

REPORT ON BIOEQUIVALENCE STUDY

(Protocol No.: BEQ-2321-LEVT-2017, Version No.: 02, Date: 19th March 2018)

Study Title: Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design: An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

Investigational Product Details		Dose
i) Test Formulation (T)	: Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India)	3 × 200 mcg
ii) Reference Formulation (R)	: Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands)	3 × 200 mcg

Duration of Clinical Phase	:	03 rd April 2018 - 25 th June 2018
Duration of Bioanalytical Phase	:	29 th May 2018 - 15 th June 2018
Duration of Statistical Phase	:	26 th June 2018
Report Status	:	Final
Version	:	01
Dated	:	13 th July 2018
Supersedes Version	:	None
Dated	:	Not Applicable

Sponsor: MACLEODS PHARMACEUTICALS LTD., G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093, India. Telephone No.: 91-22-61132900 Fax No.: 91-22-28304641	Clinical Facility MACLEODS PHARMACEUTICALS LTD. Bioequivalence Department R & D: II, Plot no. 95, Road no. 16, Opp. Suncity Hotel, MIDC, Andheri - (East), Mumbai 400 093, India. Telephone No.: 91-22-67258412 Email: drashish@macleodspharma.com

Statement of Compliance: This study was conducted in compliance with ICH GCP including archiving of essential documents.

Principal Investigator : Dr. Rajendra Sonde
Study Director : Dr. Ashish Mungantiwar
Sponsor's Representative : Ms. Shalmali Ambekar

2.0 SYNOPSIS OF THE REPORT

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India	Individual Study Table Referring to part of the Dossier Volume: N/AP Page: N/AP	(For National Authority Use only)																		
Name of the Finished Product: Levothyroxine Sodium Tablets 200 mcg																				
Name of Active Ingredient: Levothyroxine Sodium																				
Title of Study: Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.																				
Investigator: Dr. Rajendra Sonde, Principal Investigator																				
Study Centre: Macleods Pharmaceuticals Ltd., Bioequivalence Department																				
Publication (reference): Not Applicable																				
Study period: <table border="1" data-bbox="363 1003 1281 1288"> <tr> <td>Date of Screening</td> <td>:</td> <td>16th March 2018 – 03rd April 2018</td> </tr> <tr> <td>Duration of Clinical Phase</td> <td>:</td> <td>03rd April 2018 – 25th June 2018</td> </tr> <tr> <td>Period 1</td> <td>:</td> <td>03rd April 2018 – 07th April 2018</td> </tr> <tr> <td>Period 2</td> <td>:</td> <td>08th May 2018 – 12th May 2018</td> </tr> <tr> <td>Duration of Bioanalytical Phase</td> <td>:</td> <td>29th May 2018 – 15th June 2018</td> </tr> <tr> <td>Duration of Statistical Phase</td> <td>:</td> <td>26th June 2018</td> </tr> </table>			Date of Screening	:	16 th March 2018 – 03 rd April 2018	Duration of Clinical Phase	:	03 rd April 2018 – 25 th June 2018	Period 1	:	03 rd April 2018 – 07 th April 2018	Period 2	:	08 th May 2018 – 12 th May 2018	Duration of Bioanalytical Phase	:	29 th May 2018 – 15 th June 2018	Duration of Statistical Phase	:	26 th June 2018
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Duration of Bioanalytical Phase	:	29 th May 2018 – 15 th June 2018																		
Duration of Statistical Phase	:	26 th June 2018																		
Objectives: i) Pharmacokinetic: To evaluate the comparative oral bioavailability of Three Tablets as Single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) with Three Tablets as Single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy, adult, human subjects under fasting condition. ii) Safety: To monitor the safety and tolerability of three tablets as single oral dose of Levothyroxine Sodium Tablets 200 mcg when administered in healthy, adult, human subjects under fasting condition.																				

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India	Individual Study Table Referring to part of the Dossier Volume: N/AP Page: N/AP	(For National Authority Use only)
Name of the Finished Product: Levothyroxine Sodium Tablets 200 mcg		
Name of Active Ingredient: Levothyroxine Sodium		
Methodology: Dosing was done under fasting condition during each period. Blood samples (1 × 6 mL) were collected in blood collection tube containing clot activator during each period. The venous blood samples were withdrawn at -0.50, -0.25 and -0.03 hours prior to dosing (pre-dose) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose (time points being relative to the investigational product dosing). The separated serum was aliquoted in duplicate in prelabelled amber colored polypropylene tubes during each period. Owing to the sensitivity of Levothyroxine to light, samples were collected and processed under yellow monochromatic light. Analysis of serum samples for levothyroxine concentration was done using an in-house validated LC-MS/MS method. A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentration time profile. Statistical comparison of the pharmacokinetic parameters of both the formulations was done to assess bioequivalence.		
Number of Subjects (planned and analyzed): A total of 30 healthy, adult, human subjects were planned and enrolled. The study was carried out in one group comprising of 30 male subjects (subject number 01 to 30). All the 30 enrolled subjects completed both the periods of the study. The serum samples of all thirty subjects (subject number 01 to 30) completing the study was analyzed for levothyroxine concentration level and the data were taken for pharmacokinetic and statistical evaluations.		
Diagnosis and main criteria for inclusion: Healthy human subjects within the age range of 18 to 45 years with body-mass index (BMI) between 18.50 kg/m² and 29.99 kg/m² (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females) and having absence of significant disease, clinically significant laboratory values, Serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH) test, absence of clinically significant medical history and normal physical examination during the screening and complying with inclusion and exclusion criteria were the criteria for inclusion.		

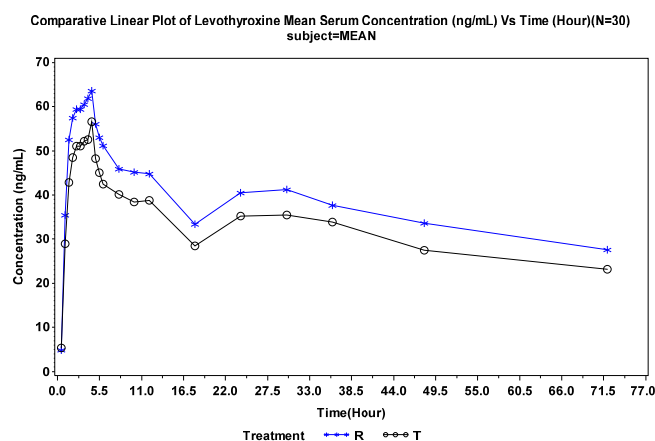
Name of the Sponsor: Macleods Pharmaceuticals Ltd., India	Individual Study Table Referring to part of the Dossier Volume: N/AP Page: N/AP	(For National Authority Use only)
Name of the Finished Product: Levothyroxine Sodium Tablets 200 mcg		
Name of Active Ingredient: Levothyroxine Sodium		
i) Test Formulation (T): Levothyroxine Sodium Tablets 200 mcg Batch No.: MLK602C Manufacturing Date: 10/2016 Expiry Date: 09/2018 Manufactured by: Macleods Pharmaceuticals Ltd. India Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water Batch size: 150000 Tablets Assay: 101.7%		
ii) Reference Formulation (R): Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg Batch No.: 209740 Manufacturing Date: N/AV Expiry Date: 11/2018 Marketing Authorization Holder: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijk Manufactured by: Merck KGaA, Frankfurter Str.250, and Darmstadt, Germany Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water Batch size: Not Available Assay: 98.2%		
Duration of treatment	Single dose in both periods	
Criteria for Evaluation: Efficacy: The 90% confidence intervals for C_{max} and AUC_{0-72} of baseline-corrected-levothyroxine formed the basis for concluding the bioequivalence of Levothyroxine sodium in product R and T. If the 90% confidence intervals are entirely included in the range of 80.00% – 125.00% for C_{max} and AUC_{0-72} log-transformed then the products would be claimed to be bioequivalent. Safety: To monitor the safety and tolerability of three tablets as single oral dose of Levothyroxine Sodium Tablets 200 mcg when administered in healthy, adult, human subjects under fasting condition.		

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India	Individual Study Table Referring to part of the Dossier Volume: N/AP Page: N/AP	(For National Authority Use only)
Name of the Finished Product: Levothyroxine Sodium Tablets 200 mcg		
Name of Active Ingredient: Levothyroxine Sodium		

Statistical Methods: The log-transformed pharmacokinetic parameters (C_{max} & AUC_{0-72}) of baseline-corrected-levothyroxine are analysed using an ANOVA models. Calculated baseline-corrected 90% confidence interval for the ratio of both the products averages (geometric means) of C_{max} & AUC_{0-72} . Ratio T/R for each subject at C_{max} & AUC_{0-72} . %Bioavailability of C_{max} & AUC_{0-72} and power test is performed using SAS® version 9.4.

SUMMARY - CONCLUSION

EFFICACY RESULTS:



Results obtained with ln-transformed primary efficacy parameters summarized as below:

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90% Confidence Interval for Baseline-Corrected Levothyroxine (N=30 Subjects)							
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)	
	Reference (R)	Test (T)				Lower	Upper
C_{max} (ng/mL)	68.303	58.722	85.97	9.07	100.00	82.62	89.46
AUC_{0-72} (ng*hrs/mL)	2611.417	2230.708	85.42	12.82	100.00	80.76	90.35

SAFETY RESULTS:

- There was no adverse event occurred during conduct of the study.
- During post-study safety assessment adverse events were reported for twelve subjects (subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30).

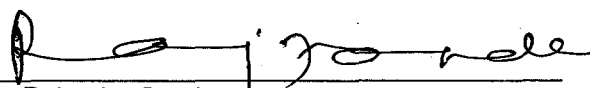
Name of the Sponsor: Macleods Pharmaceuticals Ltd., India	Individual Study Table Referring to part of the Dossier Volume: N/AP Page: N/AP	(For National Authority Use only)
Name of the Finished Product: Levothyroxine Sodium Tablets 200 mcg		
Name of Active Ingredient: Levothyroxine Sodium		
CONCLUSION: The 90% confidence intervals for the ratio (Test/Reference) of C_{max} and AUC_{0-72} for baseline-corrected-levothyroxine were within the acceptable limits of bioequivalence 80.00% - 125.00%. Thus it is concluded that the test formulation, three tablets as single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) is bioequivalent to reference formulation, three tablets as single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects under fasting condition. Both the formulations are safe and well tolerated following a single dose administration of the investigational product under fasting condition.		
Date of the report	13 th July 2018	

2.1 STATEMENT OF INVESTIGATORS

Study Title: Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

The study was conducted in accordance with the protocol and comply with all requirements regarding the obligations of investigators and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, national and ICH 'Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

We the undersigned have read this report and confirm that to the best of our knowledge it accurately describes the conduct and results of the study.



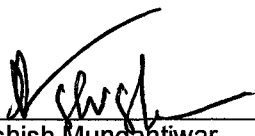
Dr. Rajendra Sonde

(M.B.B.S., PGDHMM, D.PHARM.)

Principal Investigator

13/07/18

Date



Dr. Ashish Mungantiwar

(Ph.D. Pharmacology)

Study Director

13/7/18

Date

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India

3.0 TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

SR. NO.	CONTENTS	PAGE NO.
1.0	TITLE PAGE	1
2.0	SYNOPSIS OF THE REPORT	2
2.1	Statement of Investigators	7
3.0	TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT	8
4.0	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	11
5.0	ETHICS	14
5.1	Independent Ethics Committee (IEC)	14
5.2	Ethical Conduct of the Study	14
5.3	Subject Information and Consent	14
6.0	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	16
7.0	INTRODUCTION	19
8.0	STUDY OBJECTIVES	24
8.1	Pharmacokinetic:	24
8.2	Safety	24
9.0	INVESTIGATIONAL PLAN	24
9.1	Overall Study Design and Plan – Description	24
9.2	Discussion of Study Design, Including the Choice of Control Group	26
9.3	Selection of Study Population	26
9.3.1	Inclusion Criteria	27
9.3.2	Exclusion Criteria	28
9.3.3	Removal of Subjects from Therapy or Assessment	29
9.4	Treatments	29
9.4.1	Treatments Administered	29
9.4.2	Identity of Investigational Product(s)	30
9.4.3	Method of Assigning Subjects to Treatment Groups	30
9.4.4	Selection of Doses in the Study	30
9.4.5	Selection and Timing of Dose for Each Subject	31
9.4.6	Blinding, Packaging and Labeling	31
9.4.7	Prior and Concomitant Therapy	32
9.4.8	Treatment Compliance	32
9.5	Efficacy and Safety Variables	32
9.5.1	Efficacy and Safety Measurements Assessed	32
9.5.2	Appropriateness of Measurements	34
9.5.3	Primary Efficacy Variable(s)	34
9.5.4	Drug Concentration Measurements	34
9.6	Data Quality Assurance	36
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size	36

9.7.1	Statistical and Analytical Plans	36
9.7.2	Determination of Sample Size	37
9.8	Changes in the Conduct of the Study or Planned Analyses.....	38
10.0	STUDY SUBJECTS	39
10.1	Disposition of Subjects.....	39
10.2	Protocol Deviations	39
11.0	EFFICACY EVALUATION	40
11.1	Data Sets Analyzed	40
11.2	Demographic and Other Baseline Characteristics	40
11.3	Measurements of Treatment Compliance	40
11.4	Efficacy Results and Tabulations of Individual Subject Data.....	40
11.4.1	Analysis of Efficacy.....	40
11.4.2	Statistical / Analytical Issues.....	41
11.4.3	Tabulation of Individual Response Data	41
11.4.4	Drug Dose, Dose Concentration and Relationships to Response.....	42
11.4.5	Drug-Drug and Drug-Disease Interactions.....	42
11.4.6	By-Subject Displays.....	42
11.4.7	Efficacy Conclusions	42
12.0	SAFETY EVALUATION	43
12.1	Extent of Exposure.....	43
12.2	Adverse Events (AEs).....	43
12.2.1	Brief Summary of Adverse Events	43
12.2.2	Displays of Adverse Events	43
12.2.3	Analysis of Adverse Events	43
12.2.4	Listing of Adverse Events by Subjects	43
12.3	Deaths, Other Serious Adverse Events and Other Significant Adverse Events.....	44
12.4	Clinical Laboratory Evaluation.....	44
12.4.1	Listing of Individual Laboratory Measurements by Subjects and Each Abnormal Laboratory Value	44
12.4.2	Evaluation of Each Laboratory Parameters	44
12.5	Vital Signs, Physical Findings and Other Observations Related to Safety.....	45
12.6	Safety Conclusions	46
13.0	DISCUSSION AND OVERALL CONCLUSIONS.....	47
14.0	TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT	48
14.1	Demographic Data	48
14.2	Efficacy Data	49
14.3	Safety Data.....	51
14.3.1	Display of Adverse Events	51
14.3.2	Listings of Deaths, Other Serious and Significant Adverse Events	51
14.3.3	Narrative of Deaths, Other Serious and Certain Other Significant Adverse Events	51

14.3.4	Abnormal Laboratory Value Listing	51
15.0	REFERENCE LIST	52
16.0	APPENDICES	
16.1	Study Information	
16.1.1	IEC Approved Protocol and Protocol Amendments	
16.1.2	Sample Case Record Form	
16.1.3	IEC Consulted IEC Approved Informed Consent Form	
16.1.4	List of Investigators and Important Participants in the Study	
16.1.5	Statement of Investigators	
16.1.6	Listing of Subjects Receiving Test Drug/ Investigational Product from Specific Batches Where More than One Batches were Used	
16.1.7	Randomization Scheme and Codes	
16.1.8	Audit Certificate	
16.1.9	Documentation of Statistical Methods	
16.1.9.1	Actual Time Points	
16.1.9.2	Statistical And Pharmacokinetic Output	
16.1.9.3	Statistical And Pharmacokinetic Sops	
16.1.10	Documentation of Inter Laboratory Standardization Methods and Quality Assurance Procedures	
16.1.11	Publications Based on the Study	
16.1.12	Important Publications Referenced in the Report	
16.2	Subject Data Listings	
16.2.1	Discontinued Subjects	
16.2.2	Protocol Deviations	
16.2.3	Subjects Excluded from the Efficacy Analysis	
16.2.4	Demographic Data	
16.2.5	Individual Serum Concentration Data	
16.2.6	Individual Efficacy Response Data	
16.2.7	Adverse Event Listing	
16.2.8	Listing of Individual Laboratory Parameters by Subject	
16.3	Case Record Forms	
16.3.1	CRF's for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events	
16.3.2	Other CRF's Submitted	
16.4	Individual Subject Data Listings	
16.5	Bioanalytical Report	

µL	: Microlitre
ADRs	: Adverse Drug Reactions
AE	: Adverse Event
ANOVA	: Analysis of Variance
AUC	: Area under Curve
AUC ₀₋₇₂	: The area under the serum concentration versus time curve from time zero to 72.00 hours, as calculated by the linear up-linear down trapezoidal method
BLQ	: Below Limit of Quantification
BMI	: Body Mass Index
B.P	: Blood Pressure
BPM	: Beats per Minute
BUN	: Blood Urea Nitrogen
CBC	: Complete Blood Count
C _{max}	: Concentration Maximum
CNS	: Central Nervous System
COA	: Certificate of Analysis
CPU	: Clinical Pharmacology Unit
CRF	: Case Record Form
CV	: Coefficient of Variance
°C	: Degree Centigrade
D	: Day
DLC	: Differential Leukocyte count
eMC	: The electronic Medicine Compendium
EMA	: European Medicine Agency
ECG	: Electro-Cardiogram
ER	: Extended Release
ESR	: Erythrocyte Sedimentation Rate
GCP	: Good Clinical Practices
GGT	: Gamma-glutamyl transferase
GGTP	: Gamma Glutamyl Transpeptidase
GLP	: Good Laboratory Practices
cGMP	: current Good Manufacturing Practices
HBsAg	: Hepatitis B Surface Antigen
HCV	: Hepatitis C Virus
HIV	: Human Immunodeficiency Virus
hrs	: Hour(s)
I.D.	: Identity
ICF	: Informed Consent Form
ICH	: International Conference for Harmonization

ICMR	: Indian Council of Medical Research
ICU	: Intensive Care Unit
IEC	: Independent Ethics Committee
IP	: Investigational Product
IR	: Immediate Release
IU	: International Unit
IUD	: Intrauterine device
LC-MS/MS	: Liquid Chromatography with Mass Spectroscopy/ Mass Spectroscopy
LDL	: Low-density lipoprotein
L/kg	: Liter / kilogram
L/h/kg	: Liter / hour / kilogram
LLOQ	: Lower Limit of Quantification
LSM	: Least Square Means
ME	: Medical Examination
mg	: milligram
mcg/ml	: microgram per millilitre
mL	: milliliter
N/AP	: Not Applicable
N/AV	: Not available
npoints	: No. of time points of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
oz	: Ounce
PA view	: Posterior Anterior View
PCV	: Packed Cell Volume
PK	: Pharmacokinetic
PLATO	: Platelet Inhibition and Patient Outcomes
PT	: Prothrombin time
QA	: Quality Assurance
R	: Reference Product
RBC	: Red Blood Cell
RH	: Relative Humidity
rpm	: Revolution Per Minute
SAE(s)	: Serious Adverse Event(s)
SADR	: Serious Adverse Drug Reactions
SAS	: Statistical Analysis System
SD	: Standard Deviation
SGOT	: Serum Glutamate Oxaloacetate Transaminase
SGPT	: Serum Glutamate Pyruvate Transaminase
SOP(s)	: Standard Operating Procedure(s)
SQ	: Subject Questionnaire

T	: Test Product
T _{max}	: Time of maximum measured serum concentration. If maximum value occurs at more than one time point, T _{max} is defined as the first time point with this value in each period.
T ₄	: L-thyroxine
T ₃	: L-triiodothyronine
TG	: Triglycerides
TBA	: thyroxine-binding albumin
TBG	: thyroxine-binding globulin
TBPA	: thyroxine-binding prealbumin
TG	: Triglycerides
TRH	: Thyrotropin-releasing hormone
TSH	: thyrotropin-stimulating hormone
w/v	: Weight / Volume

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol, BEQ-2321-LEVT-2017, version no. 02, dated: 19th March 2018; English ICF, version no. 02, dated: 19th March 2018; Hindi and Marathi ICFs, version no. 01, dated: 19th March 2018; Case Record Form (CRF), version no. 01, dated: 19th March 2018 and Questionnaire for subject (English, Hindi and Marathi), version no. 01 were sent to HumanCare Independent Ethics Committee on 23rd March 2018. HumanCare Independent Ethics Committee in its meeting held on 28th March 2018 gave approval to the submitted protocol, ICFs, CRF and Questionnaire for subject.

Approval was granted after the review of documents and the approved version which was followed for the study conducted bears the following version number and date:

Documents	Version No.	Dated
Protocol	02	19 th March 2018
English ICF	02	19 th March 2018
Hindi ICF	01	19 th March 2018
Marathi ICF	01	19 th March 2018
Case Record Form	01	19 th March 2018
Questionnaire for Subject	01	-

Dr. Pachpute Amol P. (Chairperson) chaired the IEC meeting. The copy of the IEC approved protocol is appended as appendix 16.1.1. The details of IEC consulted along with approval letter and IEC approved ICFs are given in appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol and comply with all requirements regarding the obligations of investigators and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, national and ICH 'Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

5.3 Subject Information and Consent

Subjects from the pool of healthy volunteers who were screened within 21 days prior to the dosing day were considered as potential participants in the study. Before admission of volunteers into the Clinical pharmacology unit (CPU) on the pre-study day, they were given a verbal presentation of the information on the study together with a written document (in the language that they can understand best) describing the purpose, procedures, and risks of the study together with a description of the obligations of the subjects. Volunteers gave their written consent for

participating in the study by signing with date the informed consent form. The signed copy of the form is kept in the study specific ICF file at the investigator's/ institution site and the subjects were also given a copy for their own retention. A copy of the consent form used is appended in appendix 16.1.3. Before the volunteers undergo the pre-screening process for acceptance into healthy volunteer bank, they were provided with written and verbal information about the nature of the tests to be performed following which all willing volunteers gave their written consent.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor's Representative

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Study Director

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The list of investigators with their affiliations, their role in the study and their curriculum vitae are appended as appendix 16.1.4. The list of other important participants in the study is appended in appendix 16.1.4. The declaration statement by the principal investigator is appended as appendix 16.1.5.

7.0 INTRODUCTION

Pharmacology ^[1]

Pharmacotherapeutic group: thyroid hormones.

The effect of the synthetic levothyroxine in Euthyrox is similar to that of the naturally occurring essential hormone, secreted by the thyroid gland. It is converted, just like the endogenous hormone in T3 in the peripheral organs and develops its specific effect through the T3 receptors. The body can not distinguish between endogenous and exogenous levothyroxine.

Clinical Pharmacokinetics ^[1]

Levothyroxine is absorbed almost entirely in the upper part of the small intestine when taken orally. Depending on the galenical form, the absorption is up to 80%. $T_{\max}$ is about 5 to 6 hours. After oral administration, the onset of action occurs after 3-5 days. Levothyroxine shows an extreme strong binding of about 99.97% on specific transport proteins. This protein hormone binding is not covalent and thus the bound hormone in the plasma is exchanged continuously and very quickly with the free hormone fraction. The volume of distribution is approximately 10-12 liter. Due to the high degree of protein binding, levothyroxine does not undergo hemodialysis or hemoperfusion.

