Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate thebioequivalence 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
Compound Number	:	CCI44
Clinical Study Identifier	:	212504
Effective Date	:	[19-MAR-2020]

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol No. 212504.
- This RAP is intended to describe the safety, tolerability, and pharmacokinetic (PK)analyses required for the study.
- This RAP will be provided to the study team members to convey the content of theStatistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2019N413557_00	07-Oct-2019	Original

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze (DBF) of the study data.

2. SUMMARY OF KEY PROTOCOL INFORMATION

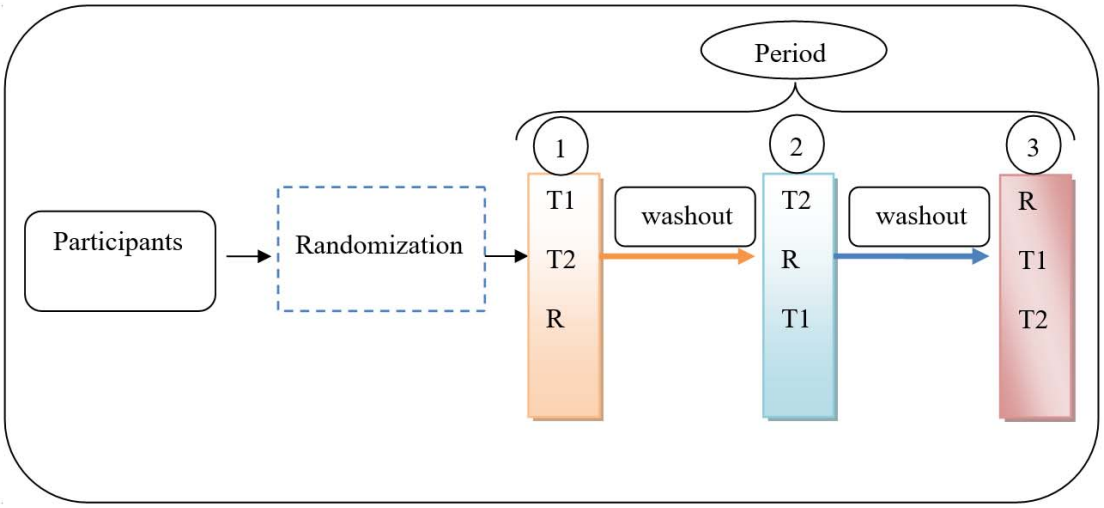
2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [(Dated: 11-DEC-2019)].

2.2. Study Objective(s) and Estimand(s) / Endpoint(s)

Objectives	Endpoints
Primary	**Primary**
• To determine whether the **Test Product (T1):**GriseofulvinTablets, 500 mg is bioequivalent to **Reference Product (R):**GriseofulvinTablets, 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):**GriseofulvinTablets, 250 mg and **Test Product (T1):**GriseofulvinTablets, 500 mg in healthy participants.	• Cmax, AUC0-t and AUC0-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 mgand**Reference Product (R):**Griseofulvin Tablets, 500 mg (Grisovin).	• Safety and tolerability as measured by adverse events, vital signs and clinical laboratory measurements

2.3. Study Design

Overview of Study Design and Key Features	
 T1 = GriseofulvinTablets, 500 mg Test Product T2 = GriseofulvinTablets, 250 mg Test Product R = GriseofulvinTablets, 500 mg (Grisovin) Reference	
DesignFeatures	• This is an open label, randomized, balanced, three treatment, three period, three sequence, single dose, crossover study to evaluate thebioequivalence 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. • Each participant will receive all 3 treatments according to their assignment to one of 3 treatment sequences (T1T2R, T2RT1 or RT1T2).
Dosing	• 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.
Time & Events	• [Refer to Appendix 1: Schedule of Activities]
Treatment Assignment	• 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.

Overview of Study Design and Key Features	
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses/ Statistical Analyses

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 $\alpha = 0.05$ 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 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 $\alpha = 0.05$ 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.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) (both the CRF data and PK data) has been declared by Data Management."

