time Curve From Time 0 To
BE	Bioequivalence
β-hCG	Serum Beta Human Chorionic Gonadotropin level
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRO	Clinical Research Organisation
CDSCO	Central Drugs Standard Control Organisation
C_{max}	Maximum Observed Drug Concentration In Plasma
cmm	Cubic Millimeter
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
CRF	Case Report Form
DCGI	Drug Controller General of India
dL	Deciliter
ECG	Electrocardiogram
EC	Ethics Committee
EMEA	European Medicines Agency
FSH	Follicle stimulating hormone
g	Grams
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
HIPAA	Health Insurance Portability and Accountability Act
hpf	High power field
hrs	Hours
HRT	Hormonal Replacement Therapy
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
K_{el}	Elimination Rate Constant
kg	Kilogram(s)
L	Liter
LC-MS/MS	Liquid Chromatography-Mass Spectrometer/Mass Spectrometer
mg	Milligram
mIU	Milli-International Units

mL	Milliliter
µm	Micrometer
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MS	Missing Sample
MSDS	Material Safety Data Sheet
MSV	Missing Sample Values
Na-Heparin	Sodium- Heparin
no.	Number
NRV	Not-reportable Value
OTC	Over The Counter
PCV	Packed Cell Volume
pg	Picogram
PK	Pharmacokinetic
QTc	Corrected QT interval
SAE(s)	Serious Adverse Event(s)
SAS	Statistical Analysis System
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLE	Systemic lupus erythematosus
SOA	Schedule of Activities
SOP(s)	Standard Operating Procedure(s)
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Terminal Half-Life
T_{max}	Time To Observe Maximum Drug Concentration In Plasma
ULN	Upper limit of normal
U/L	Units per liter
USFDA	United States Food and Drug Administration
vs.	Versus
WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies

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SAS

11. REFERENCES

1. Generating randomization schedule using SAS® Programming, Chunqin Deng and Julia Graz. PPD, Inc, Research Triangle Park, North Carolina, available on Website: - http://www2.sas.com/proceedings/sugi27/p267-27.pdf.

2. ICH HARMONISED GUIDELINE, INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) 9 November 2016

3. Ministry of Health and Family Welfare (Department of Health), Notification, New Delhi, the 30th January, 2013.

4. New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E)

5. National Ethical Guidelines For Biomedical And Health Research Involving Human Participants, Indian Council Of Medical Research 2017

6. Summary of Product Characteristics Griseofulvin 500mg Tablets DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 28th June 2005

7. Product Information GRISOVIN Aspen Pharma Pty Ltd, 34-36 Chandos Street, St. Leonards NSW 2065, Australia, Date of most recent amendment: 20 January 2015

8. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con088189.pdf

9. Rajagopalan et al. Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India) BMC Dermatology (2018) 18:6

10. Rengasamy M, Chellam J, Ganapati S. Systemic therapy of dermatophytosis: Practical and systematic approach. Clin Dermatol Rev 2017;1:S19-23

11. Grisovin FP prescribing information. Available at:http://india-pharma.gsk.com/en-in/products/prescribing-information/

12. GRISEOFULVIN. Available at: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono79-12.pdf. Accessed on 30th June 2018

13. Toh MR, et al. Association between number of doses per day, number ofmedications andpatient's non-compliance, and frequency of readmissions in a multi-ethnicAsian population. Preventive Medicine Reports 1 (2014) 43–47

14. Guidelines on the investigation of bioequivalence. Committee for Medicinal Products for Human Use. (CHMP). European Medicines Agency, Doc ref: CPMP/QWP/EWP/1401/98 Rev. 1, Rev.20, Jan 2010.

15. Public assessment report of Griseofilvon 500mg Tablets; UK/H/1773/001/DC; UK licence no: PL 20117/0109; Morningside healthcare Limited.

16. WHO Technical Report Series, No. 937, 2006; Annex 8 Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms

17. IARC MONOGRAPHS VOLUME 79, GRISEOFULVIN, 291-315.

18. Clinical Laboratory References:

    a. Todd. Sanford. Davidson. Clinical Diagnosis and Management by Laboratory Methods, 20th Edition. W.B. Saunders Company, Philadelphia, U.S.A.

    b. Dacie & Lewis Practical Haematology, S. Mitchell Lewis, Barbara J. Bain, Imelda Bates, Churchill Livingstone, 9th Edition, 2001, U.K.

    c. Textbook of Medical Laboratory Technology, Praful B. Godkar, Darshan P. Godkar, 2nd edition, 2003.

    d. According to manufacturer‟s kit reference.

    e. Internal Laboratory Reference.

    f. Health Status of Indian Population - Current Scenario JAPI • VOL. 52 • MAY 2004.