The half-life of levothyroxine is approximately 7 days. With hyperthyroidism this is shorter (3-4 days). In hypothyroidism this is longer (about 9-10 days). The liver contains 1/3 of the whole extrathyroid levothyroxine. This is quickly exchangeable with levothyroxine in the serum.

Thyroid hormone is metabolised primarily in the liver, kidneys, brain and muscles. The metabolites are excreted in the urine and faeces. The total metabolic levothyroxine clearance is about 1.2 l of plasma per day.

Indications and Uses ^[1]

Euthyrox 25 - 200 µg:

- Treatment of euthyroid goiter, especially in adults when iodine is not indicated
- Recurrence of prophyllaxis after a resection, depending on the postoperative hormone status
- Substitution in hypothyroidism
- Suppression treatment for thyroid carcinoma

Euthyrox 25 - 100 µg:

- Substitution during the concomitant treatment with thyrostatics in hyperthyroidism

Euthyrox 100/150/200 µg:

- Diagnostic use in thyroid suppression testing

Posology and method of administration ^[1]

Dosage

In order to treat each patient according to his / her individual needs, tablets are available with a sodium levothyroxine content ranging from 25 to 200 µg. As a result, patients usually have to only one tablet per day.

The dosages listed below are guidelines.

The individual daily dose should be determined on the basis of laboratory tests and clinical trials.

Because a number of patients exhibit increased concentration T4 and free T4 concentration, the basal "Thyroid stimulating hormone (TSH) serum concentration" provides a more reliable basis for the therapy.

Thyroid hormone therapy should be started with a low dose and gradually every 2 to 4 weeks until the full replacement dose is reached.

Indication	Recommended dose (µg sodium levothyroxine / day)			
Treatment of euthyroid body	75 - 200			
Recurrent prophylaxis after contract resection	75 - 200			
Substitution in hypothyroidism in adults - starting dose - maintenance dose	25 - 50 100 - 200			
Substitution in children with hypothyroidism obtained - starting dose - maintenance dose	12.5 - 50 100 - 150 µg / m ² body surface area			
Substitution during simultaneous treatment with thyrostatics in hyperthyroidism	50 - 100			
Suppression treatment for thyroid carcinoma	150-300			
Diagnostic use at Thyroid suppression examination	Week 4 for the test	Week 3 for the test	Week 2 for the test	Week 1 for the test
Euthyrox 200 µg	---	---	1 tabl /day	1 tabl /day
Euthyrox 100 µg	---	---	2 tabl /day	2 tabl /day
Euthyrox 150 µg	½ tabl /day	½ tabl /day	1 tabl /day	1 tabl /day

Method of administration

The daily doses can be given in a single administration.

Ingestion: one-time daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with some liquid (for example half a glass of water).

The duration of treatment is generally lifelong in the case of hypothyroidism substitution and after strumectomy or thyroidectomy and in recurrent prophylaxis after contract resection.

Simultaneous treatment of hyperthyroidism after an euthyroid condition has been achieved is indicated during the period that a thyrostatic is given.

For a benign euthyroid head, a treatment period of 6 months to 2 years is necessary. To prevent recurrence, prophylaxis with low dose of iodine (100 - 200 µg / day) recommended after taking the head size. If the medical treatment during this period appears insufficient, surgery or treatment with radioactive iodine should be considered.

Adverse Reactions ^[1]

Side effects

The frequency category for the following side effects is not known

Immune system disorders	Hypersensitivity Angio-edema

If the individual tolerance limit of sodium levothyroxine or overdose is exceeded the following clinical symptoms, characteristic of hyperthyroidism, may occur, mainly if the dose is increased too quickly at the start of treatment. In such cases the daily dose should be reduced or the medication for a number of times days to be stopped. The treatment can be carefully started again as these effects have disappeared.

Endocrine disorders	Hyperthyroidism Irregular menstruation
Nervous system disorders	Headache Benign intracranial Hypertension Tremor Restlessness Insomnia
Cardiac disorders	Arrhythmia Atrial fibrillation Extrasystoles Tachycardia Palpitations Angina pectoris
Gastrointestinal disorders	Vomiting Diarrhea
Skin and subcutaneous tissue disorders	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle weakness Muscle spasms
General disorders and administration site conditions	Excessive flushing Pyrexia
To investigate	Weight reduced

Precautions/ Warning/ Special warning ^[1]

Before the start of treatment with thyroid hormones or to carry out one thyroid suppression test, the following conditions should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency (hypopituitarism), adrenal insufficiency, autonomously functioning thyroid gland.

At the start of treatment with levothyroxine in patients at risk of psychotic disorders, it is recommended to start with a low dose of levothyroxine and the dose to it gradually increases the beginning of treatment. It is advised to monitor the patient. At the occurrence of symptoms of psychotic disorders, adjustment of the dose of levothyroxine should be considered.

Even a drug-induced mild hyperthyroidism should occur in patients with coronary artery disease insufficiency, cardiac insufficiency or tachycardia arrhythmias are avoided. That is why in this case regular checks of the thyroid hormone parameters.

In the case of secondary hypothyroidism, the cause must be determined before replacement therapy is given and, if necessary, replacement therapy of a compensated adrenal insufficiency.

If the suspicion of an autonomously functioning thyroid gland exists, one should be treated before treatment TRH test or a suppression scintigram must be made.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, serve supraphysiologic serum levothyroxine levels are to be avoided and therefore the thyroid function to be closely monitored.

Levothyroxine should not be given in other hyperthyroid conditions, except in concomitant supplementation during thyreostatics treatment of hyperthyroidism.

If treatment with levothyroxine is initiated, it is recommended to change it when changing it levothyroxine product, the dosage to adjust to the clinical response of the patient and the laboratory results.

With concomitant administration of orlistat and levothyroxine, hypothyroidism and / or decreased Hypothyroidism control. Patients who should take levothyroxine should be advised to consult their physician before treatment with orlistat is started, stopped, or is adjusted, because orlistat and levothyroxine may have to be at different times ingested and the dose of levothyroxine may need to be adjusted. Further recommended to monitor the patient by monitoring the hormonal serum levels.

Euthyrox contains lactose. Patients with rare, congenital galactose intolerance problems, Lap-lactase deficiency or glucose-galactose malabsorption should not be used.

For diabetic patients and patients undergoing anticoagulant therapy.

Contraindications ^[1]

- Hypersensitivity to the active substance or to any of the excipients.
- Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Euthyrox should not be started in acute myocardial infarction, acute myocarditis and acute pancarditis.
- Combination therapy of levothyroxine with a thyrostatic agent is not indicated during the pregnancy.

Study Rationale

The Macleods Pharmaceuticals Ltd. has developed generic alternative to the reference medicinal product of Levothyroxine Sodium Tablets 200 mcg. Therefore, its bioequivalence to the reference medicinal product must be evaluated in fasting conditions. In the present study, test product of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) was compared with Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) under fasting condition.

Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) is qualified as reference medicinal product in the electronic Medicine Compendium (eMC) by European Union (EU).

8.0 STUDY OBJECTIVES

The bioequivalence study presented here was carried out for evaluating the following objectives:

8.1 Pharmacokinetic:

To evaluate the comparative oral bioavailability of Three Tablets as Single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) with Three Tablets as Single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy, adult, human subjects under fasting condition.

8.2 Safety

To monitor the safety and tolerability of three tablets as single oral dose of Levothyroxine Sodium Tablets 200 mcg when administered in healthy, adult, human subjects under fasting condition.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

This was an open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

The study was carried out in single group comprising of 30 male subjects (subject number 01 to 30). Subjects from the pool of healthy volunteers who were screened within 21 days prior to the first dosing day were considered as potential participants in the study. The inclusion and exclusion criteria were applied to all subjects as a condition of admission into the study.

Before admission of volunteers into the CPU, on the pre-study day, the volunteers were given full details of the study. Volunteers gave their written consent for participating in the study by signing with date the informed consent form. Tests for drugs of abuse and alcohol consumption by breath alcohol analyzer was carried out followed by pre-entry vital signs, medical examination, inclusion and exclusion criteria check.

After check-in, there was a supervised overnight fasting period of at least 10.00 hours before dosing. Three pre-dose samples were taken before dosing thereafter a series of blood samples were taken till 72 hours post-dose with the subject remaining in the CPU. After the 72 hours post-dose blood sample collection, the subjects were allowed to leave CPU after checking their vital signs and medical examination.

After a washout period of 35 days, the same procedure was repeated in subsequent period except for the ICF presentation, obtaining of written informed consent.

Post-study safety assessment was carried out after last blood collection of period II.

After the subjects have been recruited for the study, the duration of their participation was 40 days with 35 days washout.

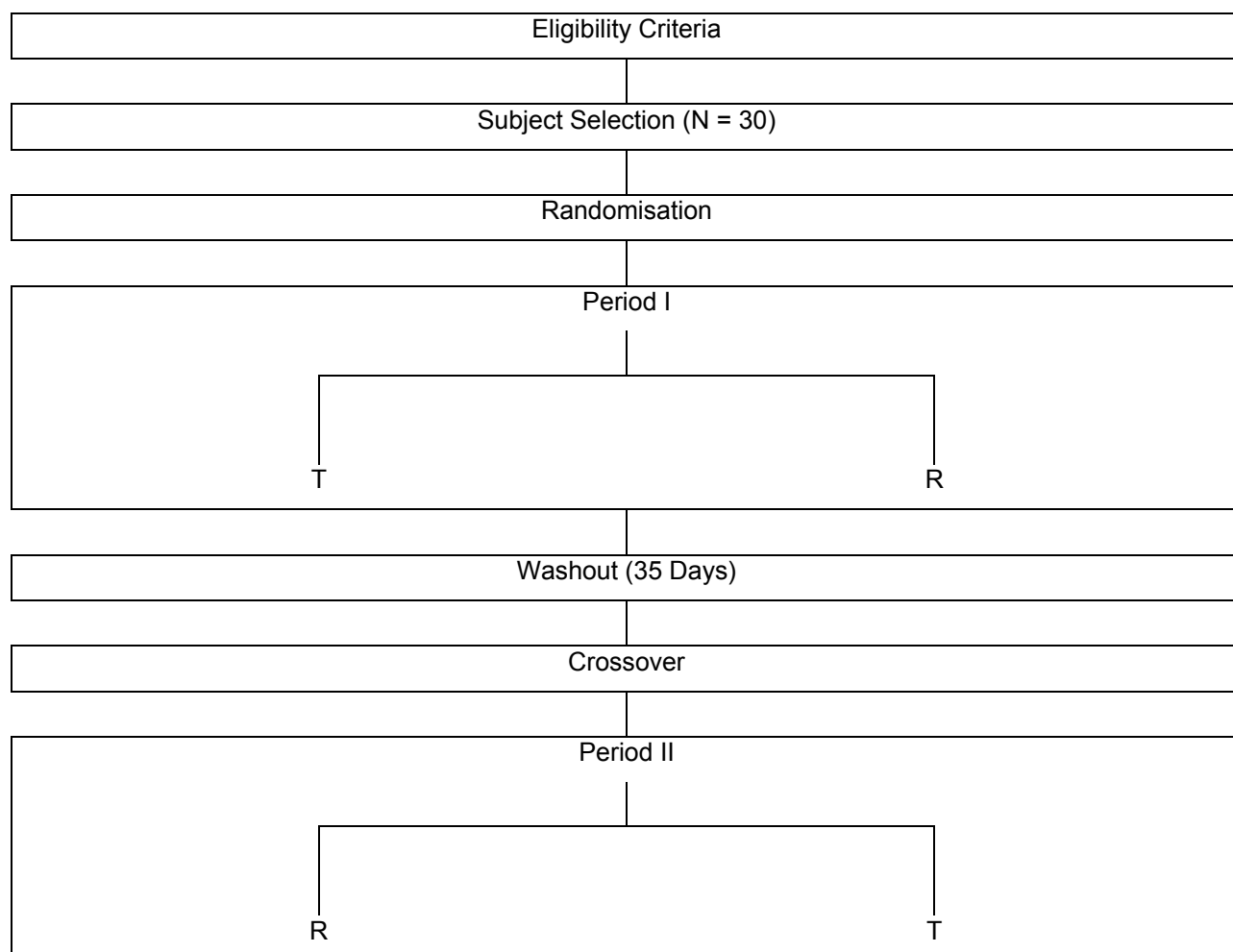
Washout Period:

There was a washout period of 35 days from the completion of dosing between two consecutive periods.

The study flow chart is given in figure-1.

FIGURE – 1

STUDY FLOW CHART



N – Number of Subjects

R – Reference Product

T – Test Product

9.2 Discussion of Study Design, Including the Choice of Control Group

It was an open labeled study because it was not possible to blind the appearance of the products. The analysts concerned, however, were blinded to the sequence of administration of test and reference product to the individual subjects.

The order of receiving treatment was randomized to avoid bias in allocation of sequence to the subjects.

There were two treatments: the sponsor's product was the test product while the innovator product was the reference product.

The subjects served as their own control, the study being crossover.

Since there were two treatments, the trial design was two periods, two sequences. The effect of period and sequence on primary efficacy criteria was analyzed by ANOVA (Analysis of variance).

To reduce variability in the biomedical experimentation and to control factors, which may affect the evaluation and comparison of primary efficacy factors; healthy, adult, human subjects were selected.

The number of subjects to be included in the study was estimated from “Published literature”.^[2]

Levothyroxine being a long half-life drug (approximately 7 days) and because of low intra-subject variability on distribution and clearance, an AUC truncated at 72.00 hours was used, thus samples till 72.00 hours for levothyroxine was collected ensuring completion of gastrointestinal tract absorption (approximately 3 days).

Levothyroxine being a long half-life drug (approximately 7 days), the two dosing days i.e. for period 1 and 2 were separated by a washout period of 35 days.

9.3 Selection of Study Population

Subjects from the pool of healthy volunteers who were screened within 21 days prior to the first dosing day were considered as potential participants in the study.

The general screening was carried out after obtaining the written consent on IEC approved 'Informed Consent for Screening' from the volunteers. The screening procedures included the following:

- Demographic data, including sex, completed age, height and weight, BMI, diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation and history of participation in a drug research study.
- Medical history, including relevant past medical/ surgical history, family history, history of allergies (food/ drug/ any other), past medication history in the last 90 days.
- Present complaints (if any), medical examination including recording of vital signs (B.P, Pulse, Temperature and respiration), and general examination, physical and systemic examination.
- 12-lead ECG for heart rate, rhythm and specific finding (if any).
- Pathology Laboratory investigation including, hematology, clinical biochemistry, serology (HbsAg, HIV1, HIV2 and HCV) and routine examination of urine.
- Chest X-ray (PA view).

- In general screening volunteers were gone through the following laboratory test: Serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH).

The volunteers with laboratory values within normal limits or with clinically non-significant values were called one day prior to the study for study informed consent form presentation.

The individual baseline (screening) laboratory results are given in appendix 16.2.8 (Table A) and the individual clinical impression of ECG and chest X-ray (PA view) are given in appendix 16.2.8 (Table C). All the laboratory results, which were outside the Reference range but within the 'acceptable limit (For Acceptable limits refer Appendix V of protocol) were considered clinically non significant.

On the pre-study day, the volunteers were given full details of the study. Volunteers gave their written consent for participating in the study by signing with date the informed consent form. Tests for drugs of abuse, and alcohol consumption by breath alcohol analyzer was carried out followed by pre-entry vital signs, medical examination, inclusion and exclusion criteria check.

Only those volunteers who signed the study informed consent form were checked in for the study on the day of check-in (one day prior to dosing).

All the volunteers who were checked in the study were found negative for breath alcohol test and urine test for drugs of abuse [Cocaine (COC), Amphetamines (AMP), Marijuana (THC), Morphine (MOP), Barbiturates (BAR), and Benzodiazepine (BZD)].

Subject number was allocated in the order of completion of check-in procedure activities by the volunteers.

Thirty fit and consenting subjects fulfilling inclusion/ exclusion criteria and complying with the requirements of the protocol were enrolled in the study.

9.3.1 Inclusion Criteria

Subjects had to fulfill all of the following criteria to be considered for inclusion into this study:

1. Healthy volunteers within the age range of 18 to 45 years.
2. Presently non-tobacco users (smokers and chewers).
3. Willingness to provide written informed consent to participate in the study.
4. Body-mass index (BMI) between 18.50 kg/m² and 29.99 kg/m² (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).
5. Absence of significant disease or clinically significant abnormal laboratory values or laboratory evaluation, medical history or physical examination during the screening.
6. Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.
7. Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.
8. Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.
9. Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).

10. Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm, and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).

9.3.2 Exclusion Criteria

The subjects were to be excluded based on the following criteria:

1. Personal history of allergy or hypersensitivity to Levodihydroxy or excipients (Magnesium stearate (E 572), maize starch, Croscarmellose sodium (E 468), Gelatin (E 441), Lactose monohydrate.)¹ or allied drugs.
2. Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure, Hepatitis, Hypotensive episodes, Hyperglycemia etc.
3. Presence of any clinically significant abnormal laboratory values during screening e.g. significant abnormality of liver function test, renal function test etc.
4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.
5. History of seizures, epilepsy or any kind of Neurological disorders.
6. Past history of Anaphylaxis or angioedema.
7. Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.
8. History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to dosing.
9. Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.
10. Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.
11. Use of any recreational drug or a history of drug addiction.
12. Participation in any clinical trial within the past 90 days.
13. History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
14. Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.
15. Consumption of any other prescription drug or over the counter (OTC) drugs [including vitamins and medicinal products from natural origin] within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study.
16. An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.
17. Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.
18. Use of oral contraceptive in last 90 days (for females).

19. Pregnant / lactating volunteers (for females).
20. Abnormal serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH) test values.

9.3.3 Removal of Subjects from Therapy or Assessment

The subjects were free to withdraw from the study at any time without having to give any reasons thereof. The Principal Investigator, at his discretion, could also withdraw the subject from the study for any of the valid reason, which he deems to be appropriate in view of the safety and well being of subject, GCP principles or objectives of the project, in particular for:

1. If the subject suffers from significant illness.
2. If the subject requires concomitant medications which may interfere with pharmacokinetic of the study drug.
3. If the subject has entered the study in violation of the inclusion and the exclusion criteria.
4. If the subject is found to be non co-operative.
5. If the subject decides to voluntarily dropout from the study.

In any of these cases the compensation to the subject would have been made as per the guidelines regarding these i.e. ICH-GCP and National guidelines (ICMR guidelines for Clinical Trials) and as per the compensation structure approved by IEC.

Whatever reasons if a subject is not satisfactorily complete the study, he would be asked to attend for the post-study examination. Whenever possible, the post-withdrawal follow up would be done immediately after the subject is withdrawn. In case a subject is not willing to undergo such medical examination, it would be documented so.

9.4 Treatments

9.4.1 Treatments Administered

An oral dose of Reference product [3 × 200 mcg tablets] or Test product [3 × 200 mcg tablets] was administered at 0.00 hour during each period with 240 mL (about 8 oz) of drinking water at room temperature as per the randomization schedule under the supervision of the medical officer where end time of the dosing are recorded in investigational product administration forms. Subjects received the alternate 'treatment' in such a way that each subject completing the study received both the treatments test and reference each at the end of the study.

Owing to the sensitivity of levothyroxine to light, Investigational Product was dosed under yellow monochromatic light.

Subjects were dosed while in upright sitting posture and were instructed to remain seated or be ambulatory (avoiding any strenuous activity) for first two hours following the investigational product administration (except during recording of vitals and blood collection time point). During this interval, under supervision, subjects were permitted to use the washroom facilities. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. However should any adverse event occur at any time during housing the subjects would be placed in an appropriate posture.

9.4.2 Identity of Investigational Product(s)

i) Test Formulation (T):

Levothyroxine Sodium Tablets 200 mcg

Batch No.: MLK602C

Manufacturing Date: 10/2016

Expiry Date: 09/2018

Manufactured by: Macleods Pharmaceuticals Ltd. India

Dose: 3 Tablets

Mode of administration: Administered orally with 240 mL of drinking water

Batch size: 150000 Tablets

Assay: 101.7%

ii) Reference Formulation (R):

Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg

Batch No.: 209740

Manufacturing Date: N/AV

Expiry Date: 11/2018

Marketing Authorization Holder: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijk

Manufactured by: Merck KGaA, Frankfurter Str.250, and Darmstadt, Germany

Dose: 3 Tablets

Mode of administration: Administered orally with 240 mL of drinking water

Batch size: Not Available

Assay: 98.2%

9.4.3 Method of Assigning Subjects to Treatment Groups

The subjects were assigned to the sequence either test or reference product, according to the randomization schedule.

The order of receiving test and reference product for each subject during the study periods was determined according to randomization schedule (generated using SAS[®] version 9.4).

Subject number was allocated in the order of completion of check-in procedure activities by the volunteers.

9.4.4 Selection of Doses in the Study

The available strengths of Euthyrox[®] (levothyroxine sodium) Tablets are 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mg, 137 mcg, 150 mcg, 175 mcg and 200 mcg. The recommended adult oral single dose of Euthyrox[®] (levothyroxine sodium) Tablets started with a low dose and gradually every 2 to 4 weeks until the full replacement dose is reached. Therefore, single oral dose of 3 tablets of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg is chosen, since it is safe (well tolerable) for healthy volunteers and was expected to provide measurable serum concentrations and single dose study is adequate for this product's bioequivalence.

9.4.5 Selection and Timing of Dose for Each Subject

Dosing was done between 09:00 hrs to 09:42 hrs (0.00 hrs) in the batch of two subjects during each period. The dosing interval between successive subjects was 3 minutes.

The test or reference products were orally administered to the subjects while in upright sitting posture, with 240 mL (about 8 oz) of drinking water at room temperature as per the randomization schedule under the supervision of the Medical Officer followed by examination of the oral cavity.

The dose was administered after an overnight fast of at least 10 hours in each period. Fasting was continued for 4.00 hours post-dose, and then meals were provided at specified intervals. Drinking water/ any fluid was disallowed for 1 hour pre-dose and 1 hour post-dose administration, except 240 mL of drinking water during administration of the drug dose. Subsequently, drinking water was provided ad libitum.

9.4.6 Blinding, Packaging and Labeling

This study comprised of a randomized, open label design. Study monitors and subjects involved in the study were not blinded. However the analyst concerned, were blinded to the sequence of administration of test or reference products to the individual subject. The serum sample storage vials were labeled; mentioning study number, period number, subject number, sample number, time point (hrs) and aliquot number, but the identity of product administered was not mentioned.

The randomization schedule was in custody of registered pharmacist and was kept in the cabinet under lock and key in the Humidity chamber and dispensing area and was not accessible/ circulated or made available to other staff members via any medium until the completion of statistical analysis. The investigational product dispensing raw data record was under lock and key until the completion of statistical analysis.

An adequate number of investigational products (IPs) in sealed condition along with certificate of analysis (COA) were received at Bioequivalence department of Macleods by the registered pharmacist.