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who signed the ICF	Screen Failure
Randomized	All participants assigned to study treatment.	Study Population
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.	PK
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	Study completion
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	PK

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study and will be documented in the Deviation form.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the CRF.

5. CONSIDERATIONS FOR DATA ANALYSESAND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Code	T1	T2	R
Treatment Name	Griseofulvin Tablets, 500 mg	GriseofulvinTablets, 250 mg	GriseofulvinTablets, 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.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. **For BE Demonstration (T1 vs. R**)
2. **For dose proportionality (T2 vs. T1)**

5.2. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.1	Appendix1: Schedule of Activities
10.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Reporting Standards for Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Abbreviations & Trade Marks
10.8	Appendix 8 :List of Data Display

6. STUDY POPULATIONANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Safety" population. Screen failures will be listed based on the "All participants" population.
Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics and prior and concomitant medications will be based on GSK Core Data Standards. Details of planned study population data displays will be presented in Appendix 7: List of Data Displays of Full RAP.

6.2. Subject's Disposition

The number and percentage of subjects who completed the study as well as subjects who withdrew prematurely from the study will be summarized by completion status and reason for withdrawal. A listing of the subjects who withdrew from the study prematurely will be provided.
The number of subjects included in the safety population, and those included in the PK population will be summarized. Subjects who are excluded from the safety population and those who are excluded from PK population will be listed with the corresponding reason.
Subject's disposition summary will be displayed by "Total".

6.3. Protocol Deviations

A listing of the inclusion/exclusion criteria deviation record for all subjects with deviations will be provided. Other deviations will be noted as applicable, including use of prohibited concomitant medications during the study, incorrect study drug administration, and any other deviations deemed to have the potential for notably influencing the study results. A summary of important protocol deviations and by-subject listing of important protocol deviations will be provided.
The summary will be displayed by "Total".

6.4. Demographic and Baseline Characteristics

6.4.1. Demographic characteristics

Demographic characteristics listed below will be summarized either with descriptive statistics for continuous variables or with frequencies and percentages for categorical variables. A by-subject listing of these characteristics will be provided.

- Continuous variables: Age, Height, Weight, and Body mass index (BMI)
- Categorical Variables: Sex, Ethnicity and Geographic Ancestry

The summary will be displayed by "Total" for demographic characteristics.

6.4.2. Substance Use

Substance use, including smoking, alcohol consumption and drug abuse, will be summarized and listed.
The summary will be displayed by "Total".

6.4.3. Medical Conditions

The reported adverse event or serious adverse event will be recorded in CRF. A collective data of incidence of adverse events will be provided in the clinical study report.

6.5. Concomitant Medications

The details of concomitant medication prescribed and used will be referred from CRF. The list of concomitant medication/ drugs will be provided in the clinical study report.

7. SAFETY ANALYSES

The safety analyses will be based on the safety population, unless otherwise specified.

Descriptive statistics will be used to assess safety and tolerability objectives. No formal tatistical analyses of safety data are planned. Data will be summarized and listed according to Accutest Data Standards and statistical principles.

7.1. Adverse Events Analyses

Adverse events analysesincluding the analysis of adverse events (AEs), Serious adverse events (SAEs) and other significant AEs will be based on Accutest Data Standards.

7.2. Clinical Laboratory Analyses

The analysis of laboratory safety test results will be based on GSK Core Data Standards, unless otherwise specified. The details of these are presented in Appendix 1: Schedule of Activities.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be ased onGSKCoreDataStandards, unless otherwise specified. The details of the planned displays are presented inAppendix: List of Data Displays.

8. PHARMACOKINETIC ANALYSES

8.1. Primary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix : Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of SAS version 9.4.All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from concentration-time data, as data permits.