Dispensing

As per the randomization schedule, the registered pharmacist prepared the doses under the supervision of trained personnel and in the presence of Quality Assurance personnel in both the periods. Remaining investigational products were stored in their original container as retention samples in stability chamber at $22 \pm 2^{\circ}\text{C}$ and $60 \pm 5\%$ RH. Owing to the sensitivity of Levothyroxine to light, dispensing of the investigational product was done under yellow monochromatic light.

The dispensed investigational products were transferred to the drug-dispensing containers as unit doses. The drug-dispensing containers used for dispensing were properly labeled for the sponsor, Instruction – (for clinical trial use only), study number, active ingredient, subject number, treatment ID, period number, batch/lot number, dosage form and expiry date, number of unit dispensed, route of administration and storage condition. The drug dispensing containers stuck

with detachable duplicate label (similar to that 1 label stuck on the dispensing container) were placed in zip lock bag.

Investigational product accountability included the records of the receipts, intake of investigational products during both the periods of the study and remaining quantities of investigational products. The investigational products were stored in stability chamber at $22 \pm 2^{\circ}\text{C}$ and $60 \pm 5\%$ RH and inventory were maintained in the logbook of investigational product. Data for temperature and humidity was monitored and recorded regularly through data logger.

Only authorized personnel has access to the investigational product storage areas.

For certificate of analysis of test and reference products, refer appendix – 16.1.12.

9.4.7 Prior and Concomitant Therapy

Consumption of any other prescription drug or over the counter (OTC) drugs [including vitamins and medicinal products from natural origin] within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study was an exclusion criterion. Further, the subjects were not supposed to consume any medication during the conduct of the study. All subjects, who checked-in the study, confirmed that they did not consume any medication within the 2 weeks of the start of first period or during the study.

9.4.8 Treatment Compliance

Subjects were provided with the identity card (I-card) and wrist band. While dosing, the staff on duty confirmed the subject's identity with I-card, wrist band and the information mentioned on the investigational product administration form.

After administration of the dose of investigational product, examination of the oral cavity was performed under supervision of medical officer to assess the compliance to this procedure and the same is noted in the drug administration form of each subject. A label is affixed to the investigational product administration form in the appropriate place to confirm correct administration of investigational product. The time of actual dose administration is recorded in the investigational product administration form.

Investigational product accountability record and evaluation of the serum drug concentration of the samples confirmed 100% compliance of all the subjects from whom the data was analyzed.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

Efficacy Measurements Assessed

The following pharmacokinetic parameters (variables) of baseline-corrected-levothyroxine were estimated after drug administration under fasting conditions:

Primary Efficacy Variables

$C_{\max}$ and AUC_{0-72}

Secondary Efficacy Variable

T_{max}

These parameters were derived individually for each subject from their baseline-corrected-levothyroxine concentration in serum. Actual time of blood collection was considered for pharmacokinetic calculations.

For estimation of PK parameters, concentrations that were below level of quantification (BLQ) were assigned a value of zero. In the calculations of PK parameters, missing values were ignored. Serum concentrations used to determine PK parameters would be listed.

The pharmacokinetic parameters were calculated by non-compartmental methods using SAS[®] version 9.4.

The calculations of the individual pharmacokinetic parameters were carried out as follows:

C_{max} : Maximum measured serum concentration.

AUC_{0-72} : The area under the serum concentration versus time curve from time zero to the 72.00 hours, as calculated by the linear up-linear down trapezoidal method.

T_{max} : Time of maximum measured serum concentration. If maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value in each period.

Subjects with Pre-dose Concentration

If the pre-dose concentration is less than or equal to 5 percent of C_{max} value in that subject in the particular period, the subject's data without any adjustments was to be included in all pharmacokinetic measurements and calculations. If the pre-dose value is greater than 5 percent of C_{max} , the subject to be dropped from bioequivalence study evaluations.

Data Deletion Due to Vomiting

Data from subjects who experience emesis during the course of a bioequivalence study was to be deleted from statistical analysis if vomiting occurs within 2 times median T_{max} .

Safety Measurements Assessed

Safety was evaluated by monitoring clinical adverse events during study periods. In each period, subject questionnaire and vital signs (Blood pressure, Temperature and Pulse Rate) was done at the time of check-in, pre-dose and 1.00, 3.00, 6.00, 9.00, 23.00, 29.00, 35.00, 48.00 and 72.00 post-dose (Time points being relative to the investigational product dosing).

Note: Subject was kept in supine position for at least 5 minutes before start of Blood Pressure recording on each time point.

Medical examinations were carried out at the time check-in and check-out post-dose of both the periods.

During the course of the study, subjects were monitored for adverse events, if any, throughout the course of the study by asking them if they were feeling fine or had any discomfort, at the time of clinical examination and recording of vital signs and recording the same in their respective CRF.

The subjects were told to inform the attending personnel or medical officer of any adverse event that may occur during the time of their stay at the clinical facility of bioequivalence department of Macleods Pharmaceuticals Ltd. and during the entire duration of the study (including the wash out period).

The following evaluations were done at screening and in the follow-up phase:

- Medical examination (vital signs, 12 lead ECG, X-ray (only during pre study screening) and general and systemic examination).
- Pathology Laboratory investigation (hematology, clinical biochemistry) and serology and routine examination of urine (only during pre study screening).

9.5.2 Appropriateness of Measurements

The serum samples of subjects were analyzed by a validated LC-MS/MS method. The limit of quantification of 10.06 ng/mL for levothyroxine was enough to quantify the analyte from the serum samples collected up to 72.00 hours after drug administration. The linearity range of 10.06 ng/mL to 304.20 ng/mL for levothyroxine was enough to quantify the expected concentration range of levothyroxine from subject serum with the proposed dose of Levothyroxine Sodium 600 mcg (3 × 200 mcg).

9.5.3 Primary Efficacy Variable(s)

The following pharmacokinetic parameters were assessed as primary bioavailability variables:

C_{max} : Maximum measured serum concentration.

AUC_{0-48} : The area under the serum concentration versus time curve from time zero to 72.00 hours, as calculated by the linear trapezoidal method

9.5.4 Drug Concentration Measurements

Concentration of levothyroxine was measured in serum samples of the subjects.

Blood samples (1 × 6 mL) were collected in blood collection tube containing clot activator during each period. The venous blood samples were withdrawn at -0.50, -0.25 and -0.03 hours prior to dosing (pre-dose) and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose (time points being relative to the investigational product dosing).

The pre-dose samples were collected prior to investigational product dosing. The post-dose samples were collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute is recorded. Any deviations above two minutes are recorded as protocol deviation.

During in-house stay blood samples were collected through an indwelling cannula placed in a forearm vein. Intravenous indwelling cannula was kept in place as long as required by injecting not more than 0.5 mL of normal saline solution during the collection of multiple samples. In such a case, the blood sample was collected after discarding the first 0.5 mL of normal saline blood from

Validated LC-MS/MS method was employed for the estimation of levothyroxine in serum. Serum samples from all treated subjects were analyzed. During estimation of Levothyroxine in serum quality control samples were distributed throughout each batch of study samples.

Whenever possible, samples from each subject were analyzed on the same standard curve. Samples with drug concentration greater than upper limit of the validated range of the analysis were reanalyzed as per the standard test procedure based on method validation report. Any missing sample or unreportable concentration value would be reported as 'missing' / 'not reported' and reasons for their missing would be documented.

The analysts concerned were blinded with respect to the randomization code, and as a result to the order of administration of the study medication.

9.6 Data Quality Assurance

The quality control personnel performed the quality control check of the case report forms and of all source documentation.

The Quality Assurance department of Macleods Pharmaceuticals Bioequivalence Department conducted both in process and retrospective audits of Clinical, Bioanalytical and Pharmacokinetic and Statistical phase of the study. The audits were conducted as per in-house standard operating procedure as appended in appendix 16.1.10. The findings in brief were reported to the management.

The Quality Assurance statement is appended as appendix 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Following were the plans for statistical analysis:

- Use descriptive statistics (Number of subjects (N), arithmetic mean, S.D., C.V., minimum, and maximum) to summarize the serum concentrations at each time of measurement.
- For purpose of descriptive linear and semi-logarithmic plots of the mean and individual serum concentration by scheduled sampling time provided.
- Report missing samples or unreportable concentration values as 'missing/ not reported' and document the reason for the same.
- Actual time of blood collection was considered for pharmacokinetic calculations.
- Use SAS® system version 9.4 for estimation of pharmacokinetic parameters and its statistical analysis of baseline-corrected-levothyroxine from their serum concentration data.
- Report the summary statistics for all pharmacokinetic parameters for both the test and reference products. The reported parameters are the minimum, maximum, arithmetic means, median, standard deviation and the coefficient of variation for untransformed data.
- Analyze the log-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) for baseline-corrected-levothyroxine using standard ANOVA model with the main effects of "sequence, period, formulation and subject nested within sequence".

- Use a separate ANOVA model to analyze each of the parameters.
- Each analysis of variance including calculation of mean square error, p-value of factors and the associated degrees of freedom.
- The sequence effect is tested at 5% level of significance with subjects nested within sequence as an error term.
- The formulation and period effects are to be tested at 5% level of significance.
- Use SAS procedure 'PROC GLM' to perform analysis of variance.
- Calculate and report ratio of geometric means using the LSM for log transformed C_{max} and AUC_{0-72} .
- Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters (C_{max} and AUC_{0-72}).
- Report the geometric means of the test and reference product.
- Report % Bioavailability of C_{max} and AUC_{0-72} .
- Calculate the power of the ANOVA model to detect the ratio of the two products averages (geometric means) being equal to 125% (or 80%) at the 5 % significance level for analyses using the log-transformed data.
- Calculate the intra subject coefficient of variation using $100 \times \sqrt{e^{MSE} - 1}$ with help of SAS® version 9.4. Where MSE is mean squared error obtained from Analysis of Variance model.
- Calculate baseline- corrected 90% confidence interval for the ratio of both the products averages (geometric means) by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- Claim the treatment to be bioequivalent if the 90% confidence intervals baseline-corrected-levothyroxine is entirely included in the range of 80.00% – 125.00% for log-transformed C_{max} and AUC_{0-72} .

9.7.2 Determination of Sample Size

Following data are obtained from "Published literature".^[2] Based on 2 x 2 Crossover study of Levothyroxine performed on 76 subjects under fasting condition and 71 subjects were used for the statistical analysis. Each subject received a single dose of 600 mcg (3*200 mcg) of one of the 2 levothyroxine formulations. Thus, Intra-subject C.V. was not available; it was calculated using the available data as shown below:

The pharmacokinetic parameters and statistical results for levothyroxine are as follows:

Pharmacokinetic Parameters	Ratio (T/R) (%)	90 % C.I. (%)	
		Lower	Upper
C_{max}	87.9000	84.9950	90.9043
AUC_{0-t}	90.2556	86.8626	93.7812

Calculation:

Assume that n1 (Number of AB sequence) = 36 and n2 (Number of BA sequence) =35

MSE for C_{max} = 0.014422 and MSE for AUC_{0-t} = 0.018748.

Intra-subject C.V. for C_{max} = $100 * \sqrt{e^{MSE} - 1}$ = 12.05%

Intra-subject C.V. for AUC_{0-t} = $100 * \sqrt{e^{MSE} - 1}$ = 13.76%

Sample size is calculated using SAS®. The highest Intra-subject C.V. was observed to be 13.76%.

Hence using this Intra-subject C.V. the sample size calculation is as follows:

Two-Sample Equivalence

Multiplicative Model Lower Bound = 0.80 Upper Bound = 1.25

Alpha=0.05

Null Ratio	Coeff of Variation	Power	N per Group
0.95	0.1376	0.800	9
	0.1376	0.850	11
	0.1376	0.900	12
	0.1376	0.950	15
1.00	0.1376	0.800	8
	0.1376	0.850	8
	0.1376	0.900	9
	0.1376	0.950	11
1.05	0.1376	0.800	9
	0.1376	0.850	10
	0.1376	0.900	12
	0.1376	0.950	15

The highest intra subject C.V. for levothyroxine was observed to be 13.76% for AUC_{0-t} from Published literature. So to achieve 80% power a sample size of 09 subjects i.e. 09 observations each formulation was concluded sufficient to conclude bioequivalence. Thus accounting for dropout or withdrawal of subjects during conduct of the study, 30 healthy subjects were decided to be recruited in a crossover study design to achieve the desired sample size to conclude bioequivalence.

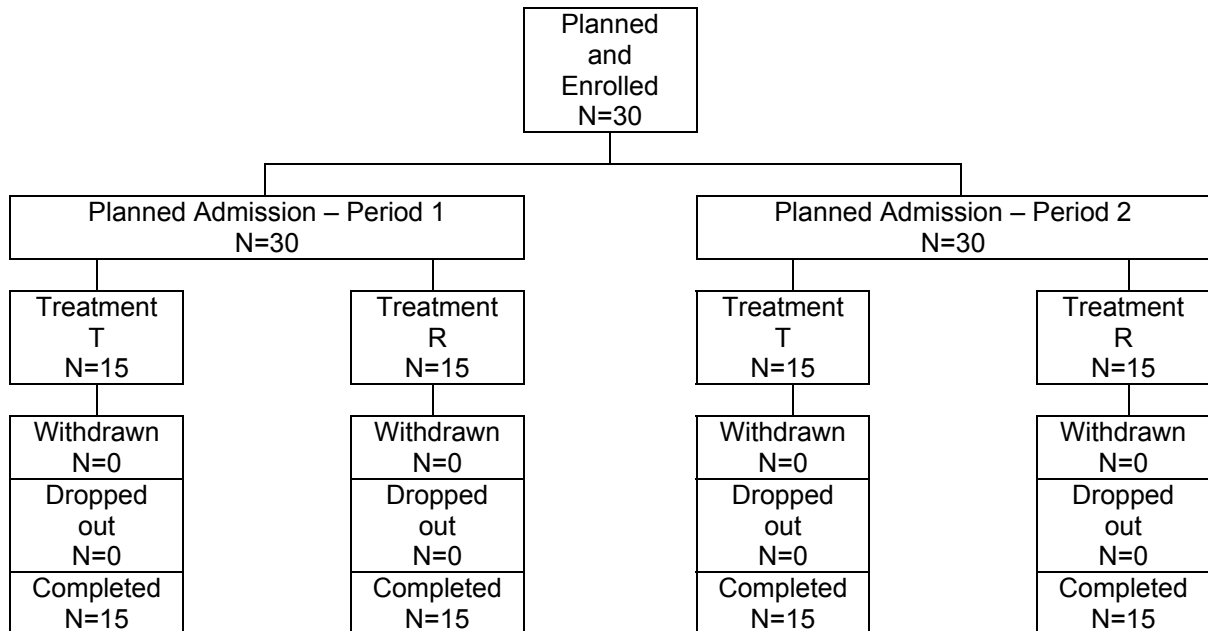
9.8 Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study or planned analyses.

10.0 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 30 healthy, adult, human subjects were planned and enrolled. All the 30 enrolled subjects completed both the periods of the study.



10.2 Protocol Deviations

- Time Point Deviation**

As per protocol blood samples should be collected within two minutes of scheduled time for blood collection for in-house samples. All actual times of the sample withdrawal were recorded in the bleed sheet. However; there were following deviations from the schedule time of the collection above the permitted deviation time in the study.

Sr. No.	Subject No.	Sample Time Point (hrs)	Scheduled Time	Actual Time	Deviation in Hour	Reason for Deviation
Period 1						
1.	23	4.50	13:51 hrs	13:55 hrs	0.07	Cannula blocked
2.	28	4.50	14:06 hrs	14:12 hrs	0.10	Cannula blocked
Period 2						
1.	23	4.50	13:51 hrs	13:54 hrs	0.05	Poor blood flow
2.	23	5.50	14:51 hrs	14:55 hrs	0.07	Cannula blocked
3.	29	3.00	12:39 hrs	12:43 hrs	0.07	Poor blood flow
4.	29	4.50	14:09 hrs	14:15 hrs	0.10	Cannula blocked
5.	30	1.00	10:42 hrs	10:45 hrs	0.05	Poor blood flow
6.	30	2.00	11:42 hrs	11:46 hrs	0.07	Poor blood flow

The above deviations were duly incorporated during pharmacokinetic analysis.

The above deviations were recorded as protocol deviation and are recorded in appendix 16.2.2.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The serum samples of all thirty subjects (subject number 01 to 30) completing the study was analyzed for levothyroxine concentration level and the data were taken for pharmacokinetic and statistical evaluations.

11.2 Demographic and Other Baseline Characteristics

The summary statistics for demographic data is summarized in section 14.1. The demographic data for individual subjects are appended in appendix 16.2.4.

11.3 Measurements of Treatment Compliance

All the subjects took the medications as administered. Examination of the oral cavity immediately after drug administration was performed under supervision of medical officer to assess the compliance to this procedure. Further, the evaluation of the serum drug concentration of the samples confirmed 100 % compliance of the all the subjects from whom the data were analyzed. Serum levels of levothyroxine in individual subjects at different time points following reference or test formulations are given in appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

The various un-transformed mean pharmacokinetic parameters estimated for both the reference and test formulations of baseline-corrected-levothyroxine under fasting conditions are as follows:

Pharmacokinetic Parameters	Baseline-Corrected-Levothyroxine - Reference Formulation					
	N	Arithmetic Mean	Median	S.D.	C.V. (%)	Range
C _{max} (ng/mL)	30	69.647	67.21	14.2765	20.50	38.71 - 115.49
AUC ₀₋₇₂ (ng*hrs/mL)	30	2671.84279	2618.9829	582.826467	21.81	1718.7516 - 4067.2396
T _{max} (hrs)	30	3.470	3.50	1.2384	35.69	1.50 - 5.50

Pharmacokinetic Parameters	Baseline-Corrected-Levothyroxine - Test Formulation					
	N	Arithmetic Mean	Median	S.D.	C.V. (%)	Range
C _{max} (ng/mL)	30	59.739	58.95	11.1848	18.72	37.24 - 82.37
AUC ₀₋₇₂ (ng*hrs/mL)	30	2275.79291	2280.2250	445.738194	19.59	1311.9150 - 3050.2654
T _{max} (hrs)	30	3.338	3.50	1.0741	32.18	1.50 - 4.57

The summary results are tabulated in section 14.2 and the individual subjects and mean pharmacokinetic parameters for both the test and reference formulations have been tabulated in appendix 16.2.6. The statistical output and pharmacokinetic from SAS® version 9.4 is appended in appendix 16.1.9.2.

90% confidence interval based on least square mean obtained from ANOVA, geometric mean, ratio of geometric means, Intra subject C.V. and power for the primary pharmacokinetic parameters $C_{\max}$ & AUC_{0-72} for baseline-corrected-levothyroxine under fasting conditions are summarized in the following table:

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90% Confidence Interval for Baseline-Corrected Levothyroxine (N=30 Subjects)							
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)	
	Reference (R)	Test (T)				Lower	Upper
$C_{\max}$ (ng/mL)	68.303	58.722	85.97	9.07	100.00	82.62	89.46
AUC_{0-72} (ng*hrs/mL)	2611.417	2230.708	85.42	12.82	100.00	80.76	90.35

ANOVA RESULTS:

Formulation Effect

Formulation effect found to be statistically significant (p-value < 0.05) for $C_{\max}$ & AUC_{0-72}

Period Effect

Period effect found to be statistically insignificant (p-value ≥ 0.05) for $C_{\max}$ & AUC_{0-72}

Sequence Effect

Sequence effect found to be statistically insignificant (p-value ≥ 0.05) for $C_{\max}$ & AUC_{0-72}

Ratio and 90% Confidence Interval

The ratio of geometric mean and 90% confidence interval for the ln-transformed primary pharmacokinetic parameters $C_{\max}$ & AUC_{0-72} were found to be respectively 85.97% & 82.62% - 89.46% and 85.42% & 80.76% - 90.35%.

Power and Intra Subject Variability

The power and intra subject variability for ln-transformed primary pharmacokinetic parameters $C_{\max}$ & AUC_{0-72} were found to be respectively 100.00% & 9.07% and 100.00% & 12.82%

11.4.2 Statistical / Analytical Issues

Statistical Issues

There were no statistical issues.

Analytical Issues

There were no analytical issues.

11.4.3 Tabulation of Individual Response Data

All individual subject concentration data that was used for pharmacokinetic analysis at each time point is appended as appendix 16.2.5. Individual serum concentration time curves are presented in linear and log-linear scale in appendix 16.2.5.

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

An oral dose of Reference product [3 × 200 mcg tablets] or Test product [3 × 200 mcg tablets] was administered as per the randomization schedule during each period of study. The details of extent of exposure to investigational product are as follows:

No. of Subject	Subject Number	Extent of Exposure
30	01 to 30	Twice

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

There was no adverse event occurred during the conduct of the study.

There were few out of reference range laboratory values obtained at the post-study assessment but these were not clinically significant except for subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30. The details for the same are given in section 12.4.2. The clinically significant out of reference range values for the post study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.2.2 Displays of Adverse Events

The post study out of reference range laboratory results is listed in section 14.3.4.

12.2.3 Analysis of Adverse Events

The out of reference range laboratory values obtained during post study evaluation except for that listed in section 12.2.4 were considered to be clinically non significant. The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is given in section 12.2.4.

12.2.4 Listing of Adverse Events by Subjects

There was no adverse event occurred during conduct of the study.

During post-study safety assessment adverse events were reported for twelve subjects (subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30). The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is as mentioned below:

Subject No.	Laboratory Parameter	Safety Assessment Results	Reference Range	Remark	Relationship with the Study Drug
05	Potassium	5.82 mmol/L	3.50 - 5.10 mmol/L	Increased	Unlikely
06	Potassium	5.76 mmol/L	3.50 - 5.10 mmol/L	Increased	Unlikely
08	SGPT	85.4 U/L	16.0 – 63.0 U/L	Increased	Unlikely
09	Haemoglobin	11.4 g/dL	13.0 – 17.0 g/dL	Decreased	Unlikely
	Potassium	5.64 mmol/L	3.50 - 5.10 mmol/L	Increased	Unlikely
14	Eosinophils	15%	1 – 6%	Increased	Unlikely
21	Alkaline Phosphatase	144.5 U/L	46.0 -116.0 U/L	Increased	Unlikely
23	SGOT	47.7 U/L	15.0 - 40.0 U/L	Increased	Unlikely
24	Alkaline Phosphatase	152.8 U/L	46.0 -116.0 U/L	Increased	Unlikely
25	Potassium	5.51 mmol/L	3.50 - 5.10 mmol/L	Increased	Unlikely
28	Potassium	5.44 mmol/L	3.50 - 5.10 mmol/L	Increased	Unlikely
29	SGPT	110.2 U/L	16.0 – 63.0 U/L	Increased	Unlikely
	SGOT	57.7 U/L	15.0 - 40.0 U/L	Increased	Unlikely
30	Alkaline Phosphatase	140.8 U/L	46.0 -116.0 U/L	Increased	Unlikely

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There was no serious adverse event reported in the study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subjects and Each Abnormal Laboratory Value

Listed in appendix 16.2.8 are the various hematological, biochemical, and urine sample assessment for the subjects, pre and post-clinical phase. The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.4.2 Evaluation of Each Laboratory Parameters

There were few out of reference range laboratory values obtained at the post-study assessment, but these were not clinically significant except for subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30 who showed clinically significant post-study out of reference range laboratory value.