Parameter	Parameter Description
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.
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 / AUC0-inf

NOTES:

- Additional parameters may be included as required.
- 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

8.1.2. Summary Measure

Parameters C_{max}, AUC_{0-t} and AUC_{0-inf} will be applicable for BE demonstration and Parameters C_{max}, and $AUC_{0-t}$for dose proportionality. These parameters will be calculated for each participant-formulation combination using the non-compartmental model by using statistical package SAS® 9.4

8.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on theBE Analysis Setpopulation, unless otherwise specified.

8.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix: List of Data Displaysand will be based on AccutestData Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.4.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
Primary end points for BE Demonstration (T1 vs. R): Cmax, AUC0-t and AUC0-inf Primary end points for dose proportionality (T2 vs. T1) :Cmax, AUC0-t
Model Specification
ANOVA will be performed on Log-transformed Cmax, AUC0-t and AUC0-inf using Proc Mixed Model. Model LCmax or LAUC0-t or LAUC0-inf = sequence period treatment (fixed factors) and random: Participant (Sequence) (random factor)]
Model Checking & Diagnostics
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. • For the Proc Mixed Model, model assumptions will be checked, and appropriate adjustments may be applied based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • Non-parametric analyses will be conducted on un-transformed parameter Tmax.
Model Results Presentation
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-transformedAUC_{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. REFERENCES

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10. APPENDICES

10.1. Appendix 1: Schedule of Activities

10.1.1. Protocol Defined Schedule of Events

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	X						X

for female [e]							
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.

10.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

10.2.1. Study Phases for Treatment Emergent Adverse Events and Concomitant Medication

Subject. No.	
Study Period	
Age (years)	
Sex	
Adverse Event	
Date & Time of Onset	
Date & Time of Reporting	
Severity	
Seriousness	
Action Taken	
Outcome	
Causality assessment	
Likelihood	
Date & Time of Resolution	
Date &Time of Last Dose Administered	
Last Investigational Medicinal Product Administered	
Concomitant Treatment	

10.3. Appendix 3: Data Display Standards& Handling Conventions

10.3.1. Reporting Process

Software
• The currently supported versions of SAS software (Version 9.4) willbe used.
Analysis Datasets
• SDTM datasets will be created according toCDISC standards (SDTM IG Version 3.2].
Generation of RTF Files
• RTF files will not be generated.
Generation of xlm Files
• xlm files will not be generated.

10.3.2. Reporting Standards

Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses:
• Sampling time deviations will be considered during the calculation of pharmacokinetic parameters.
• Graphical summaries for individual subjects will be presented using actual sampling times.
• Graphical summary for mean data will be presented using nominal sampling times
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in .
  • Unscheduled or unplanned readings will be presented within the subject'slistings.	

Unscheduled Visits	
• Unscheduled visits will be included in subject visit domain.	
Descriptive Summary Statistics	
Concentration Data	Descriptive summary (mean, standard deviation, coefficient of variation, median, minimum and maximum) will be computed for each pharmacokinetic parameter for the test and reference products.
Graphical Displays	
Graphical summary for mean data will be presented using nominal sampling times.	

10.3.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows	Pharmacokinetic data will be calculated using the non-compartmental model by using statistical package SAS® 9.4.
Descriptive Summary Statistics, Graphical Displays and Listings	Descriptive summary (mean, standard deviation, coefficient of variation, median, minimum and maximum) will be computed for each pharmacokinetic parameter for the test and reference products. Graphical summaries for individual subjects will be presented using actual sampling times
Pharmacokinetic Parameter Derivation	
PK Parameter to be	The following PK parameters will be derived by the Programmer: C_{max}, AUC_{0-t},

Derived by Programmer	$AUC_{0\text{-}inf}$, T_{max}, $AUC_{0\text{-}t}$ /$AUC_{0\text{-}inf}$, Residual area, K_{el}, $t_{1/2}$, Vd, CL
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	N, arithmetic mean, median, min, max, SD will be provided for untransformed data. For log-transformed data, geometric mean, 90% CI of geometric mean, T/R ratio (%), mean square error (mse), , intra-subject variability, power of log-transformed data will be reported.
Untransformed PK parameter	tmax, AUC0-t /AUC0-inf, Residual area, Kel, t1/2, Vd, CL, Tlin, Lqct,

10.4. Appendix 4: Derived and Transformed Data

10.4.1. Pharmacokinetic

PK
• Plasma sample analysis will be carried out by Accutest Research Laboratories (I) Pvt Ltd. Griseofulvin plasma concentrations will be determined using the currently validated methodology. The actual sampling times, will be used in the PK calculations. • Griseofulvin plasma concentration-time data will be analyzed by non-compartmental methods with SAS software version 9.4 and derived PK parameters will be summarized and listed. Derived Pharmacokinetic parameters will be summarized by treatment group. Mean, Median, Min, Max, SD for untransformed pharmacokinetic parameters • For log-transformed data, geometric mean, 90% CI of geometric mean, T/R ratio (%), mean square error (mse), , intra-subject variability, power of log-transformed data will be reported. • Graphical summary for mean data will be presented using nominal sampling times. Graphical summaries for individual subjects will be presented using actual sampling times.

10.5. Appendix 5: Reporting Standards for Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of all phases of the study. • Withdrawn subjects will be notreplaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.5.2. Handling of Missing Data

Element	Reporting Detail
General	Missing samples can be due to withdrawal of participant and accidental spillage of samples as mentioned in current version of SOP for 'Missing Sample'. 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 Cmax and Tmax 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.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in case report forms of subjects • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions: Missing start day: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: ○ If month and year of start date = month and year of study

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
○ Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
• Completely missing start or end dates will remain missing, with no imputation applied.
</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail
	• The recorded partial date will be displayed in listings.
[Insert as required…]	

Concomitant medication details:

Drug Name (Brand Name)	Dosage form	Strength	Frequency	Start date	End date	Recorded By

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Laboratory Values

All Individual laboratory measurements by subject will be provided with the CRFs of individual subject as clinical laboratory test report.

10.6.2. ECG

All Individual ECG measurement by subject will be provided with the CRFs.

10.6.3. Vital Signs

All Individual Vital Sign measurement by subject will be provided with the CRFs.

10.7. Appendix 7: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling& Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b/ CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library (GSK Standards Library)
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

10.7.2. Trademarks

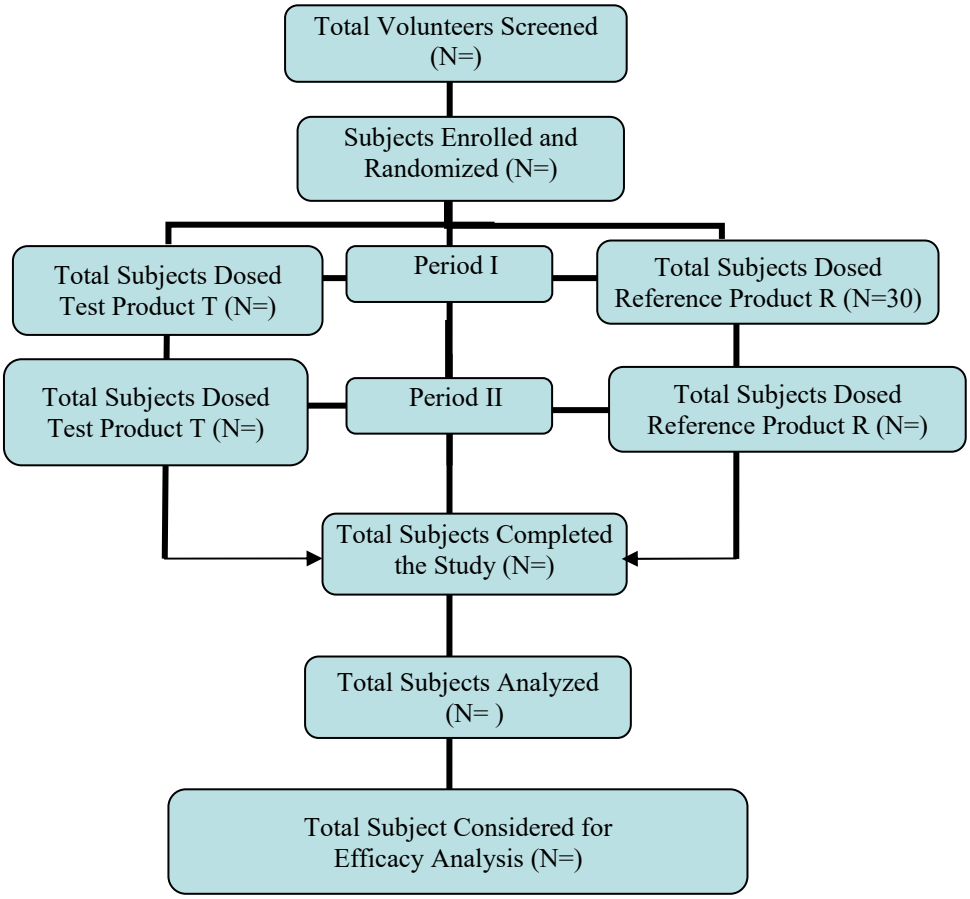
Trademarks of the GlaxoSmithKline Group of Companies