All the post-study safety assessment clinical and laboratory results are given in appendix 16.2.8, 'Listing of Individual Laboratory Parameters by Subject' [B- Laboratory Tests Report (Post-study safety Assessment)]. All the laboratory results, which were outside the reference range but within the 'acceptable limit', (for acceptable limit refer IEC approved Protocol, appendix V) were not considered clinically significant. There was one value as given below, which was outside the

acceptable limit, however not considered clinically significant based on the clinical co-relation and has not been included as adverse event. For subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30 the laboratory result outside acceptable range is considered as clinically significant based on the clinical co-relation and is reported as adverse event.

Sub. No.	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
05	Potassium	5.82 mmol/L	4.47mmol/L	3.50 - 5.10 mmol/L	Clinically significant
06	Potassium	5.76 mmol/L	4.39 mmol/L	3.50 - 5.10 mmol/L	Clinically significant
08	SGPT	85.4 U/L	25.9U/L	16.0 – 63.0 U/L	Clinically significant
09	Haemoglobin	11.4 g/dL	11.7 g/dL	13.0 – 17.0 g/dL	Clinically significant
	Potassium	5.64 mmol/L	4.73 mmol/L	3.50 - 5.10 mmol/L	Clinically significant
14	Eosinophils	15%	8%	1 – 6%	Clinically significant
21	Alkaline Phosphatase	144.5 U/L	112.4 U/L	46.0 -116.0 U/L	Clinically significant
23	Triglycerides	181.8 mg/dL [#]	139.6mg/dL	< 150.0 mg/dL	Clinically not significant
	SGOT	47.7 U/L	16.1 U/L	15.0 - 40.0 U/L	Clinically significant
24	Alkaline Phosphatase	152.8 U/L	121.0 U/L	46.0 -116.0 U/L	Clinically significant
25	Potassium	5.51 mmol/L	4.18 mmol/L	3.50 - 5.10 mmol/L	Clinically Significant
28	Potassium	5.44 mmol/L	5.17 mmol/L	3.50 - 5.10 mmol/L	Clinically significant
29	SGPT	110.2 U/L	66.0 U/L	16.0 – 63.0 U/L	Clinically significant
	SGOT	57.7 U/L	35.8 U/L	15.0 - 40.0 U/L	Clinically significant
30	Alkaline Phosphatase	140.8 U/L	123.3 U/L	46.0 -116.0 U/L	Clinically significant

[#]**Note:** Triglycerides levels of subject number 23 were outside acceptable limit. On medical officer's advice, the subject was called to repeat the parameter under fasting condition. However, after repeated follow-up subject failed to report to the clinical facility, and informed that he had no health related problem and was not willing to report to the facility for follow-up due to personal reason. The case was considered as clinically not significant as the subject was asymptomatic and his ECG was normal during safety assessment.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Laboratory assessments, including urine test for drugs of abuse and alcohol breath test were carried out prior to the study.

In the pre-study assessments, all out of range clinical laboratory values were clinically acceptable, for the subjects enrolled in the study.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

A total of 30 healthy, adult, human subjects were planned and enrolled. The study was carried out in one group comprising of 30 male subjects (subject number 01 to 30). All the 30 enrolled subjects completed both the periods of the study.

Three tablets as single dose of Levothyroxine Sodium Tablets 200 mcg was well tolerated and no new safety issues were identified during the study.

There was no adverse event occurred during conduct of the study. During post-study safety assessment adverse events were reported for twelve subjects (subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30). The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is given in section 12.2.4. The detailed description of the adverse events and their handling are given in appendix 16.2.7.

No subject discontinued study treatment due to adverse event. No deaths, serious adverse events or adverse events classified as 'other significant AEs' occurred during the study.

The serum samples of all thirty subjects (subject number 01 to 30) completing the study was analyzed for levothyroxine concentration level and the data were taken for pharmacokinetic and statistical evaluations.

The mean serum concentration time profiles of baseline-corrected-levothyroxine for the two treatments are shown in figure 1 to 2 (Refer section 14.2 'Efficacy Data').

Bioequivalence was assessed using standard equations. 90% confidence intervals for the ratio (Test/Reference) of C_{max} & AUC_{0-72} for baseline-corrected-levothyroxine were within the acceptable limits of bioequivalence 80.00% - 125.00%.

In summary, the test formulation is bioequivalent to the reference formulation in terms of both the rate and extent of absorption.

Both the formulations are safe and well tolerated following a single dose administration of the investigational product under fasting condition.

14.0 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Demographic Data of Subjects Recruited & Completed the Study				
	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m ²)
Number	30	30	30	30
Median	33.00	1.68	67.40	23.40
Mean	31.9	1.681	67.07	23.720
Standard Deviation	6.55	0.0555	9.015	2.9387
Minimum	21	1.55	53.3	19.85
Maximum	44	1.84	87.3	29.51

14.2 Efficacy Data

Summary Statistics of Primary Pharmacokinetic Parameters for Baseline-Corrected-Levothyroxine (N=30 Subjects)		
Product/Statistics	C _{max} (ng/mL)	AUC ₀₋₇₂ (ng*hrs/mL)
Untransformed Reference Product (R)		
N	30	30
Arithmetic Mean	69.647	2671.84279
S.D.	14.2765	582.826467
C.V. %	20.50	21.81
Untransformed Test Product (T)		
N	30	30
Arithmetic Mean	59.739	2275.79291
S.D.	11.1848	445.738194
C.V. %	18.72	19.59
Ratio of Arithmetic Mean (% Bioavailability)		
T/R (%)	85.77	85.18
Log Transformed (Natural Log) - Least Square Mean		
Reference	4.224	7.868
Test	4.073	7.710
Geometric Mean		
Reference	68.303	2611.417
Test	58.722	2230.708
Ratio of Geometric Mean		
T/R (%)	85.97	85.42
90% Confidence Interval (T/R)		
Lower limit (%)	82.62	80.76
Upper limit (%)	89.46	90.35
Power (%)		
	100.00	100.00
Error D.F.		
	28	28
Intra Subject C.V. (%)		
	9.07	12.82
Mean Square Error (MSE)		
	0.008194	0.016309
ANOVA Factor Effect - P-value (ANOVA) for In-transformed Data		
Period	0.1333	0.8470
Formulation	<.0001	<.0001
Sequence	0.9884	0.9565

Figure 1

**Comparative Linear Plot of Levothyroxine Mean Serum Concentration (ng/mL) Vs Time (Hour)(N=30)
subject=MEAN**

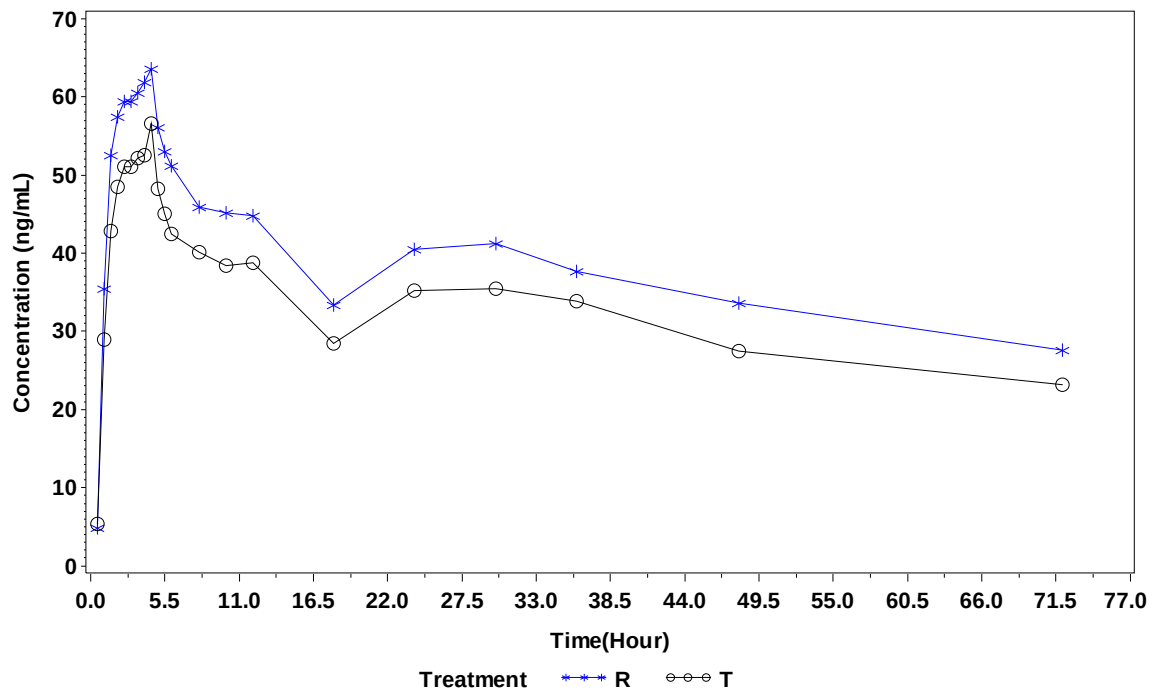
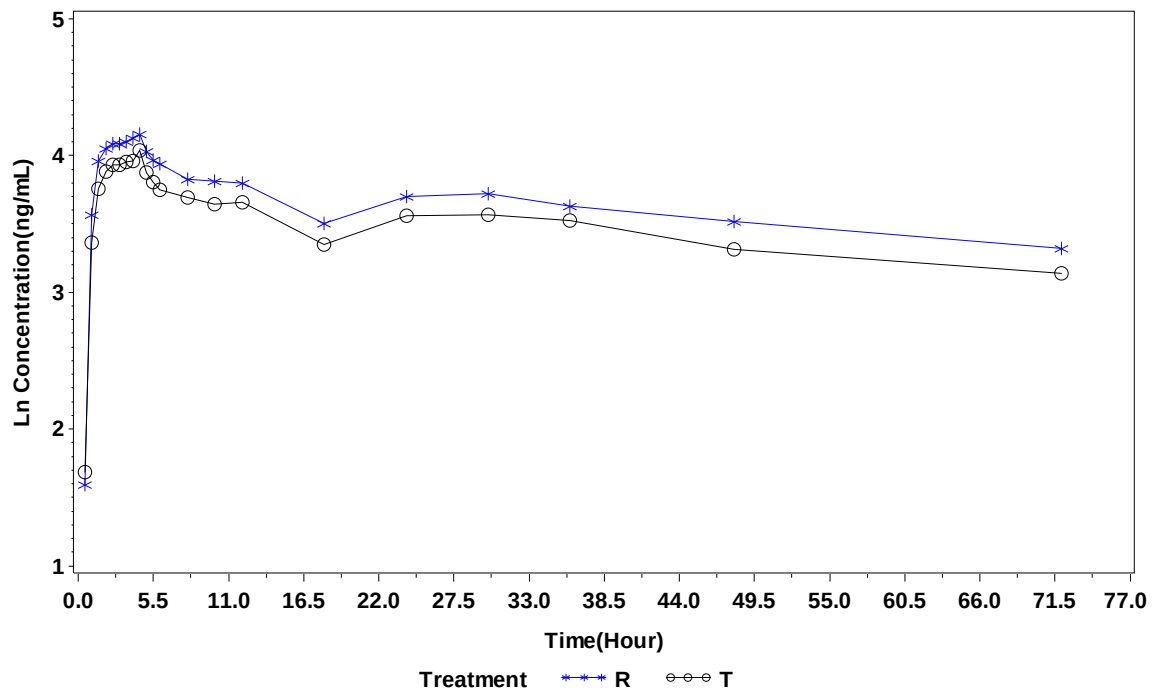


Figure 2

**Comparative Semi Log Plot of Levothyroxine Mean Serum Concentration (ng/mL) Vs Time (Hour)(N=30)
subject=MEAN**



14.3 Safety Data

14.3.1 Display of Adverse Events

There was no adverse event occurred during conduct of the study.

Twelve subjects (subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30) enrolled in the study were found to have clinically significant post-study laboratory value. The list of clinically significant post-study out of reference range laboratory value is listed in section 14.3.4.

The detailed description of the adverse events and their handling are given in appendix 16.2.7.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

No deaths or other serious adverse events or any other significant adverse events were observed in the study.

14.3.3 Narrative of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing

Following table gives details of outside acceptable limit findings, which are clinically significant in laboratory test of subjects post-study.

Subject No.	Laboratory Parameter	Safety Assessment Results	Reference Range	Follow-up Result	Comments
05	Potassium	5.82 mmol/L	3.50 - 5.10 mmol/L	Not done	Lost for follow-up
06	Potassium	5.76 mmol/L	3.50 - 5.10 mmol/L	Not done	Lost for follow-up
08	SGPT	85.4 U/L	16.0 – 63.0 U/L	Not done	Lost for follow-up
09	Haemoglobin	11.4 g/dL	13.0 – 17.0 g/dL	Not done	Lost for follow-up
	Potassium	5.64 mmol/L	3.50 - 5.10 mmol/L	Not done	Lost for follow-up
14	Eosinophils	15%	1 – 6%	Not done	Lost for follow-up
21	Alkaline Phosphatase	144.5 U/L	46.0 -116.0 U/L	Not done	Lost for follow-up
23	SGOT	47.7 U/L	15.0 - 40.0 U/L	Not done	Lost for follow-up
24	Alkaline Phosphatase	152.8 U/L	46.0 -116.0 U/L	Not done	Lost for follow-up
25	Potassium	5.51 mmol/L	3.50 - 5.10 mmol/L	Not done	Lost for follow-up
28	Potassium	5.44 mmol/L	3.50 - 5.10 mmol/L	Not done	Lost for follow-up
29	SGPT	110.2 U/L	16.0 – 63.0 U/L	Not done	Lost for follow-up
	SGOT	57.7 U/L	15.0 - 40.0 U/L	Not done	Lost for follow-up
30	Alkaline Phosphatase	140.8 U/L	46.0 -116.0 U/L	Not done	Lost for follow-up

(Refer appendix 16.1.12; 'Important Publications Referenced in the Report')

- Clinical Report
- ANX/GN/SOP-021-01

APPENDIX 16.1.1

IEC APPROVED PROTOCOL AND PROTOCOL AMENDMENTS

STUDY PROTOCOL

Study Title:

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design:

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

Protocol No.: BEQ-2321-LEVT-2017

Status: Final

Version no.: 02

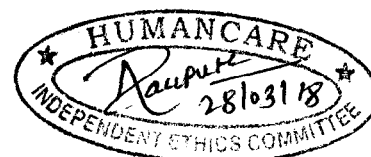
Date: 19th March 2018

Supersedes: 01

Date: 23rd November 2017

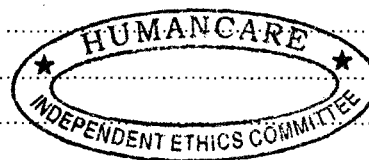
Sponsor: MACLEODS PHARMACEUTICALS LTD., G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093, India. Telephone No.: 91-22-61132900 Fax No.: 91-22-28304641	Clinical Facility MACLEODS PHARMACEUTICALS LTD. Bioequivalence Department R & D: II, Plot no. 95, Road no. 16, Opp. Suncity Hotel, MIDC, Andheri - (East), Mumbai 400 093, India. Telephone No.: 91-22-67258412 Email: drashish@macleodspharma.com

Protocol Author : Mr. Tejas Wattamwar
Principal Investigator : Dr. Rajendra Sonde
Study Director : Dr. Ashish Mungantiwar
Sponsor's Representative : Ms. Shalmali Ambekar



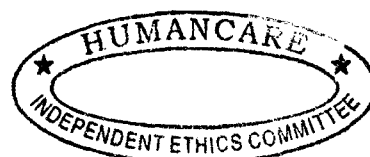
2.0 LIST OF CONTENTS

Contents	Page No.
1.0 TITLE PAGE.....	1
2.0 LIST OF CONTENTS.....	2
3.0 ABBREVIATIONS.....	5
4.0 CONTACT PERSONNEL.....	8
5.0 FACILITIES.....	9
6.0 DECLARATION.....	10
6.1 Reviewer Declaration.....	10
6.2 Investigator Declaration.....	11
7.0 SPONSOR'S APPROVAL.....	12
8.0 PROTOCOL SYNOPSIS.....	13
9.0 BACKGROUND.....	18
9.1 Investigational Products.....	18
9.2 Pharmacology.....	18
9.3 Clinical Pharmacokinetics.....	18
9.4 Indications and Uses ^[1]	19
9.5 Posology and method of administration.....	19
9.6 Adverse Reactions.....	20
9.7 Precautions/ Warning/ Special warning.....	21
9.8 Contraindications.....	21
9.9 Study Rationale.....	22
9.10 Study Population.....	22
9.11 References.....	22
10.0 STUDY OBJECTIVES AND PURPOSE.....	23
10.1 Pharmacokinetics.....	23
10.2 Safety.....	23
11.0 STUDY DESIGN.....	24
11.1 Design.....	24
11.2 Evaluation Parameters.....	24
11.2.1 Primary Bioavailability Variables.....	24
11.2.2 Secondary Bioavailability Variables.....	24
11.3 Procedures to Minimize / Avoid Bias.....	24
11.4 Investigational Products, Dosing Regimen and Labelling.....	25
11.4.1 Investigational Products.....	25
11.4.2 Selection of Doses.....	25
11.4.3 Justification of Choice of Reference Product.....	25
11.4.4 Supply of Investigational Products.....	25
11.4.5 Dispensing and Labeling of Investigational Product.....	26
11.5 Sequence and Duration of Study Periods.....	26
11.5.1 Overall Study Plan.....	26





16.2.7	Confidence Intervals For Primary Pharmacokinetic Parameters	40
16.2.8	Acceptance Criteria for Bioequivalence For Primary Pharmacokinetic Parameters	40
16.2.9	Number of Subjects	41
16.2.10	Justification for Design	42
17.0	DIRECT ACCESS TO SOURCE DATA / DOCUMENTS	43
18.0	QUALITY CONTROL AND QUALITY ASSURANCE	43
19.0	ETHICS	44
19.1	Ethics Committee	44
19.2	Ethical Conduct of the Study	44
19.3	Informed Consent	44
19.4	Compensation to Subjects	44
20.0	INSURANCE AND FINANCING	46
21.0	DATA HANDLING AND RECORD KEEPING	46
22.0	PUBLICATION POLICY	46
	APPENDIX I (STUDY FLOW CHART)	
	APPENDIX II (EVENT SCHEDULE)	
	APPENDIX III (SCHEDULE FOR BLOOD COLLECTION, INVESTIGATIONAL PRODUCT DOSING, SAFETY ASSESSMENT AND MEALS)	
	APPENDIX IV (MEAL PLAN)	
	APPENDIX V (NORMAL RANGES FOR PATHOLOGY LABORATORY)	
	APPENDIX VI (UNDERTAKING BY THE INVESTIGATOR)	
	APPENDIX VII (WMA – DECLARATION OF HELSINKI)	
	APPENDIX VIII (LIST OF AMENDMENTS)	



µL	: Microlitre
ADRs	: Adverse Drug Reactions
AE	: Adverse Event
ANOVA	: Analysis of Variance
AUC	: Area Under Curve
AUC ₀₋₇₂	: The area under the serum concentration versus time curve from time zero to 72.00 hours, as calculated by the linear up-linear down trapezoidal method
BLQ	: Below Limit of Quantification
BMI	: Body Mass Index
B.P	: Blood Pressure
BPM	: Beats Per Minute
BUN	: Blood Urea Nitrogen
CBC	: Complete Blood Count
C _{max}	: Concentration Maximum
CNS	: Central Nervous System
COA	: Certificate of Analysis
CPU	: Clinical Pharmacology Unit
CRF	: Case Record Form
CV	: Coefficient of Variance
°C	: Degree Centigrade
D	: Day
DLC	: Differential Leukocyte count
eMC	: The electronic Medicine Compendium
EMA	: European Medicine Agency
ECG	: Electro-Cardiogram
ER	: Extended Release
ESR	: Erythrocyte Sedimentation Rate
GCP	: Good Clinical Practices
GGT	: Gamma-glutamyl transferase
GGTP	: Gamma Glutamyl Transpeptidase
GLP	: Good Laboratory Practices
cGMP	: current Good Manufacturing Practices
HBsAg	: Hepatitis B Surface Antigen
HCV	: Hepatitis C Virus
HIV	: Human Immunodeficiency Virus
hrs	: Hour(s)
I.D.	: Identity
ICF	: Informed Consent Form

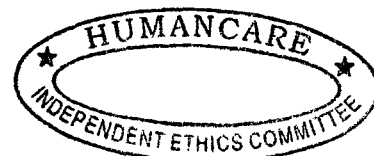




The logo is an oval shape with the word "HUMANCARE" at the top and "INDEPENDENT ETHICS COMMITTEE" at the bottom. Two stars are positioned on the left and right sides of the oval.



SQ	: Subject Questionnaire
T	: Test Product
T _{max}	: Time of maximum measured serum concentration. If maximum value occurs at more than one time point, T _{max} is defined as the first time point with this value in each period.
T ₄	: L-thyroxine
T ₃	: L-triiodothyronine
TG	: Triglycerides
TBA	: thyroxine-binding albumin
TBG	: thyroxine-binding globulin
TBPA	: thyroxine-binding prealbumin
TG	: Triglycerides
TRH	: Thyrotropin-releasing hormone
TSH	: thyrotropin-stimulating hormone
w/v	: Weight / Volume



4.0 CONTACT PERSONNEL

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BIOEQUIVALENCE DEPARTMENT PERSONNEL

Study Director

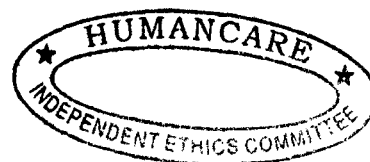
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5.0 FACILITIES

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C. Screening and X-Ray Facility	:	Macleods Pharmaceuticals Ltd., Bioequivalence Department, G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai 400 093, India. Tel.: 91-22-61132900 Ext. No.: 127/150/319 Fax: 91-22-28304641
D. Bioanalytical Facility	:	Macleods Pharmaceuticals Ltd., Bioequivalence Department, G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093, India. Tel.: 91-22-61132900 Ext. No.: 142/ 145 Fax: 91-22-28304641
E. Statistical Operations	:	Macleods Pharmaceuticals Ltd., Bioequivalence Department, G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093, India. Tel.: 91-22-61132900 Ext. No.: 267 Fax: 91-22-28304641



6.0 DECLARATION

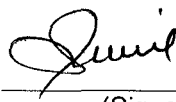
6.1 Reviewer Declaration

The Protocol No.: BEQ-2321-LEVT-2017; Version No. 02; has been authored and reviewed by following signatories:

Authored by

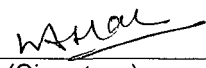
<u>Tejas Wattamwar</u> Name	<u></u> (Signature)	<u>19/03/18</u> (Date)

Reviewed By

<u>Sunil Maurya</u> Name	<u></u> (Signature)	<u>19/03/18</u> (Date)

The protocol has been reviewed by Quality Assurance for completeness, accuracy and compliance with applicable regulatory expectations.