Trademarks not ownedby the GlaxoSmithKline Group of Companies
[SAS]

10.8. Appendix8: List of Data Displays

All data displays will use the term “subject” rather than “participant” in accordance with Accutest SOP and CDSIC Standards

10.8.1. Study PopulationTables



10.8.2. Pharmacokinetic Tables

The SAS System, Version: 9.4
Accutest Research Laboratories (I) Pvt. Ltd.
Study Code -
Individual Pharmacokinetic Parameters of Griseofulvin for 'Test Products (T1 and T2)'

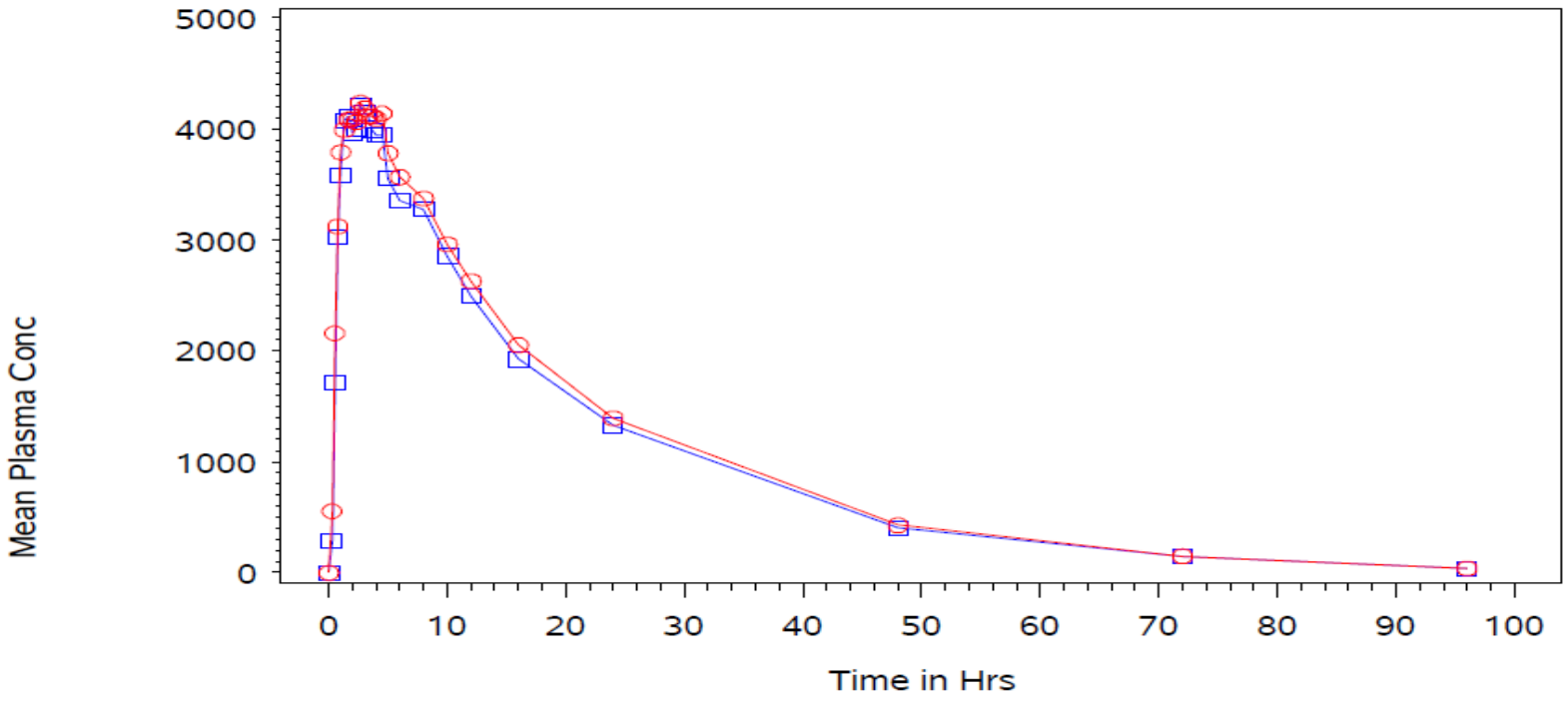
Subject	Sequence	Period	Treatment	Cmax (ng/mL)	Tmax (hrs)	AUC(0-t) (ng*hr/mL)	AUC(0-inf) (ng*hr/mL)	AUC Ratio (%)	Residual Area (%)	Kel (hrs-1)	Kel_First (hrs)	Kel_Last (hrs)	Thalf (hrs)