Quality reviewed By

<u>Hemal shah</u> Name	<u></u> (Signature)	<u>19/03/18</u> (Date)



6.2 Investigator Declaration

We, the undersigned declare that we have read and understood this protocol (Protocol No.: BEQ-2321-LEVT-2017; Version No. 02; Dated 19th March 2018) and hereby agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, national and ICH 'Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

We further agree to ensure that all associates assisting in the conduct of the study are informed regarding their obligations. We agree to comply with all relevant Standard Operating Procedures (SOPs) required for the conduct of this study and would report to IEC and Sponsor and document any significant deviation occurring during this study.

Principal Investigator:
Dr. Rajendra Sonde
(M.B.B.S., PGDHHM, D.PHARM.)

Rajendra Sonde
(Signature)

19/03/18
(Date)

Study Director:
Dr. Ashish Mungantiwar
(Ph.D. Pharmacology)
Head Bioequivalence

Ashish Mungantiwar
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(Date)

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India.



7.0 SPONSOR'S APPROVAL

I, on behalf of MACLEODS PHARMACEUTICALS LTD., Mumbai, India, have read, reviewed and understood this protocol (Protocol No.: BEQ-2321-LEVT-2017; Version No. 02; Dated 19th March 2018) and approved it.

I agree to comply with all requirements regarding the obligations and role of the sponsors and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, and ICH, "Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

Gumbel

Authorized Signatory

19103118

Date _____

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8.0 PROTOCOL SYNOPSIS

Study Title:

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design:

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

Objective :

- i) Pharmacokinetic:** To evaluate the comparative oral bioavailability of Three Tablets as Single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy, adult, human subjects under fasting condition.
- ii) Safety:** To monitor the safety and tolerability of three tablets as single oral dose of Levothyroxine Sodium Tablets 200 mcg when administered in healthy, adult, human subjects under fasting condition.

Number of Subjects : 30

Study Duration : Total 40 days approximately with 35 days washout. If period II is scheduled later the duration of study will change accordingly.

Diagnosis and main

Criteria for Inclusion : Healthy human subjects within the age range of 18 to 45 years with body-mass index (BMI) between 18.50 kg/m² and 29.99 kg/m² (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females) and having absence of significant disease, clinically significant laboratory values, Serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH) test, absence of clinically significant medical history and normal physical examination during the screening and complying with inclusion and exclusion criteria.



Investigational Product

Administration : An oral dose of Reference product (R) or Test product (T) will be administered as per the randomisation schedule. Subjects will receive the alternate ‘treatments’ in the subsequent period in such a way that each subject will receive both the ‘treatments’ test and reference each, by the end of the study. Owing to the sensitivity of Levothyroxine to light, dosing will be done under yellow monochromatic light.

Investigational Products:

i) Test Formulation (T)	: Levothyroxine Sodium Tablets 200 mcg Batch No.: MLK602C Manufacturing Date: 10/2016 Expiry Date: 09/2018 Manufactured by: Macleods Pharmaceuticals Ltd. India Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water.
ii) Reference Formulation (R)	: Euthyrox® (levothyroxine sodium) Tablets 200 mcg Batch No.: 209740 Manufacturing Date: N/AV Expiry Date: 11/2018 Marketed by: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijk Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water

Dietary Plan : The dose will be administered after an overnight fast of at least 10 hours in each period. Fasting will continue for at least four hours post-dose, then meals will be provided approximately at 4.00, 8.00 and 13.00 hours post-dose on dosing day 1 and approximately at 24.50, 28.00, 32.00 and 37.00 hours post dose on day 2 and at 48.50, 52.00, 56.00 and 61.00 hours post dose (i.e. breakfast, lunch, snacks and dinner on day 3) each study.

Study Restriction : Drinking water will be disallowed for one hour pre-dose and one hour post-dose. Subsequently, drinking water will be provided ad libitum. Subjects will be dosed while in upright sitting posture and will be instructed to remain seated or be ambulator (avoiding any strenuous activity) for first two hours following the investigational product

administration (except during recording of vitals and blood collection time point). During this interval, under supervision, subjects will be permitted to use the washroom facilities. Thereafter the subjects will be allowed to engage only in normal activities while avoiding severe physical exertion. However should any adverse event occur at any time during housing the subjects will be placed in an appropriate posture.

Collection Schedules

: Blood samples (1 × 6 mL) will be collected in blood collection tube containing clot activator during each period. The venous blood samples will be withdrawn at -0.50, -0.25 hours prior to dosing at pre-dose (-0.03) and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose (Time points being relative to the investigational product dosing).

Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light.

Note: Blood sample withdrawn at -0.03 will be considered as collection at 0.00 hrs.

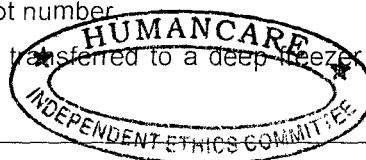
Blood Loss

: For each subject, the total number of blood draws will be 48 (24 per period). The total volume of blood withdrawn will not exceed 325 mL (including 13 mL for safety assessment and 24 mL discarded normal saline blood). Should circumstances arise, like breakage of tube after collection, adverse event (including abnormal laboratory values) where more blood needs to be withdrawn, additional blood samples may be taken for laboratory investigation. The consent of the subject would be taken and the IEC would be informed and subject will be compensated accordingly.

Handling of Blood Samples

: After collection these tubes will be inverted shaken for five times. The blood samples collected at each time point will be kept at room temperature ($\approx 20 - 30^{\circ}\text{C}$) for at least 30 minutes after the blood collection of last subject and then centrifuged at set temperature of 25°C at 3000 rpm for 10 minutes to separate serum. The separated serum will be aliquoted in duplicate in prelabelled amber colored polypropylene tubes during each period. These tubes will be labelled with study number, period number, subject number, sample number, time point (hrs) and aliquot number.

These tubes will then be transferred to a deep freezer set at -75°C for storage.



Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light.

Washout Period : There will be washout period of at least 35 days from the completion of dosing between two periods.

Safety Assessment : In each period, subject questionnaire and vital signs (Blood Pressure, Temperature and Pulse Rate) will be done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 23.00, 29.00, 35.00, 48.00 and 72.00 hours post-dose (time points being relative to the investigational product dosing).

Note: Subject will be kept in supine position for at least 5 minutes before start of Blood Pressure recording on each time point.

If any adverse events are observed by either clinical staff or reported by subjects at times other than scheduled times, will be recorded.

In each period, the breath of the subject will be checked to see whether they have consumed alcohol or not at the time of check-in using breath alcohol analyzer.

Medical examination, ECG and clinical laboratory tests will be performed to cater to the post-study safety assessments after the last blood collection of Study Period-II.

Medical examination will be carried out during check-in and check-out of each study period and whenever attending medical officer thinks necessary.

Urine test for drugs of abuse will be carried out at the time of check-in of both periods.

For females urine pregnancy test will be done during pre-study screening and on the day before dosing of Period-I and Period-II.

Risk Evaluation and Mitigation Strategies:

Risk evaluated:

- The Investigational product can cause various adverse effects.

Mitigation strategies:

- Ambulance will be made available before start of study.
- All medical staff including nurses and doctors will be informed to be available at clinical site.
- ICU will be checked for availability of all emergency medicines and other devices will be checked for proper functioning.
- Volunteers with abnormal serum T_4 (total), serum T_3 (total), serum thyroid-stimulating hormone (TSH) test values will be excluded from the study.

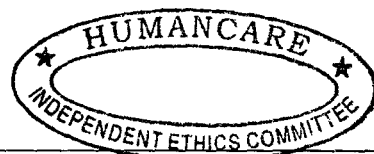
Clinical Residency : Subject will be admitted and housed in the facility sufficient time before to maintain 10 hours fasting condition before the administration of dose and until 72 hours post-dose, during each period of the study.

Bioanalytical Method : Levothyroxine will be estimated in serum using validated LC-MS/MS method.

Pharmacokinetic Parameters : 1) Primary parameters : C_{max} and AUC_{0-72} .
2) Secondary parameters : T_{max} .
Both parameters will be estimated using SAS®

Statistical Analysis : Summary statistics, ANOVA, Intra subject variability, 90% Confidence interval and Power will be calculated using SAS® Linear & Semi log graphs will be plot using SAS®

Criteria for Bioequivalence : The 90% confidence interval for C_{max} and AUC_{0-72} of baseline corrected Levothyroxine will form the basis for concluding the bioequivalence of Levothyroxine sodium in product R and T. If the 90% confidence intervals are entirely included in the range of 80.00% – 125.00% for C_{max} and AUC_{0-72} log-transformed then the products will be claimed to be bioequivalent.



9.0 **BACKGROUND**

9.1 **Investigational Products**

- i) Test Formulation (T)** : Levothyroxine Sodium Tablets 200 mcg
Batch No.: MLK602C
Manufacturing Date: 10/2016
Expiry Date: 09/2018
Manufactured by: Macleods Pharmaceuticals Ltd. India
Dose: 3 Tablets
Mode of administration: Administered orally with 240 mL of drinking water.
- ii) Reference Formulation (R)** : Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg
Batch No.: 209740
Manufacturing Date: N/AV
Expiry Date: 11/2018
Marketed by: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijik
Dose: 3 Tablets
Mode of administration: Administered orally with 240 mL of drinking water

9.2 **Pharmacology** ^[1]

Pharmacotherapeutic group: thyroid hormones.

The effect of the synthetic levothyroxine in Euthyrox is similar to that of the naturally occurring essential hormone, secreted by the thyroid gland. It is converted, just like the endogenous hormone in T₃ in the peripheral organs and develops its specific effect through the T₃ receptors. The body can not distinguish between endogenous and exogenous levothyroxine.

9.3 **Clinical Pharmacokinetics** ^[1]

Levothyroxine is absorbed almost entirely in the upper part of the small intestine when taken orally. Depending on the galenical form, the absorption is up to 80%. T_{max} is about 5 to 6 hours.

After oral administration, the onset of action occurs after 3-5 days. Levothyroxine shows an extreme strong binding of about 99.97% on specific transport proteins. This protein hormone binding is not covalent and thus the bound hormone in the plasma is exchanged continuously and very quickly with the free hormone fraction. The volume of distribution is approximately 10-12 liter.

Due to the high degree of protein binding, levothyroxine does not undergo hemodialysis or hemoperfusion.

The half-life of levothyroxine is approximately 7 days. With hyperthyroidism this is shorter (3-4 days). In hypothyroidism this is longer (about 9-10 days). The liver contains 1/3 of the whole extrathyroid levothyroxine. This is quickly exchangeable with levothyroxine in the serum.

Thyroid hormone is metabolised primarily in the liver, kidneys, brain and muscles. The metabolites are excreted in the urine and faeces. The total metabolic levothyroxine clearance is about 1.2 l of plasma per day.

9.4 Indications and Uses ^[1]

Euthyrox 25 - 200 µg:

- Treatment of euthyroid goiter, especially in adults when iodine is not indicated
- Recurrence of prophylaxis after a resection, depending on the postoperative hormone status
- Substitution in hypothyroidism
- Suppression treatment for thyroid carcinoma

Euthyrox 25 - 100 µg:

- Substitution during the concomitant treatment with thyrostatics in hyperthyroidism

Euthyrox 100/150/200 µg:

- Diagnostic use in thyroid suppression testing

9.5 Posology and method of administration ^[1]

Dosage

In order to treat each patient according to his / her individual needs, tablets are available with a sodium levothyroxine content ranging from 25 to 200 µg. As a result, patients usually have to only one tablet per day.

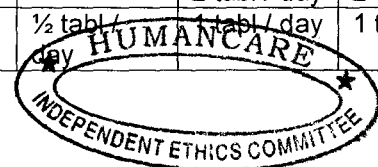
The dosages listed below are guidelines.

The individual daily dose should be determined on the basis of laboratory tests and clinical trials.

Because a number of patients exhibit increased concentration T4 and free T4 concentration, the basal "Thyroid stimulating hormone (TSH) serum concentration" provides a more reliable basis for the therapy.

Thyroid hormone therapy should be started with a low dose and gradually every 2 to 4 weeks until the full replacement dose is reached.

Indication	Recommended dose (µg sodium levothyroxine / day)			
Treatment of euthyroid body	75 - 200			
Recurrent prophylaxis after contract resection	75 - 200			
Substitution in hypothyroidism in adults				
- starting dose	25 - 50			
- maintenance dose	100 - 200			
Substitution in children with hypothyroidism obtained				
- starting dose	12.5 - 50			
- maintenance dose	100 - 150 µg / m ² body surface area			
Substitution during simultaneous treatment with thyrostatics in hyperthyroidism	50 - 100			
Suppression treatment for thyroid carcinoma	150-300			
Diagnostic use at Thyroid suppression examination	Week 4 for the test	Week 3 for the test	Week 2 for the test	Week 1 for the test
Euthyrox 200 µg	---	---	1 tabl / day	1 tabl / day
Euthyrox 100 µg	---	---	2 tabl / day	2 tabl / day
Euthyrox 150 µg	½ tabl / day	½ tabl / day	1 tabl / day	1 tabl / day



Method of administration

The daily doses can be given in a single administration.

Ingestion: one-time daily dose in the morning on an empty stomach, half an hour before breakfast, preferably with some liquid (for example half a glass of water).

The duration of treatment is generally lifelong in the case of hypothyroidism substitution and after strumectomy or thyroidectomy and in recurrent prophylaxis after contract resection.

Simultaneous treatment of hyperthyroidism after an euthyroid condition has been achieved is indicated during the period that a thyrostatic is given.

For a benign euthyroid head, a treatment period of 6 months to 2 years is necessary. To prevent recurrence, prophylaxis with low dose of iodine (100 - 200 µg / day) recommended after taking the head size. If the medical treatment during this period appears insufficient, surgery or treatment with radioactive iodine should be considered.

9.6 Adverse Reactions ^[1]

Side effects

The frequency category for the following side effects is not known

Immune system disorders	Hypersensitivity Angio-edema

If the individual tolerance limit of sodium levothyroxine or overdose is exceeded the following clinical symptoms, characteristic of hyperthyroidism, may occur, mainly if the dose is increased too quickly at the start of treatment. In such cases the daily dose should be reduced or the medication for a number of times days to be stopped. The treatment can be carefully started again as these effects have disappeared.

Endocrine disorders	Hyperthyroidism Irregular menstruation
Nervous system disorders	Headache Benign intracranial Hypertension Tremor Restlessness Insomnia
Cardiac disorders	Arrhythmia Atrial fibrillation Extrasystoles Tachycardia Palpitations Angina pectoris
Gastrointestinal disorders	Vomiting Diarrhea
Skin and subcutaneous tissue disorders	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle weakness Muscle spasms
General disorders and administration site conditions	Excessive flushing Pyrexia
To investigate	Weight reduced



9.7 Precautions/ Warning/ Special warning^[1]

Before the start of treatment with thyroid hormones or to carry out one thyroid suppression test, the following conditions should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency (hypopituitarism), adrenal insufficiency, autonomously functioning thyroid gland.

At the start of treatment with levothyroxine in patients at risk of psychotic disorders, it is recommended to start with a low dose of levothyroxine and the dose to it gradually increases the beginning of treatment. It is advised to monitor the patient. At the occurrence of symptoms of psychotic disorders, adjustment of the dose of levothyroxine should be considered.

Even a drug-induced mild hyperthyroidism should occur in patients with coronary artery disease insufficiency, cardiac insufficiency or tachycardia arrhythmias are avoided. That is why in this case regular checks of the thyroid hormone parameters.

In the case of secondary hypothyroidism, the cause must be determined before replacement therapy is given and, if necessary, replacement therapy of a compensated adrenal insufficiency.

If the suspicion of an autonomously functioning thyroid gland exists, one should be treated before treatment TRH test or a suppression scintigram must be made.

In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, serve supraphysiologic serum levothyroxine levels are to be avoided and therefore the thyroid function to be closely monitored.

Levothyroxine should not be given in other hyperthyroid conditions, except in concomitant supplementation during thyreostatics treatment of hyperthyroidism.

If treatment with levothyroxine is initiated, it is recommended to change it when changing it levothyroxine product, the dosage to adjust to the clinical response of the patient and the laboratory results.

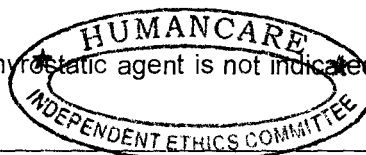
With concomitant administration of orlistat and levothyroxine, hypothyroidism and / or decreased Hypothyroidism control. Patients who should take levothyroxine should be advised to consult their physician before treatment with orlistat is started, stopped, or is adjusted, because orlistat and levothyroxine may have to be at different times ingested and the dose of levothyroxine may need to be adjusted. Further recommended to monitor the patient by monitoring the hormonal serum levels.

Euthyrox contains lactose. Patients with rare, congenital galactose intolerance problems, Lap-lactase deficiency or glucose-galactose malabsorption should not be used.

For diabetic patients and patients undergoing anticoagulant therapy.

9.8 Contraindications^[1]

- Hypersensitivity to the active substance or to any of the excipients.
- Untreated adrenal insufficiency, untreated pituitary insufficiency, and untreated thyrotoxicosis.
- Treatment with Euthyrox should not be started in acute myocardial infarction, acute myocarditis and acute pericarditis.
- Combination therapy of levothyroxine with a thyrostatic agent is not indicated during the pregnancy.



9.9 Study Rationale

The Macleods Pharmaceuticals Ltd. has developed generic alternative to the reference medicinal product of Levothyroxine Sodium Tablets 200 mcg. Therefore, its bioequivalence to the reference medicinal product must be evaluated in fasting conditions. In the present study, test product of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) will be compared with Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) under fasting condition.

9.10 Study Population

The study will be conducted in healthy, adult, human subjects of age 18 to 45 years (inclusive) recruited from the pool of healthy volunteers.

9.11 References

1. Summary of Product Characteristics of Euthyrox® (levothyroxine sodium) Tablets 200 mcg, Last update on 15/10/2017. Cited on 18/03/2018, Available from:
<https://db.cbg-meb.nl/IB-teksten/h09009.pdf>
2. Public Assessment Report for levothyroxine sodium, NL/H/2700/001-011/DC dated 30/11/2015. Cited on 22/11/2017, Available from:
https://mri.cts-mrp.eu/download/NL_H_2700_004_PAR.pdf





10.0 STUDY OBJECTIVES AND PURPOSE

10.1 Pharmacokinetics

To evaluate the comparative oral bioavailability of Three Tablets as Single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) with Three Tablets as Single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy, adult, human subjects under fasting condition.

10.2 Safety

To monitor the safety and tolerability of three tablets as single oral dose of Levothyroxine Sodium Tablets 200 mcg when administered in healthy, adult, human subjects under fasting condition.



11.0 STUDY DESIGN

11.1 Design

- This will be an open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.
- Levothyroxine being a long half-life drug (approximately 7 days) and because of low intra-subject variability on distribution and clearance, an AUC truncated at 72.00 hours will be used, thus samples till 72.00 hours for Levothyroxine will be collected ensuring completion of gastrointestinal tract absorption (approximately 2 days).
- The study flowchart, event schedule and Schedule for "Blood Collection, Investigational Product Dosing, Safety Assessment and Meals" for period I and II, are given in Appendix - I, II and III respectively.

11.2 Evaluation Parameters

Pharmacokinetic parameters of Levothyroxine will be calculated using the SAS®.

11.2.1 Primary Bioavailability Variables

C_{max} : Maximum measured serum concentration.

AUC_{0-72} : The area under the serum concentration versus time curve from time zero to 72.00 hours, as calculated by the linear trapezoidal method.

11.2.2 Secondary Bioavailability Variables

$T_{\max}$: Sampling time at which $C_{\max}$ occurred. If $C_{\max}$ value occurs at more than one time point, $T_{\max}$ is defined as the first time point with this value in each period.

11.3 Procedures to Minimize / Avoid Bias

This will be an open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study. The investigational products will be administered to each subject according to a predetermined random sequence. To avoid bias the analyst will not have access to the Randomisation code.



11.4 Investigational Products, Dosing Regimen and Labelling

11.4.1 Investigational Products

- i) **Test Formulation (T)** : Levothyroxine Sodium Tablets 200 mcg
Batch No.: MLK602C
Manufacturing Date: 10/2016
Expiry Date: 09/2018
Manufactured by: Macleods Pharmaceuticals Ltd. India
Dose: 3 Tablets
Mode of administration: Administered orally with 240 mL of drinking water.
- ii) **Reference Formulation (R)** : Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg
Batch No.: 209740
Manufacturing Date: N/AV
Expiry Date: 11/2018
Marketed by: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijk
Dose: 3 Tablets
Mode of administration: Administered orally with 240 mL of drinking water

11.4.2 Selection of Doses

The available strengths of Euthyrox[®] (levothyroxine sodium) Tablets are 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mg, 137 mcg, 150 mcg, 175 mcg and 200 mcg. The recommended adult oral single dose of Euthyrox[®] (levothyroxine sodium) Tablets started with a low dose and gradually every 2 to 4 weeks until the full replacement dose is reached. Therefore, single oral dose of 3 tablets of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg is chosen, since it is safe (well tolerable) for healthy volunteers and provides measurable serum concentrations and single dose study is adequate for this product's bioequivalence.

11.4.3 Justification of Choice of Reference Product

Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) is qualified as reference medicinal product in the electronic Medicine Compendium (eMC) by European Union (EU).

11.4.4 Supply of Investigational Products

An adequate number of investigational products will be provided. The investigational product will be properly labeled according to the requirements of cGMP for administration along with certificate of analysis (COA) will be provided by the sponsor. The investigational product will be received at Bioequivalence department of Macleods Pharmaceuticals Ltd. by the registered pharmacist.



11.4.5 Dispensing and Labeling of Investigational Product

Under the supervision of the trained study personnel, the registered pharmacist will prepare doses for the study as per the randomisation schedule in presence of Quality Assurance personnel. After dispensing investigational products will be placed into appropriately labeled containers. An additional label will be made available for attachment to each investigational product administration form at the time of dosing to confirm correct administration of investigational products. Remaining investigational products will be stored in their original container as retention samples. The issued investigational products will be transferred to the investigational product dispensing containers as doses.

Owing to the sensitivity of Levothyroxine to light, dispensing of the investigational product will be done under yellow monochromatic light.

11.5 Sequence and Duration of Study Periods

11.5.1 Overall Study Plan

Subjects from the pool of healthy volunteers who were screened within 21 days prior to the first dosing day will be considered as potential participants in the study. The inclusion and exclusion criteria will be applied to all subjects as a condition of admission into the study.

Before admission of volunteers into the CPU, on or before the pre-study day, the volunteers will be given full details of the study. Volunteers are required to give their written consent for participating in the study by signing with date the informed consent form. Tests for drugs of abuse, urine pregnancy test (for females only) and alcohol consumption by breath alcohol analyzer will be carried out followed by pre – entry vital signs, medical examination, inclusion and exclusion criteria check.

After check-in, there will be a supervised overnight fasting period of at least 10 hours before dosing. All three pre-dose sample will be taken before dosing thereafter a series of blood samples will be taken till 72 hour post-dose with the subject remaining in the CPU. After the 72 hours post-dose blood sample is taken, the subjects will be allowed to leave CPU after checking their vital signs and medical examination.

After a washout period of at least 35 days, the same procedure will be repeated in period II except for the ICF presentation, obtaining of written informed consent.

Post-study safety assessment will be carried out after last blood collection of study period II.

After the subjects have been recruited for the study, the duration of their participation will be approximately 40 days with 35 days washout. If period II is scheduled later the duration and compensation of study may change accordingly.

Pre-Study day	ICF presentation, obtaining written informed consent, test for drugs of abuse, alcohol consumption by breath alcohol analyzer followed by vital signs and subject questionnaire, inclusion and exclusion criteria check and medical examination. For females, urine pregnancy tests will also be done. Admission to CPU. Ten hours overnight fasting starts after dinner.
Day 1	Allocated dose of Investigational Product will be given at scheduled time. Blood sample collection, catering, vital signs and subject questionnaire will be carried out at scheduled time.
Day 4	After 72.00-hour the subjects will be allowed to leave provided the health check is satisfactory.
After washout period of at least 35 days from dosing, subjects will be dosed for period II.	

ICF presentation and obtaining informed consent will be done only in period I.
Post-study safety assessment will be done after last blood collection of study period II.
Urine pregnancy tests on the day before dosing of period I and period II (for females only).

11.5.2 Study Restrictions

No medication whether prescribed or over-the-counter products (including vitamins and medicinal products from natural origin) will be allowed within 14 days prior to dosing and during the entire duration of the study.

Subjects will be instructed to abstain from alcohol and products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) and tobacco products for at least 48 hours, prior to dosing and during their participation in the study.

Subjects will be instructed to abstain from grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration and during their participation in the study.

Subjects will be instructed to abstain from an unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving the first investigational product and during their participation in the study.

11.5.3 Procedures on Pre-Study and Study Day

Eligible volunteers will attend the ICF presentation on or before pre-study day. Volunteers will be given full details about the study on this occasion, written informed consent will be obtained from all willing volunteers. Urine samples of all the volunteers who have given written informed consent will be tested for drugs of abuse which include; Cocaine (COC), Amphetamines (AMP), Marijuana (THC), Morphine (MOP), Barbiturates (BAR), Benzodiazepine (BZD), followed by alcohol consumption by breath alcohol analyser, vital signs and subject questionnaire, medical examination, inclusion and exclusion criteria check. For females urine pregnancy test will be carried out. The group of first 30 eligible and willing volunteers who comply with all the inclusion and exclusion criteria will be recruited into the study.

A standardised meal will be served at scheduled time to have at least 10 hours fasting prior to dosing.

On the first study day, vital signs and subject questionnaire will be done; pre dose sample will be taken prior to administration of the Investigational product. Drinking water will be disallowed 1.00 hour prior to dosing and until 1.00 hour post-dose except at time of dosing. Also no food will be permitted until about 4.00 hours post-dose. Subjects will be dosed while in upright sitting posture and will be instructed to remain seated or be ambulatory (avoiding any strenuous activity) for first two hours following the investigational product administration (except during recording of vitals and blood collection time point). During this interval, under supervision, subjects will be permitted to use the washroom facilities. Thereafter the subjects will be allowed to engage only in normal activities while avoiding severe physical exertion. However if any adverse event occurs at any time during housing the subjects will be placed in an appropriate posture.



11.5.4 Blood Sampling Schedule

Blood samples (1 × 6 mL) will be collected in blood collection tube containing clot activator during each period. The venous blood samples will be withdrawn at -0.50, -0.25 hours prior to dosing at pre-dose (-0.03) and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose (Time points being relative to the investigational product dosing).

Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light.

Note: Blood sample withdrawn at -0.03 will be considered as collection at 0.00 hrs.

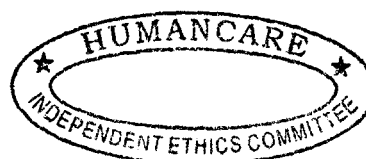
The pre-dose samples will be collected within one hour prior to investigational product dosing. The post-dose samples will be collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. Any deviations above two minutes would be recorded as protocol deviation and actual time point of blood collection will be recorded.

During in-house stay blood samples will be collected through an indwelling cannula placed in a forearm vein. Intravenous indwelling cannula would be kept in place as long as required by injecting not more than 0.5 mL of normal saline solution during the collection of multiple samples. In such a case, the blood sample would be collected after discarding the first 0.5 mL of normal saline blood from the tubing. Blood may also be withdrawn from vein by using disposable syringe and needle if the cannula is blocked /removed or the cannula is removed for other reasons. The proposed time points against the clock time have been given in appendix - III, 'Schedule for blood collection, investigational product dosing, safety assessment and meals'.

The choice of the blood collection time scheduled is intended to cover the expected mean T_{max} of Levothyroxine which is reported 5 to 6 hour post-dose. It is also extended for sufficient time to be able to obtain a reliable estimate of the extent of absorption. Levothyroxine being a long half-life drug (approximately 7 days) and because of low intra-subject variability on distribution and clearance, an AUC truncated at 72.00 hours will be used, thus samples till 72.00 hours for Levothyroxine will be collected ensuring completion of gastrointestinal tract absorption (approximately 2 days).

11.5.5 Total Blood Loss

For each subject, the total number of blood draws will be 48 (24 per period). The total volume of blood withdrawn will not exceed 325 mL (including 13 mL for safety assessment and 24 mL discarded normal saline blood). Should circumstances arise, like breakage of tube after collection, adverse event (including abnormal laboratory values) where more blood needs to be withdrawn, additional blood samples may be taken. The consent of the subject would be taken and the IEC would be informed and subject will be compensated accordingly.



Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light.

- Subjects will be required to fast overnight for at least 10 hours. There will be fasting for at least 4.00 hours after dosing.
- Subjects will be instructed to abstain from alcohol and products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) and tobacco products for at least 48 hours, prior to dosing and during their participation in the study.
- Subjects will be instructed to abstain from grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.
- Subjects will be instructed to abstain from an unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to the first investigational product and throughout their participation in the study.
- Subjects will not be allowed to drink water from 1.00 hour before dosing until 1.00 hour after dosing except during administration of the dose. At all other times, drinking water will be given ad libitum.

During clinical residence, the meal plan will be kept identical for both the periods. Information on the standardized meal, quantity and time will be recorded on the relevant raw data forms. In case the mealtime coincides with the sample collection time, vitals and subject questionnaire the sequence of events will be blood sample collection followed by vital signs and subject questionnaire and then meals.

The principal investigator reserves the right to terminate the study at any time for safety reasons or in the best interest of the subject's welfare. The ethics committee can also cancel the study for major ethical violations. The subjects would be briefed on the reasons for the termination and compensated adequately.

The remaining investigational products, which are not used in the study, will be archived for a period of at least 5 years following on which the application or supplemental application is approved or if such application or supplemental application is not approved at least 5 years following date of completion of the study.

The person involved in the dispensing of investigational products will be accountable for ensuring compliance to randomisation schedule.

All recordings relating to each subject in the study will be made directly in the relevant forms or on the designated documentation related to the study. Any other information relevant to the study and considered to be source data will be filed with the study documentation.



12.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects from the pool of healthy volunteers who were screened within 21 days prior to the first dosing day will be considered as potential participants in the study. Volunteers are only admitted to the study after having signed the informed consent form.

12.1 Inclusion Criteria

The subjects will be included based on the following criteria:

1. Healthy volunteers within the age range of 18 to 45 years.
2. Presently non-tobacco users (smokers and chewers).
3. Willingness to provide written informed consent to participate in the study.
4. Body-mass index (BMI) between 18.50 kg/m² and 29.99 kg/m² (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).
5. Absence of significant disease or clinically significant abnormal laboratory values or laboratory evaluation, medical history or physical examination during the screening.
6. Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.
7. Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.
8. Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.
9. Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).
10. Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm, and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).



12.2 Exclusion Criteria

The subjects will be excluded based on the following criteria:

1. Personal history of allergy or hypersensitivity to Levothyroxine or excipients (Magnesium stearate (E 572), maize starch, Croscarmellose sodium (E 468), Gelatin (E 441), Lactose monohydrate.)¹ or allied drugs.
2. Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure, Hepatitis, Hypotensive episodes, Hyperglycemia etc.
3. Presence of any clinically significant abnormal laboratory values during screening e.g. significant abnormality of liver function test, renal function test etc.
4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.
5. History of seizures, epilepsy or any kind of Neurological disorders.
6. Past history of Anaphylaxis or angioedema.
7. Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.
8. History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to dosing.
9. Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.
10. Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.
11. Use of any recreational drug or a history of drug addiction.
12. Participation in any clinical trial within the past 90 days.
13. History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
14. Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.
15. Consumption of any other prescription drug or over the counter (OTC) drugs [including vitamins and medicinal products from natural origin] within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study.
16. An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.
17. Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.
18. Use of oral contraceptive in last 90 days (for females).
19. Pregnant / lactating volunteers (for females).
20. Abnormal serum T_4 (total), serum T_3 (total), serum thyroid-stimulating hormone (TSH) test values.



13.0 TREATMENT OF SUBJECTS

13.1 Dose and Route of Administration

An oral dose of Reference product (R) or Test product (T) will be administered at 0.00 hour during each period with 240 mL (about 8 oz) of drinking water at room temperature as per the randomisation schedule under the supervision of the medical officer where end time of the dosing will be recorded in investigational product administration forms. The dosing interval between two consecutive subjects will be 3 minutes.

Subjects will receive the alternate 'treatment' in the subsequent period, in such a way that each subject would have received both the 'treatments' test and reference each, by the end of the study.

Owing to the sensitivity of Levothyroxine to light, Investigational Product will be dosed under yellow monochromatic light.

13.2 Concomitant Medication

No medication whether prescribed or over-the-counter products (including vitamins and medicinal products from natural origin) will be allowed within 14 days prior to dosing and during the entire duration of the study.

If the principal investigator considers that some medication is essential for the well being of the subject, it may be given. If any of the subjects take any medication during the course of the study, they must inform the principal investigator. All occasions of the drug intake will be recorded in the respective forms.

13.3 Compliance

Subjects will be provided with the identity card (I-card). While dosing, the staff on duty will confirm the subjects identity with I-card and the information mentioned on the investigational product administration form.

After administration of the dose of investigational product, examination of the oral cavity will be performed under supervision of medical officer to assess the compliance to this procedure and the same will be noted in the drug administration form of each subject. A label will be affixed to the investigational product administration form in the appropriate place to confirm correct administration of investigational product. The time of actual dose administration will be recorded in the investigational product administration form.



14.0 ASSESSMENT OF BIOAVAILABILITY

14.1 Bioavailability Parameters

- 1) Primary Parameters: $C_{\max}$ and AUC_{0-72} .
- 2) Secondary Parameters: $T_{\max}$.

Both parameters will be calculated using SAS®.

14.2 Subjects with Pre-dose Concentration

If the pre-dose concentration is less than or equal to 5 percent of $C_{\max}$ value in that subject in the particular period, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations. If the pre-dose value is greater than 5 percent of $C_{\max}$, the subject will be dropped from bioequivalence study evaluations.

14.3 Data Deletion Due to Vomiting

Data from subjects who experience emesis during the course of Bioequivalence study will be deleted from statistical analysis if vomiting occurs within 2 times median T_{max} .

14.4 Drug Assay

Validated LC-MS/MS method will be employed for the estimation of Levothyroxine in serum. Serum samples from all treated subjects (including dropout and withdrawal subjects) will be analyzed. During estimation of Levothyroxine in serum in serum quality control samples will be distributed throughout each batch of study samples.

Whenever possible, samples from each subject will be analyzed on the same standard curve. Samples with drug concentration greater than upper limit of the validated range of the analysis may be diluted with the appropriate drug free biological matrix and reanalyzed as per the method validation report. Any missing sample or unreportable concentration value will be reported as 'missing' / 'not reported' and reasons for their missing will be documented.



15.0 ASSESSMENT OF SAFETY PARAMETERS

15.1 Pre-Study Screening

Only volunteers who have been previously screened and are part of healthy volunteer pool will be considered for acceptance into this study. Any subject enrolled must have been screened within 21 days preceding the administration of Investigational Product. Screening tests are detailed in Appendix II.

The screening will be carried out after taking an initial informed consent from volunteers for study screening procedures and will include the following:

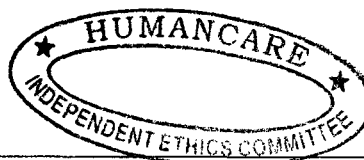
1. Demographic data, including sex, completed age, height and weight, BMI, diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation and history of participation in a drug research study.
2. Medical history, including relevant past medical/ surgical history, family history, history of allergies (food/ drug/ any other), past medication history in the last 90 days.
3. Present complaints (if any), medical examination including recording of vital signs (B.P, Pulse, Temperature and respiration), general examination, physical and systemic examination.
4. Obstetrics and Gynecological History (only for females).
5. 12-lead ECG for heart rate, rhythm and specific finding (if any).
6. Blood and Urine analysis.
7. Chest X-ray (PA view).
8. Urine Pregnancy Test (only for females).
9. Serology Test (HIV, HbsAg, HCV).

Note: Volunteers who passes all the screening parameters will go through the following laboratory test: Serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH).

15.2 Post-Study Examination

Medical examination, ECG and clinical laboratory tests will be performed to cater to the post-study safety assessments after the last blood sample collection of period II.

Whatever is the reason of withdrawal, if a subject does not satisfactorily complete the study, he/ she will be asked to attend for the post-study examination. Clinical laboratory tests will be done as per appendix II which includes CBC (leukocyte count, erythrocyte count, PCV, ESR, platelet count, haemoglobin, and DLC), Biochemistry: Blood sugar (fasting, it can be fasting or random if subject is withdrawn or dropout accordingly), triglycerides and cholesterol, Hepatic profile: SGOT, SGPT, Alkaline Phosphatase, GGT and serum bilirubin (direct, indirect and total), Renal profile: Serum creatinine, BUN, serum calcium, serum electrolytes (sodium, potassium, chlorides). Whenever possible, the post-withdrawal follow-up will be done immediately after the subject is withdrawn. In case a subject refuses to undergo such examination, it will be documented so.



15.3 Subjects Monitoring During the Study

15.3.1 Vital Signs, Subject Questionnaire and Medical Examination

In each period, subject questionnaire and vital signs (Blood pressure, Temperature and Pulse Rate) will be done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 23.00, 29.00, 35.00, 48.00 and 72.00 hours post-dose (Time points being relative to the investigational product dosing).

Note: Subject will be kept in supine position for at least 5 minutes before start of Blood Pressure recording on each time point.

Assessment of vital signs may also be done, if the attending physician finds it necessary at any time during the conduct of the study. In case of any abnormality in vital signs before dosing, medical opinion will be taken as to whether to dose the subject or not.

Medical examination will be carried out during check-in and check-out of each study period and whenever attending medical officer thinks necessary.

Risk Evaluation and Mitigation Strategies:

Risk evaluated:

- The Investigational product can cause various adverse effects.

Mitigation strategies:

- Ambulance will be made available before start of study.
- All medical staff including nurses and doctors will be informed to be available at clinical site.
- ICU will be checked for availability of all emergency medicines and other devices will be checked for proper functioning.
- Volunteers with abnormal serum T4 (total), serum T3 (total), serum thyroid-stimulating hormone (TSH) test values will be excluded from the study.

15.3.2 Adverse Events

Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

An AE that is associated with death, inpatient hospitalization (in case the study was being conducted on out-patients), prolongation of hospitalization (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

Or;

A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any doses results in:

- a. Death
- b. Requires inpatient hospitalization or prolongation of existing hospitalization
- c. Results in persistent or significant disability / incapacity, or

- d. Results in a congenital anomaly / birth defect
- e. Is life- threatening

Note:

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

During the course of the study, subjects will be monitored for any adverse event, which will be recorded in the appropriate raw data forms. The subjects would be required to inform the attending personnel or medical officer of any adverse event that may occur during the time of their stay at the clinical facility of bioequivalence department of Macleods Pharmaceuticals Ltd. and during the entire duration of the study (including the wash out period). The medical officer or nurse shall also enquire about any adverse events that may occur during the course of the study while monitoring the vital parameters. A medical officer will be available round the clock during the time of housing at the clinical facility of bioequivalence department of Macleods Pharmaceuticals Ltd. All investigational product and/or study related adverse events would be treated by the medical officer free of cost either at bioequivalence department of Macleods or at a suitable nearby hospital. Any adverse event discovered shall be appropriately treated and will be covered by an appropriate insurance policy.

15.3.3 Adverse Event Documentation

All adverse events that are reported will be properly documented on the adverse event form. In particular the information required will include: a full description of the event, date and time of onset, time lapse since administration of the Investigational Product, description of the severity of the event, any treatment or diagnostic steps taken in relation to the event, description of the outcome of the event, judgment by the physician of any relationship of the event to the investigational product or procedures. If physician considers the event to be serious as per the criterias stated above the information shall be captured in serious adverse event form.

15.3.4 Reporting of Adverse Events

Any serious adverse event will be reported to the ethics committee and PV Department and sponsor on identification either by telephone / fax within 24 hours of occurrence of event and full follow-up report to follow as soon as further information is available. SAE report will be submitted to IEC within fourteen calendar days of the occurrence of the serious adverse event. PV department will process, assess the information related to serious adverse event and will further submit to DCGI in the desired format within fourteen calendar days of the occurrence of the serious adverse event.

PV Department Contact:

Address : Macleods Pharmaceuticals Ltd.,
R & D-II, Plot no. 95,
Road no. 16, Opp. Suncity Hotel,
MIDC, Andheri - (East), Mumbai 400 093, India.
Email I.D.: safety@macleodspharma.com
Telephone No.: 18002671222
91-22-61278368



16.0 PHARMACOKINETIC ANALYSIS AND STATISTICS

16.1 Pharmacokinetic analysis

- Pharmacokinetic analysis will be performed on serum concentrations of Levothyroxine using the SAS®.

16.1.1 Pharmacokinetic Parameters

- For estimation of PK parameters, concentrations that are below level of quantification (BLQ) will be assigned a value of zero.
- In the calculations of PK parameters, missing values will be ignored. Serum concentrations will be used to determine PK parameters would be listed.
- Actual time point of blood collection will be considered for estimation of pharmacokinetic parameters.

16.2 Statistical Methods

- Statistical analysis will be performed on serum concentrations using the SAS®. The statistical analysis will include data from all subjects complete the study. If necessary, an unequal number of subjects per sequence will be used.

16.2.1 Serum Concentrations

- Descriptive statistics (number of subjects (N), arithmetic mean, S.D., C.V., minimum and maximum) will be used to summarize the serum concentrations at each time of measurement. For purposes of descriptive statistics, serum concentrations below level of quantification (BLQ) will be set to zero.
- Individual linear and semi-logarithmic graphs, mean graphs and individual serum concentration by scheduled sampling time will be provided.
- Missing samples or unreportable concentration values will be reported as 'missing/ not reported' and reasons for the same will be documented.

16.2.2 Summary Statistics

- The summary statistics for all pharmacokinetic parameters will be reported for both the test and reference products.
- The reported parameters will be the number of subjects (N), minimum, maximum, median, arithmetic mean, standard deviation and the coefficient of variation for untransformed data.

16.2.3 Ratio Analysis For Primary Pharmacokinetic Parameters

- Ratios of geometric mean of test to geometric mean of reference product will be calculated using the LSM for log transformed C_{max} and AUC_{0-72} .
- % Bioavailability of C_{max} and AUC_{0-72} will be calculated.
- Ratio T/R for each subject at C_{max} & AUC_{0-72} will be calculated.



16.2.4 Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters

- The log-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) for Levothyroxine will be analysed using standard ANOVA model with the main effects of “sequence, period, formulation and subject (sequence)”.
- A separate ANOVA model will be used to analyse each of the parameters.
- Each analysis of variance will be including calculation of mean square error, p-value of factors and the associated degrees of freedom.
- The sequence effect will be tested at 5% level of significance with subject (sequence) as an error term.
- The formulation and period effects will be tested at 5% level of significance.
- SAS® procedure ‘PROC GLM’ will be used to perform Analysis of Variance.

16.2.5 Power Test For Primary Pharmacokinetic Parameters

- For analysis using the log-transformed data, the power of the ANOVA model to detect the ratio of the two products averages (geometric means) being equal to 125.00% or 80.00% at the 5% significance level will be calculated.

16.2.6 Intra- Subject Variability For Primary Pharmacokinetic Parameters

- Intra subject coefficient of variation will be calculated using $100 \times \sqrt{e^{MSE} - 1}$ with help of SAS®. Where, MSE is mean square error obtained from analysis of variance (ANOVA) model.

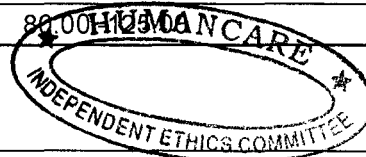
16.2.7 Confidence Intervals For Primary Pharmacokinetic Parameters

- The 90% confidence interval for the ratio of both the products averages (geometric means) will be calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.

16.2.8 Acceptance Criteria for Bioequivalence For Primary Pharmacokinetic Parameters

- The 90% confidence interval for C_{max} and AUC_{0-72} of baseline corrected Levothyroxine will form the basis for concluding the bioequivalence of Levothyroxine Sodium in product R and T.
- If the 90% confidence intervals are entirely included in the range of 80.00% – 125.00% for C_{max} and $AUC_{0-72,00}$ log-transformed then the products will be claimed to be bioequivalent.
- To be considered bioequivalent, 90% Confidence Interval of Levothyroxine should lie between following acceptance range.

Primary Parameters	Acceptance range of log transformed data
	90% Confidence Interval (%)
C_{max}	80.00 -125.00
AUC_{0-72}	80.00-125.00



16.2.9 Number of Subjects

Following data are obtained from "Published literature".^[2] Based on 2 x 2 Crossover study of Levothyroxine performed on 76 subjects under fasting condition and 71 subjects were used for the statistical analysis. Each subject received a single dose of 600 mcg (3*200 mcg) of one of the 2 levothyroxine formulations. Thus, Intra-subject C.V. was not available; it was calculated using the available data as shown below:

The pharmacokinetic parameters and statistical results for levothyroxine are as follows:

Pharmacokinetic Parameters	Ratio (T/R) (%)	90 % C.I. (%)	
		Lower	Upper
C _{max}	87.9000	84.9950	90.9043
AUC _{0-t}	90.2556	86.8626	93.7812

Calculation:

Assume that n1 (Number of AB sequence) = 36 and n2 (Number of BA sequence) =35

MSE for C_{max} = 0.014422 and MSE for AUC_{0-t} = 0.018748.

Intra-subject C.V. for C_{max} = $100 \cdot \sqrt{e^{MSE} - 1} = 12.05\%$

Intra-subject C.V. for AUC_{0-t} = $100 \cdot \sqrt{e^{MSE} - 1} = 13.76\%$

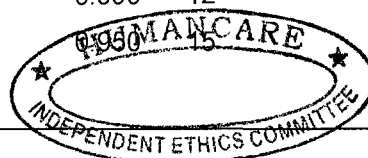
Sample size is calculated using SAS[®]. The highest Intra-subject C.V. was observed to be 13.76%. Hence using this Intra-subject C.V. the sample size calculation is as follows:

Two-Sample Equivalence

Multiplicative Model Lower Bound = 0.80 Upper Bound = 1.25

Alpha=0.05

Null Ratio	Coeff of Variation	Power	N per Group
0.95	0.1376	0.800	9
	0.1376	0.850	11
	0.1376	0.900	12
	0.1376	0.950	15
1.00	0.1376	0.800	8
	0.1376	0.850	8
	0.1376	0.900	9
	0.1376	0.950	11
1.05	0.1376	0.800	9
	0.1376	0.850	10
	0.1376	0.900	12
	0.1376		



As per SAS output, sample size of 09 i.e. 09 Observations each formulation will be required to achieve minimum 80% power at 5% level of significance for establishing bioequivalence between test and reference formulation.