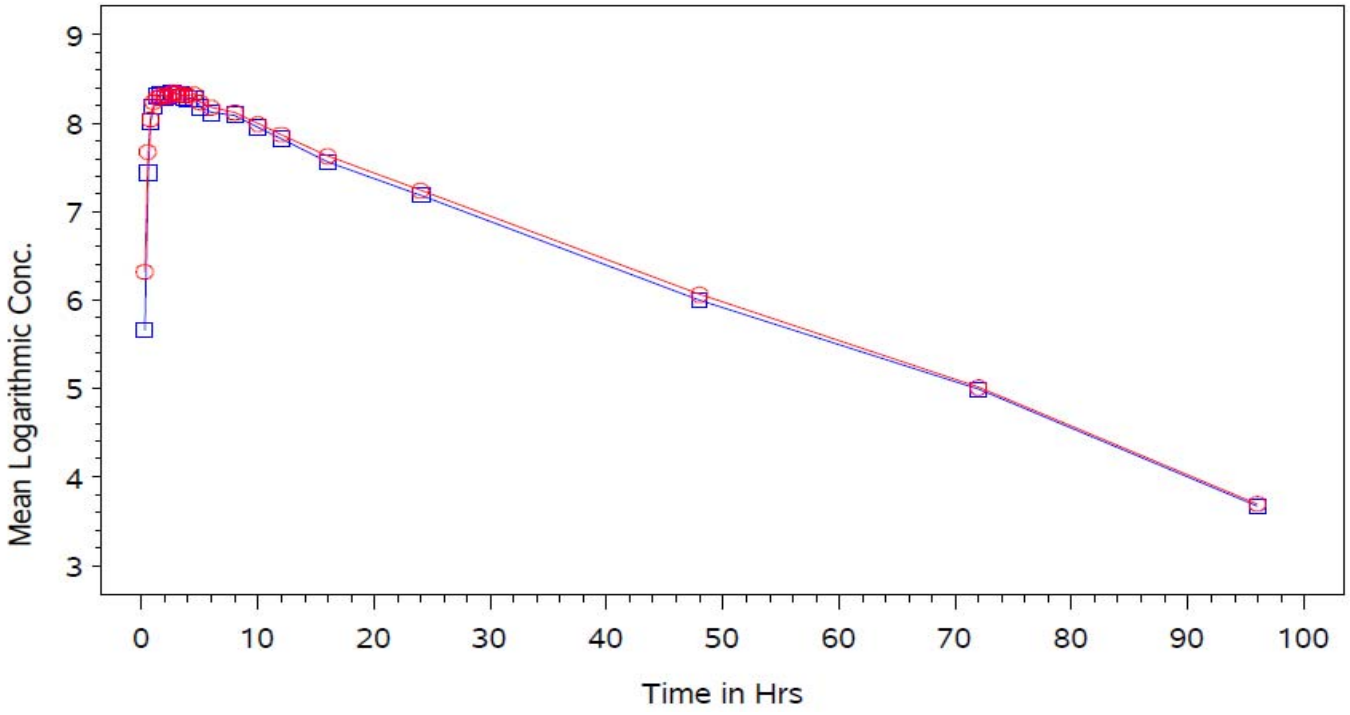
The SAS System, Version: 9.4
Accutest Research Laboratories (I) Pvt. Ltd.
Study Code -
Individual Pharmacokineric Parameters of Griseofulvin for 'Reference Product (R)'