Thus a 2x2 crossover study on 09 subjects will be conclude bioequivalence within normal acceptance limits of 80%-125% with 80% power at 5% level of significance.

16.2.10 Justification for Design

- The highest intra subject C.V. for levothyroxine was observed to be 13.76% as per literature of bioequivalence study. ^[2]
- Sample size of 09 subjects is required to conclude bioequivalence.
- Thus accounting for dropout or withdrawal of subjects during conduct of the study, 30 healthy volunteers will be recruited in a crossover study design to achieve the desired sample size to conclude bioequivalence.



17.0 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

A monitor or auditor for the sponsor may visit the principal investigator or co-investigators and the study facilities at any time in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. Prior to the start of the study, the principal investigator will be contacted and informed of any impending visits and the frequency of such visits. At each visit, the principal investigator or co-investigators will assist the study monitor / auditor in terms of reviewing and verifying those records associated with the study.

The entire proceedings of the study, the raw data generated for the study including scientific, non-scientific data (e.g. correspondence), analytical, clinical data, final reports, will be kept and be available for:

- Inspection and quality audits for compliance to the approved protocol.
- Inspection and quality audits for compliance to the corresponding SOPs.
- Inspection and quality audits for compliance to the regulations and Guidelines: ICH GCP, GLP.

18.0 QUALITY CONTROL AND QUALITY ASSURANCE

The Quality Assurance personnel will do quality audits. The clinical, bioanalytical and statistical raw data and reports generated during the course of the study will be liable for inspection and quality audit for conformance to this protocol and all the governing SOPs of Bioequivalence department of Macleods pharmaceuticals Ltd. and compliance to the regulations and Guidelines: ICH GCP, GLP by the quality assurance and sponsor. An audit schedule will be drawn prior to the study, audit reports will also be drawn and audit certification will be issued after the audit of the reports.



19.0 ETHICS

19.1 Ethics Committee

The protocol will be submitted to the HumanCare Independent Ethics Committee, for approval. All subsequent amendments to the protocol prior to commencement of the study will be subject to the written approval of the HumanCare Independent Ethics Committee and Sponsor. During the course of the study, the Principal Investigator reserves the right to make minor administrative amendments to protocol, without changing the meaning of the content of protocol. The same will be conveyed to the HumanCare Independent Ethics Committee and the Sponsor.

19.2 Ethical Conduct of the Study

This study will be in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, national and ICH 'Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

19.3 Informed Consent

Designated personnel will inform the volunteers before the initiation of the study. Volunteers will be required to understand and sign and date the consent form prior to initiation of any study specific activity. A copy of the signed and dated informed consent form will be given to the respective volunteers for their reference. The original signed and dated ICF will be archived at Bioequivalence department of Macleods Pharmaceuticals Ltd.

19.4 Compensation to Subjects

The subjects will be compensated for the overall inconvenience borne during the study. The total compensation for participation in all aspects of study would be Rs. 14400/-. If due to unexpected circumstances period II is scheduled later then the compensation will be given as rupees 75/- for each day. Subject will be covered by an appropriate insurance policy up to last follow up.

During check out Rs 500 /- will be given as a part compensation to subject or as per principle investigator's decision.

If required more blood is withdrawn after subject's consent and subject will be compensated as per mention in below table for each mL blood.

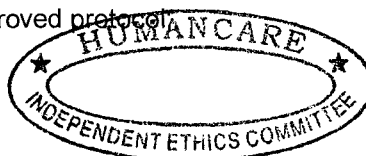
Sr. No.	Purpose	Compensation (Rs.)
1.	Compensation for each mL of blood collected. Rs. 25/mL	325 × 25 = 8125
2.	Conveyance allowance for each check-in to the facility. Rs. 200/visit	2 × 200 = 400
3.	Compensation for each day stay (for stay of 8 hrs. and above). Rs. 400/day	6 × 400 = 2400
4.	Compensation for each night stay. Rs. 200/night	8 × 200 = 1600
5.	Wash out more than 10 days, Rs 75/day	25 × 75 = 1875
	Total	14400/-

In case of dropouts / withdrawal of a subject before completion of the study, the amount of proportionate compensation to the dropout / withdrawal subject will be as follows:

Sr. No.	Reasons of Withdrawal from the Study	Compensation
1.	Principal Investigator/ Medical Officer withdraws the subject from the study based on medical decision or due to any adverse event	Proportionate participation up to the entire period in which subject is withdrawn
2.	After the initiation of the study, subject drop out on his own free will.	Proportionate participation dues
3.	If subject is withdrawn from the study on humanitarian grounds, with the permission of the Principal Investigator/Medical Officer.	Proportionate participation dues
4.	If subject is withdrawn from the study due to violation of requirements of the study by the Principal Investigator/Medical Officer after signing the Informed Consent Form but before receiving any medications.	Proportionate participation dues
5.	If subject is withdrawn from the study by the Principal Investigator/Medical Officer because of willful misinformation on present and /or past medical illness/history.	Proportionate participation dues
6	If subject is withdrawn from the study due to any serious adverse event	Full

Compensation in case of injury or death during clinical study:

- a) In case of an injury occurring to subject, subject shall be given free medical management as long as required.
- b) In case of an injury occurring to subject related to the clinical study, subject shall also be entitled for financial compensation as per order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of subject.
- c) In case of clinical study related death, subject's nominee(s) would be entitled for financial compensation as per order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of subject.
- d) The financial compensation for clinical study related injury or death could be in the form of :
 - i) payment for medical management;
 - ii) financial compensation for study related injury;
 - iii) financial compensation to nominee(s) of the study subject in case of death;
- e) The sponsor (M/s Macleods Pharmaceuticals Ltd., Mumbai) will provide financial compensation, if the injury or death has occurred because of any of following reasons, namely:
 - i) adverse effect of Investigational Product(s);
 - ii) Any study procedures involved in the study;
 - iii) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the investigator;
 - iv) failure of Investigational Product to provide intended therapeutic effect;
 - v) adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol.





- f) The sponsor (M/s Macleods Pharmaceuticals Ltd., Mumbai) will pay the quantum of compensation decided by Licensing Authority in case of clinical study related injury or death within thirty days of the receipt of order from Licensing Authority.

20.0 INSURANCE AND FINANCING

Subject will be covered by an appropriate insurance policy.

21.0 DATA HANDLING AND RECORD KEEPING

Entire data except the analytical data of pathology laboratory and other tests generated during conduct of the study will be directly recorded in raw data forms as per the related SOPs of bioequivalence department of Macleods Pharmaceuticals Ltd. The computer generated chromatograms will also be treated as bioanalytical raw data. Raw data will be completed by the study personnel and checked by the respective group leaders, designated research associate and medical officer wherever applicable. All clinical raw data related to the study will be in the custody of Section head in clinical section and analytical raw data in the custody of bioanalytical head/group leader in bioanalytical section till archiving.

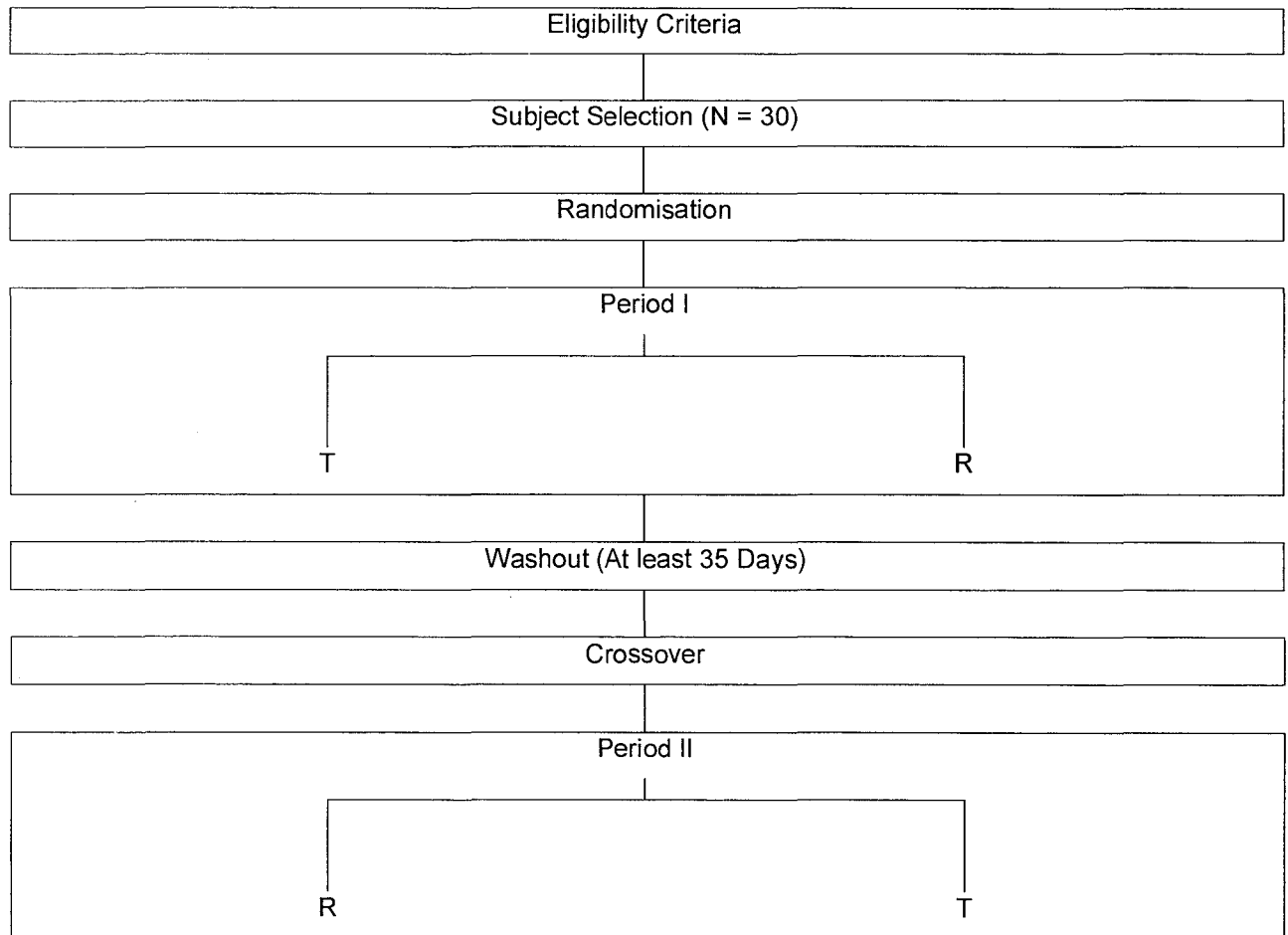
22.0 PUBLICATION POLICY

Publication of the results of the study, whether in whole or in part, shall be within the sole and absolute discretion of Sponsors and Bioequivalence department of Macleods Pharmaceuticals Ltd. shall not be entitled to publish any of the data or information arising during or out of the provision of the services without the prior written consent of Sponsor. For the avoidance of doubt, Sponsors reserves the unqualified right to reject any papers or articles utilizing any data generated from the services before such paper or article is presented or submitted for publication.



APPENDIX - I

STUDY FLOW CHART



N – Number of Subjects

R – Reference Product

T – Test Product

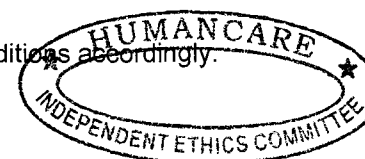


APPENDIX - II
EVENT SCHEDULE

Sr. No.	Requirement		Screening	Period I		Period II		Post-study Safety assessment
				Check-in	Check -Out	Check -In	Check -Out	
1.	Written informed consent		*	*				
2.	Demographics		*					
3.	Medical and treatment history		*	*				
4.	Subject Questionnaire		*	*	*	*	*	*
5.	Medical examination	Vital signs	Blood Pressure	*	*	*	*	*
			Temperature	*	*	*	*	*
			Pulse Rate	*	*	*	*	*
			Respiratory rate	*				
		12 lead ECG		*				*
		General and systemic		*	*	*	*	*
		Blood Collection		*				*
6.	Clinical laboratory tests	CBC (leukocyte count, erythrocyte count, PCV, ESR, platelet count, haemoglobin and DLC)		*				*
		Biochemistry	Blood sugar (random)	*				#
			Blood sugar (fasting)					
			Triglycerides and cholesterol.	*				*
		Hepatic profile: SGOT, SGPT, Alkaline Phosphatase, GGT and serum bilirubin (direct, indirect and total)		*				*
		Renal profile: Serum creatinine, BUN, serum calcium, serum electrolytes (sodium, potassium, chlorides)		*				*
		Infectious diseases (HIV, HbsAg, HCV)		*				
		Urine (Routine)		*				
		Breath Alcohol Test			*	*		
		Urine pregnancy test		*	*	*		
		Drugs of abuse			*	*		
		Chest X-ray PA view		*				
7.	Investigational Product administration				*		*	
8.	Blood sampling				*		*	

- Note: * when the particular activity is applicable.

if subject is withdrawn or drop out the blood sugar may be reported in fasting or random conditions accordingly.



DOSE ADMINISTRATION AND BLOOD SAMPLING

SAFETY ASSESSMENT



HUMANCARE
INDEPENDENT ETHICS COMMITTEE



MEDICAL EXAMINATION

Time Relative to Dose Administration (Hrs)	Prior to –11.00	72.00
Clock Time in Hrs (Days)	Prior to 2200 (D 0)	After 0900 (D 4)

MEALS

Meal	Dinner	Lunch	Snacks	Dinner	Breakfast	Lunch	Snacks	Dinner	Breakfast	Lunch	Snacks	Dinner
Time Relative to Dose Administration (Hrs)	– 11.00	4.00	8.00	13.00	24.50	28.00	32.00	37.00	48.50	52.00	56.00	61.00
Clock Time in Hrs (Days)	2200 (D 0)	1300 (D 1)	1700 (D 1)	2200 (D 1)	0930 (D 2)	1300 (D 2)	1700 (D 2)	2200 (D 2)	0930 (D 3)	1300 (D 3)	1700 (D 3)	2200 (D 3)

Note:

- The clock time is just an example; it may change all corresponding activities according to the time of Investigational Product dosing.
- Medical examination, ECG and clinical laboratory tests will be performed to cater to the post study safety assessments after the last blood collection of study period II.
- Actual time for blood collection will be based on end time of dosing.
- Medical examination will be carried out during check-in and check-out of each period of the study and whenever attending medical officer thinks necessary.

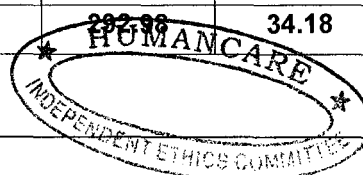




APPENDIX - IV

MEAL PLAN

Day 0: Dinner						
Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Alu tomato Curry	100	207.9	65.2	21.2	121.5
2	Peas Capsicum Veg	100	73.4	20.8	7.6	45.0
3	Dal	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Tomato Onion Raita	100	60.4	12.0	12.4	36.0
7	Carrot Halwa	50	136.0	88.0	12.0	36.0
8	Salad (mixed) no cabbage	50	-	-	-	-
9	Salt	As required	-	-	-	-
Total			1169.18	677.4	135.2	356.58
Day 1: Lunch						
Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Chawli Curry	100	97.32	44.92	16.4	36.0
2	French Beans Dry	100	104.4	59.2	9.2	36.0
3	Dal	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Cucumber Raita	100	60.4	12.0	12.4	36.0
7	Gulab jamun	60/2	199.94	146.0	14.16	39.78
8	Salad (mixed) no cabbage	50	-	-	-	-
9	Salt	As required	-	-	-	-
Total			1153.54	753.52	134.16	265.86
Day 1: Snacks						
Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Kanda poha	100	110.06	64.48	8.68	36.9
2	Dal vada with Chutney	90/1	251.1	119.7	20.7	110.7
3	Banana	100/1	116.3	108.8	4.8	2.7
Total			477.46	292.96	34.18	150.3



Day 1: Dinner

Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Chatpati Bhindi	100	128.8	51.6	19.6	57.6
2	Dudhi chana	100	105.3	55.2	9.6	40.5
3	Dal	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Curd	100	60.4	12.0	12.4	36.0
7	Malai Burfi	35/1	149.0	64.4	21.6	63.0
8	Salad (mixed) No cabbage	50	-	-	-	-
9	Salt	As required	-	-	-	-
Total			1134.98	674.6	145.2	315.18

Day 2: Breakfast

Sr. No.	Food Item	Quantity (gm)/No.)	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Veg cutlet with chutney (no cabbage)	120/2	348.4	194.4	28	126
2	Banana	100/1	116.3	108.8	4.8	2.7
Total			464.7	303.2	32.8	128.7

Day 2: Lunch

Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Black chana masala	100	73.0	24.0	4.0	45.0
2	Doodhi bhaji	100	73.0	24.0	4.0	45.0
3	Masoor Dal	50	152.8	92.0	32.0	28.8
4	Steam Rice	160	235.0	210.0	25.0	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Pyasam	100	264.7	136.0	28.8	99.9
7	Salad (mixed) no cabbage	50	-	-	-	-
8	Salt	As required	-	-	-	-
Total			1213.0	758.0	141.8	313.2





Day 2: Snacks						
Sr. No.	Food Item	Quantity (g) /No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Missal Pav	60	274.8	178.4	6.4	90.0
2	Chiku milk shake	300 mL	198.7	112.0	22.8	63.9
	Total		473.5	290.4	29.2	153.9

Day 2: Dinner

Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Masoor Ussal	100	128.8	51.6	19.6	57.6
2	Beans Dry	100	100.1	50.0	9.6	40.5
3	Dal	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Curd	100	60.4	12.0	12.4	36.0
7	Malai Burfi	35/1	149.0	64.4	21.6	63.0
8	Salad (mixed) no cabbage	50	-	-	-	-
9	Salt	As required	-	-	-	-
	Total		1129.78	669.4	145.2	315.18

Day 3: Breakfast

Sr. No.	Food Item	Quantity (g) /No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Kanda bhaji with chutney	120/2	348.4	194.4	28.0	126.0
2	Banana	100/1	116.3	108.8	4.8	2.7
	Total		464.7	303.2	32.8	128.7





Day 3: Lunch

Sr. No.	Food Item	Quantity (g) /No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Rajmah Curry	100	97.32	44.92	16.4	36.0
2	Alu Sukhi	100	104.4	59.2	9.2	36.0
3	Dal fry	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Cucumber Raita	100	60.4	12.0	12.4	36.0
7	Gulab jamun	60/2	199.94	146.0	14.16	39.78
8	Salad (mixed)	50	-	-	-	-
Total			1153.54	753.52	134.16	265.86

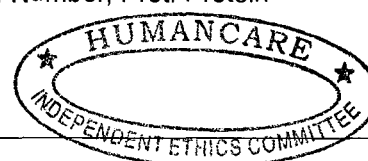
Day 3: Snacks

Sr. No.	Food Item	Quantity (g)/No.	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Kanda poha	100	110.06	64.48	8.68	36.9
2	Dal vada with Chutney	90/1	251.1	119.7	20.7	110.7
3	Banana	100/1	116.3	108.8	4.8	2.7
Total			477.46	292.98	34.18	150.3

Day 3: Dinner

Sr. No.	Food Item	Quantity (gm/No.)	Cals. (kcal)	CHO (kcal)	Prot. (kcal)	Fat (kcal)
1	Moong dry	100/1	207.9	65.2	21.2	121.5
2	Alu Capsicum Veg	100	73.4	20.8	7.6	45.0
3	Dal	150	107.18	63.4	20.2	23.58
4	Rice	150	169.8	156.0	13.8	-
5	Chapatti	125/5	414.5	272.0	48.0	94.5
6	Tomato Onion Raita	100	60.4	12.0	12.4	36.0
7	Doodhi Halwa	50	136.0	88.0	12.0	36.0
8	Salad (mixed)no cabbage	50	-	-	-	-
9	Salt	As required	-	-	-	-
Total			1169.18	677.4	135.2	356.58

Kcal.: Calorie, Cals: Calories, CHO: Carbohydrate, g: Gram, No.: Number, Prot: Protein



APPENDIX - V

NORMAL RANGES FOR PATHOLOGY LABORATORY

HAEMATOLOGY		
Specified tests/ Examination performed (Method)	Biological Reference Interval	Units
Leucocyte Count (WBC)	4.00 – 10.00	x1000/ μ L
Erythrocyte count (RBC)	Male 4.50 – 5.50 Female 3.80 – 4.80	x million/ μ L
Haemoglobin (Hb)	Male 13.0 – 17.0 Female 12.0 – 15.0	g/dL
Hematocrit (HCT)	Male 40.0 – 50.0 Female 36.0 – 46.0	%
Platelet Count (PLT)	150 – 410	x1000/ μ L
Differential Leucocyte Count (DLC)		
Neutrophils	40 – 80	%
Eosinophils	1 – 6	%
Lymphocytes	20 – 40	%
Monocytes	2 – 10	%
Basophils	< 1 – 2	%
ESR	(Below 50 Yrs) Male < 15 (Below 50 Yrs) Female < 20 (50-85 Yrs) Male < 20 (50-85 Yrs) Female < 30	mm/hr

CLINICAL BIOCHEMISTRY		
Specified tests/ Examination performed (Method)	Biological Reference Interval	Units
Blood Sugar (Hexokinase)	Fasting 70.0 – 110.0 Random 70.0 – 150.0 Post Prandial Less than 140.0	mg/dL
Total Cholesterol (CHOD/EPOD)	Less than 200.0	mg/dL
Triglyceride (Enzymatic)	Less than 150.0	mg/dL
Blood Urea Nitrogen (BUN)(Urease)	7.00 – 18.00	mg/dL
Creatinine (Alkaline Picrate, Kinetic)	Male 0.70 – 1.30 Female 0.55 – 1.02	mg/dL
Alkaline Phosphatase (PNPP,AMP Buffer)	46.0 – 116.0	U/L
SGOT (UV with P5P)	Male 15.0 – 40.0 Female 13.0 – 35.0	U/L
SGPT (UV with P5P)	Male 16.0 – 63.0 Female 14.0 – 59.0	U/L
Calcium (o-CPC)	8.50 – 10.10	mg/dL
GGT (GCNA)	Male 15.0 – 85.0 Female 5.0 – 55.0	U/L
Bilirubin Total (Jendrassick & Jroff)	0.10 – 1.20	mg/dL
Bilirubin Direct (Diazotization)	Less than 0.30	mg/dL
Bilirubin Indirect (Calculated)	0.10 – 1.00	mg/dL
Sodium (Direct ISE)	136.0 – 145.0	mmol/L
Potassium (Direct ISE)	3.50 – 5.10	mmol/L
Chloride (Direct ISE)	98.0 – 107.0	mmol/L