Subject	Sequence	Period	Treatment	Cmax (ng/mL)	Tmax (hrs)	AUC(0-t) (ng*hr/mL)	AUC(0-inf) (ng*hr/mL)	AUC Ratio (%)	Residual Area (%)	Kel (hrs-1)	Kel_First (hrs)	Kel_Last (hrs)	Thalf (hrs)

10.8.3. Pharmacokinetic Figures

The SAS System, Version: 9.4
Accutest Research Laboratories (I) Pvt. Ltd.
Study code -
***Mean Plasma Concentration of* Griseofulvin*for* 'Test Products (T1 and T2)' and Refernce Product (R)**




Mean Logarithmic Conc.
9
8
7
6
5
4
3
0
10
20
30
40
50
60
70
80
90
100
Time in Hrs

10.8.4. ICH & Non- ICH Listings

• **01**	**Protocol and protocol amendments**
• **02**	Sample Case Report Form
• **03**	List of IECs or IRBs and Representative Written Information for Subject and Sample Consent Forms
• **04**	List and Description of Investigators and other Important Participants in the Study, Including their CVs or equivalent summaries of training and experience relevant to the performance of the study
• **05**	Signature of Principal or coordinating investigator or sponsor's responsible personnel
• **06**	Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) From Specific Batches, where more than One Batch was Used
• **07**	Randomization Scheme and Codes
• **08**	Audit Certificates
• **09**	Documentation of Statistical Methods
• **9.1**	Sample Size Calculation

• **9.2**	Actual Time Points Considered
• **9.3**	Mean Plasma Concentration
• **9.4**	Individual Subject's Concentration Graph
• **9.5**	**Individual Subject's Kel Graph**
• **9.6**	SAS Output
• **10**	Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures
• **11**	Publications Based on the Study
• **12**	Important Publications Referenced in the Report
	SUBJECT DATA LISTINGS
• **13**	Discontinued Subjects
• **14**	Protocol Deviations
• **15**	Subjects Excluded from the Efficacy Analysis

• **16**	Demographic Data
• **17**	Compliance and/or drug Concentration Data
• **18**	Individual Pharmacokinetic Data
• **19**	Adverse Event Listing
• **20**	Listing of Individual Laboratory Measurements by Subject
	CASE REPORT FORMS
• **21**	CRFs for Deaths, other Serious Adverse Events and Withdrawals for AE
• **22**	Other CRFs Submitted
• **23**	**BIO-ANALYTICAL REPORT**