SEROLOGY	
No Biological Reference Ranges for Serology tests, However it will be reported as follows:	
Specified tests/ Examination performed (Method)	Biological Reference Interval
HBsAg	Not Detected/ Detected
HIV 1	Non Reactive/ Reactive
HIV 2	Non Reactive/ Reactive
HCV	Non Reactive/ Reactive

Drugs of Abuse		
Specified tests/ Examination performed (Method)	Limit of Detection	Units
Cocaine (COC)	> 300	ng/mL
Amphetamine (AMP)	> 1000	ng/mL
Marijuana (THC)	> 50	ng/mL
Morphine (MOP)	> 300	ng/mL
Barbiturates (BAR)	> 300	ng/mL
Benzodiazepines (BZD)	> 300	ng/mL

Positive: Indicates > Limit of Detection

Negative: Indicates < Limit of Detection



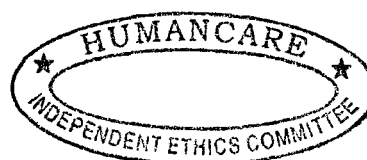
ROUTINE EXAMINATION OF URINE

Specified tests/ Examination performed (Method)	Biological Reference Interval
Physical Examination	
Colour	Colourless to Yellow
Appearance	Clear
Deposits	Absent
Ph	5.0 – 9.0
Specific Gravity	1.001-1.035
Chemical Examination (Semiquantitative method)	
Protein	Negative
Glucose	Negative
Ketones Bodies	Negative
Occult Blood	Negative
Bile pigments (Bilirubin)	Negative
Bile Salts	Absent
Urobilinogen	Normal
Microscopic Examination	
Red Blood cells/hpf	0-2
Leucocytes or Pus cells/hpf	2-3
Epithelial cells/hpf	2-5
Casts	Absent
Crystals	Absent
Amorphous material	Absent
Trichomonas Vaginalis	Absent
Bacteria	Absent

URINE PREGNANCY TEST

Specified tests/ Examination performed (Method)	Biological Reference Interval	Units
Urine Pregnancy Test	Negative	--

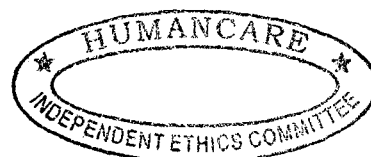
Cut off Value 25 mIU / mL



LABORATORY PARAMETERS ACCEPTABLE RANGE

Parameter	Normal Range	Clinically Relevant Direction with Abnormality %	Decrease	Increase
Haemoglobin (g/dL)	M: 13.00-17.00 F: 12.00-15.00	10% Decrease	M: 11.7 F: 10.8	-
Hematocrit (%)	M: 40.00-50.00 F: 36.00-46.00	10% Decrease	M: 36.00 F: 32.4	-
Erythrocyte Count (mil/uL)	M: 4.50-5.50 F: 3.80-4.80	10% Either	M: 4.05 F: 3.42	M: 6.05 F: 5.28
Platelets (thou/uL)	150-410	10% Decrease	135	-
Leucocyte Count (thou/uL)	4.00-10.00	10% Either	3.60	11.00
Neutrophils	40.00-80.00%	10% Either	36.00	88.00
Eosinophil	1.00-6.00%	25% Increase	-	7.5
Basophil	< 1-2.00%	25% Increase	-	2.5
Lymphocytes	20.00-40.00%	10% Either	18.00	44.00
Monocytes	2.00-10.00%	25% Increase	-	12.50
ESR	(Below 50 Yrs) M: < 15mm/hr	10% Increase	-	16.50
	(Below 50 Yrs) F: < 20mm/hr		-	22.0
	(50-85 Yrs) M: < 20mm/hr		-	22.0
	(50-85 Yrs) F: < 30 mm/hr		-	33.0
T Bili (mg/dL)	0.10 – 1.20	10% Increase	-	1.32
D Bili (mg/dL)	Less than 0.30	10% Increase	-	0.33
ID Bili (mg/dL)	0.10-1.00	10% Increase	-	1.10
SGOT (U/L)	Male 15.0 – 40.0 Female 13.0 – 35.0	10% Increase	-	M: 44 F: 38.5
SGPT (U/L)	Male 16.0- 63.0 Female 14.0 – 59.0	10% Increase	-	M: 69.3 F: 64.9
GGT (U/L)	M:15.00-85.00 F: 5.0-55.00	10% Increase	-	M: 93.5 F: 60.5
Alkaline Phosphatase (U/L)	46.00-116.00	10% Increase	-	127.6
BUN (mg/dL)	7.00-18.00	10% Increase	-	19.8
Creatinine (mg/dL)	M: 0.70-1.30	10% Increase	-	1.43
	F: 0.55-1.02		-	1.10
Sodium (mmol/L)	136.00-145.00	5% Either	129.20	152.25
Potassium (mmol/L)	3.50-5.10	5% Either	3.33	5.36
Chloride (mmol/L)	98.00-107.00	5% Either	93.10	112.35
Calcium (mg/dL)	8.50-10.10	5% Either	8.08	10.61
Blood Sugar (mg/dL)	Fasting: 70.0 – 110.0	10% Either	63.00	121.00
	Random: 70.0 – 150.0	10% Either	63.00	165.00
	Post Prandial Less than 140.0	10% Increase	-	154.0
Triglyceride (mg/dL)	Less than 150	10% Increase	-	165.00
Cholesterol (mg/dL)	Less than 200	10% Increase	-	220.00

Note: In case any of the above tests are done by sub contracted lab of Pathology Laboratory of Macleods Pharmaceuticals, the Normal range for the respective test, of the Contractual Laboratory should be considered.



APPENDIX VI
UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator
Education, training & experience that qualify the Investigator for the clinical trial

Name: Dr. Rajendra Sonde

Address: Macleods Pharmaceuticals Ltd.,
Bioequivalence Department
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri – (East), Mumbai 400 093
Tel.: 91-22-61132900
Fax: 91-22-28304641

Education : (M.B.B.S., PGDHHM, D.PHARM.)

Experience : 26 years

Medical Council registration number : 074821 (Maharashtra Medical Council)

2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted:

Clinical Facility: Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
R and D II, Plot no. 95,
Road no. 16, Opp. Suncity Hotel,
MIDC, Andheri - (East),
Mumbai 400 093, India.
Telephone No.: 91-22-67258412

Screening and X-Ray Facility: Macleods Pharmaceuticals Ltd.,
Bioequivalence Department
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri – (East), Mumbai 400 093.
Tel.: 91-22-61132900
Ext no.: 127/150/316
Fax: 91-22-28304641

3. Name and address of all clinical laboratory facilities to be used in the study.

Pathological Laboratory: Pathology Department
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093.
Tel.: 91-22-61132900
Fax: 91-22-28304641



4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.

HumanCare Independent Ethics Committee

Shop No. 4, Chandresh Krishna,
Near Nilje Railway Station,
Kalyan Shil Road, Lodha Heaven
Dombivali (East), Thane - 421204
Mobile: +91 7738360789

5. Names of the other member of the research team (Co- or sub-Investigators) who will be assisting the Investigator in the conduct of the investigation (s).

- Dr. S. Vijay Kumar
- Dr. Atul Patil
- Dr. Milind A. Jadhav
- Dr. Pratip Sen

6. Protocol Title and Study number of the clinical trial to be conducted by the Investigator.

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Protocol No.: BEQ-2321-LEVT-2017

Status: Final

Version no.: 02

Date: 19th March 2018

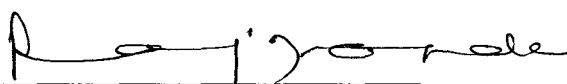
Supersedes: 01

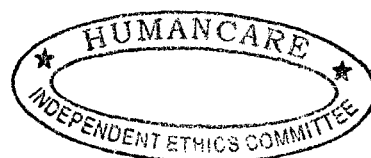
Date: 23rd November 2017



7. Commitments:

- i. I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.
- ii. I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval / favorable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard (s) to the trial Subjects or when the change(s) involved are only logistical or administrative in nature.
- iii. I agree to personally conduct and/or supervise the clinical trial at my site.
- iv. I agree to inform all Subjects that the drugs are being used for investigational purpose and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the GCP guidelines are met.
- v. I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.
- vi. I have read and understand the information in the Investigator's brochure, including the potential risks and side effects of the drug.
- vii. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.
- viii. I agree to maintain adequate and accurate records and to make those records available for audit / inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.
- ix. I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others.
- x. I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within twenty four hours of their occurrence.
- xi. I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.
- xii. I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials.


(Signature of Investigator with Date) 19/03/18



APPENDIX VII
WMA – DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

A) Preamble

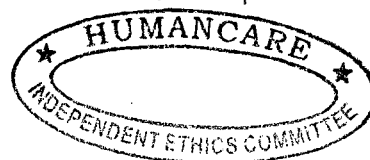
1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

B) General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

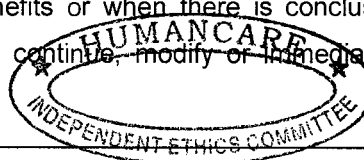


8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

C) Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.



D) Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E) Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F) Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.



G) Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

H) Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.



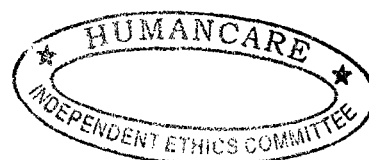
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I) Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

J) Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

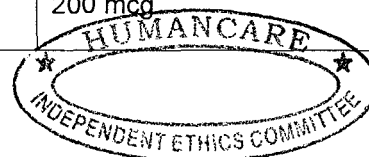


APPENDIX -VII
LIST OF AMENDMENTS

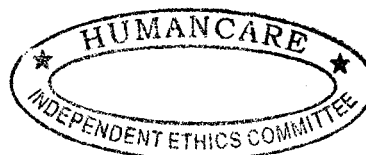
Protocol BEQ-2321-LEVT-2017, version number 01; dated 23rd November 2017

Protocol BEQ-2321-LEVT-2017, version number 02; dated 19th March 2018

Serial No.	Section No.	BEQ-2321-LEVT-2017 Status: Final Version No.: 01 Date: 23 rd November 2017	BEQ-2321-LEVT-2017 Status: Final Version No.: 02 Date: 19 th March 2018
1.	General	Number of Subjects: 24	Number of Subjects: 30 Changes made in all the respective sections
		Clinical residency Subject will be admitted and housed in the facility sufficient time before to maintain 10 hours fasting condition before the administration of dose and until 48 hours post-dose, during each period of the study.	Clinical residency Subject will be admitted and housed in the facility sufficient time before to maintain 10 hours fasting condition before the administration of dose and until 72 hours post-dose, during each period of the study. Changes made in all the respective sections
		Dietary Plan The dose will be administered after an overnight fast of at least 10 hours in each period. Fasting will continue for at least four hours post-dose, then meals will be provided approximately at 4.00, 8.00 and 13.00 hours post-dose on dosing day (day1) and approximately at 24.50, 28.00, 32.00 and 37.00 hours post dose on day 2 during each period.	Dietary Plan The dose will be administered after an overnight fast of at least 10 hours in each period. Fasting will continue for at least four hours post-dose, then meals will be provided approximately at 4.00, 8.00 and 13.00 hours post-dose on dosing day 1 and approximately at 24.50, 28.00, 32.00 and 37.00 hours post dose on day 2 and at 48.50, 52.00, 56.00 and 61.00 hours post dose (i.e. breakfast, lunch, snacks and dinner on day 3) each study. Changes made in all the respective sections
2.	3.0	<u>ABBREVIATIONS</u> -	<u>ABBREVIATIONS</u> Modified
3.	5.0 Appendix – VI	X-Ray Facility Ext. No.: 127	Screening and X-Ray Facility Ext. No.: 127/150/319
4.	8.0	Investigational Products: i) Test Formulation (T) Levothyroxine Sodium Tablets 200 mcg Batch No.: N/AV Manufacturing Date: N/AV Expiry Date: N/AV Manufactured by: Macleods Pharmaceuticals Ltd. India Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water.	Investigational Products: i) Test Formulation (T) Levothyroxine Sodium Tablets 200 mcg Batch No.: MLK602C Manufacturing Date: 10/2016 Expiry Date: 09/2018 Manufactured by: Macleods Pharmaceuticals Ltd. India Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water.
	9.1	ii) Reference Formulation (R) Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg	ii) Reference Formulation (R) Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg



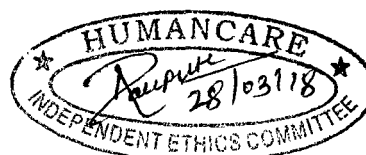
Serial No.	Section No.	BEQ-2321-LEVT-2017 Status: Final Version No.: 01 Date: 23 rd November 2017	BEQ-2321-LEVT-2017 Status: Final Version No.: 02 Date: 19 th March 2018
	11.4.1	Lot No.: N/AV Manufacturing Date: N/AV Expiry Date: N/AV Marketed by: Merck B.V., Schiphol-Rijk, Netherlands Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water	Batch No.: 209740 Manufacturing Date: N/AV Expiry Date: 11/2018 Marketed by: Merck B.V., tupolevlaan, 41 – 61, 1119 NW Schiphol-Rijk Dose: 3 Tablets Mode of administration: Administered orally with 240 mL of drinking water
5.	9.11	References Summary of Product Characteristics of Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg, Last update on 12/05/2015. Cited on 22/11/2017, Available from: https://db.cbg-meb.nl/IB-teksten/h09009.pdf	References Summary of Product Characteristics of Euthyrox [®] (levothyroxine sodium) Tablets 200 mcg, Last update on 15/10/2017. Cited on 18/03/2018, Available from: https://db.cbg-meb.nl/IB-teksten/h09009.pdf
6.	8.0 15.3.1	-	Added Risk Evaluation and Mitigation Strategies:
7.	8.0 11.5.4 Appendix III	Collection Schedules Blood samples (1 × 6 mL) will be collected in blood collection tube containing clot activator during each period. The venous blood samples will be withdrawn at -0.50, -0.25 hours prior to dosing at pre-dose (-0.03) and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours post-dose (Time points being relative to the investigational product dosing).	Collection Schedules Blood samples (1 × 6 mL) will be collected in blood collection tube containing clot activator during each period. The venous blood samples will be withdrawn at -0.50, -0.25 hours prior to dosing at pre-dose (-0.03) and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 and 72.00 hours post-dose (Time points being relative to the investigational product dosing).
8.	8.0 11.5.5	Blood Loss For each subject, the total number of blood draws will be 42 (21 per period). The total volume of blood withdrawn will not exceed 286 mL (including 13 mL for safety assessment and 21 mL discarded normal saline blood).	Blood Loss For each subject, the total number of blood draws will be 48 (24 per period). The total volume of blood withdrawn will not exceed 325 mL (including 13 mL for safety assessment and 24 mL discarded normal saline blood).
9.	8.0 15.3.1 Appendix III	Safety Assessment In each period, subject questionnaire and vital signs (Blood Pressure, Temperature and Pulse Rate) will be done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 23.00, 29.00, 35.00 and 48.00 hours post-dose (time points being relative to the investigational product dosing).	Safety Assessment In each period, subject questionnaire and vital signs (Blood Pressure, Temperature and Pulse Rate) will be done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 23.00, 29.00, 35.00, 48.00 and 72.00 hours post-dose (time points being relative to the investigational product dosing).
10.	15.1	Pre-Study Screening -	Pre-Study Screening Modified Note



Serial No.	Section No.	BEQ-2321-LEVT-2017 Status: Final Version No.: 01 Date: 23 rd November 2017	BEQ-2321-LEVT-2017 Status: Final Version No.: 02 Date: 19 th March 2018
11.	19.4	Compensation to Subjects The total compensation for participation in all aspects of study would be Rs. 12225/-. During check out Rs 500 /- will be given as a part compensation to subject	Compensation to Subjects The total compensation for participation in all aspects of study would be Rs. 14400/-. During check out Rs 500 /- will be given as a part compensation to subject or as per principle investigator's decision Modified Table for compensation in case of dropout/withdrawal
12.	Appendix VI	Co- or sub-Investigators ➤ Dr. S. Vijay Kumar ➤ Dr. Atul Patil ➤ Dr. Milind A. Jadhav ➤ Dr. Pratip Sen ➤ Dr. Santosh Patil ➤ Dr. Merlyn Gomes	Co- or sub-Investigators ➤ Dr. S. Vijay Kumar ➤ Dr. Atul Patil ➤ Dr. Milind A. Jadhav ➤ Dr. Pratip Sen

INFORMED CONSENT FORM (English)

Serial No.	Section No.	Version No.: 01 Date: 23 rd November 2017	Version No.: 02 Date: 19 th March 2018
1.	-	-	Related changes as per protocol
2.	[2]	General information about study drug -	General information about study drug Modified
3.	[7]	What are the possible risks, side effects and discomforts of the study? -	What are the possible risks, side effects and discomforts of the study? Modified



APPENDIX 16.1.2

SAMPLE CASE RECORD FORM

CASE RECORD FORM

Study Title:

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design:

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

Protocol No.	:	BEQ-2321-LEVT-2017
CRF Status	:	Final
Version	:	01
Dated	:	19 th March 2018
Supersedes Version	:	N/AP
Dated	:	N/AP

Volunteer Registration No. BEQ-

Subject No. _____

Subject Initials			

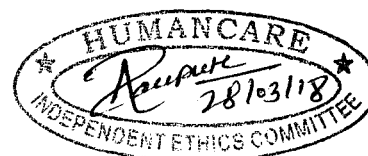
Date of Birth

D	D	M	M	Y	Y

Date of ICF Presentation

D	D	M	M	Y	Y

Principal Investigator : Dr. Rajendra Sonde
Study Director : Dr. Ashish Mungantiwar
Sponsor's Representative : Ms. Shalmali Ambekar





SCREENING CRF	Vol. Reg. Number	: BEQ-
	Subject Number	:
	Subject Initials	:

SCREENING CRF

(Attach Screening Record)



Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18**SCREENING RECORD**

Volunteer Reg. No	Initial	Date of Screening
BEQ-		

STUDY ALLOTTEMENT

(To be filled on the day of check-in)

Study No. allotted	:	
Subject No.	:	
Date of allocation	:	
Recorded By	:	(Signature and Date)
Verified by (PI/ CI)	:	(Signature and Date)



Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

Volunteer Reg. No	BEQ-	Initial	

DEMOGRAPHICS											
Date of Birth	:		Completed Age (Yrs)	:		Sex	:	Male		Female	
Height (Meter)	:		Weight (Kg)	:		BMI (Kg/m ²)	:				
Done by (Sign. and Date)	:										

VITALS SIGN					
Start time of supine posture	Posture (Sitting/ Supine)				
	Respiration (Rate/minute)	Pulse (Per min.)	Temp.(°F)	Start time of Blood Pressure	Blood Pressure (mmHg)
Recorded by: (Nurse / MO)			Sign. and Date: _____		

HISTORY

A) Personal Habits and History					
a	Diet	Mixed		Vegetarian	
b	History of Tobacco Use	No		Yes	
	If yes, Present	Past	Specify:		
c	Intake of abusive/recreational drugs	No		Yes	
	If yes, Present	Past	Specify:		
d	Alcohol intake	No		Yes	
	If yes, Present	Past	Specify:		
e	History of blood donation	No		Yes	
	If yes, Period since last donation				Amount:
f	History of participation in a drug research study	No		Yes	
	If yes, Period since last participation				Amount:
	Drug (Group):				
g	History of Allergy (food, medicine, etc.)	No		Yes	
	If yes, Present	Past	Specify:		
Remark (if any):					



Macleods Pharmaceuticals Limited**Biocquivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

Volunteer Reg. No	BEQ-	Initial	

B) Medical / Surgical History

Sr. No.	History	No	Yes
1.	Any major past medical illnesses like ischemic heart disease, diabetes, hypertension, Asthma, epilepsy, tuberculosis, Hepatitis B., HIV, psychiatry disorder, any other significant medical illness etc.?		
2.	Any history of diminished or blurred vision/ diminished hearing		
3.	Have you suffered from any major medical event / hospitalization in last 6 months		
4.	Did you have any major surgery in past?		
5.	Are you on any current medical treatment /or history of drug intake in last 90 days.		
6.	Any History of skin associated lesion		
7.	Family History of any Significant Illness for e.g. diabetes, hypertension, asthma, epilepsy?		

Remark (if any):

MEDICAL EXAMINATION**A) General Examination**

1.	Any present complaints	Yes	No
2.	Conscious/Co-operative/Oriented	Yes	No
3.	Cyanosis / clubbing / Icterus / pallor	Absent	Present
4.	Lymphadenopathy	Absent	Present
5.	Edema or Varicosities	Absent	Present
6.	Scalp examination	Normal	Abnormal

Remark (if any):



Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

Volunteer Reg. No.	BEQ-	Initial	

B) Physical and Systemic Examination**1. Cardiovascular system (CVS)**

1.	Heart sounds S1 & S2	Normal		Abnormal	
2.	Any abnormal heart sounds i.e. murmurs, split sounds, gallop etc	Absent		Present	

Remark (if any):

2. Respiratory system (RS)

1.	Air Entry – Vesicular Breath Sounds equal on both sides	Yes		No	
2.	Any abnormal breath sounds like wheezing, crepitus rales etc	Absent		Present	

Remark (if any):

3. Gastrointestinal system (GIT)

1.	Guarding, rigidity, tenderness or rebound tenderness	No		Yes	
2.	Liver, Spleen, kidneys, any mass	Not Palpable		Palpable	
3.	Bowel sounds	Normal		Abnormal	

Remark (if any):

4. Ear, Nose & Throat

		Normal		Abnormal	

Remark (if any):

5. Eyes

1.	Wearing spectacles/contact lens	No		Yes	
2.	Gross Vision	Normal		Abnormal	
3.	Conjunctiva, eye lids	Normal		Abnormal	

Remark (if any):

6. Musculoskeletal and Skin

1.	Overall body and skin appearance	Normal		Abnormal	
2.	Any skin lesions (infection, rashes, nodules, etc.)	No		Yes	
3.	Walking (gait) abnormally, any misalignment, asymmetry	No		Yes	
4.	Assessment of muscle strength & tone	Normal		Abnormal	

Remark (if any):



Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

Volunteer Reg. No.	BEQ-	Initial	

7. Central Nervous system (CNS) & Psychiatric

1.	Higher centers, gait, sensory and motor system	Normal		Abnormal	
2.	Mental status which may include orientation of time, place	Normal		Abnormal	

Remark (if any):

8. Genito-Urinary (Male)

1.	Examination of male genitalia	Normal		Abnormal	

Remark (if any):

9. Genito /Obstetric and gynecological (Female)

1.	Marital Status	Married		Unmarried	
2.	Menstrual History: Date of last menstrual period ____/____/____	Regular		Irregular	
3.	Obstetric History	Gravida		Para	
4.	History of MTP	Yes		No	
5.	Post Menopausal period for at least one year	Yes		No	
6.	Lactating	No		Yes	
7.	Contraceptive method used	Yes		No	
8.	Surgical history of any major/minor obstetric/gynec operation	No		Yes	
9.	Examination of External genitalia/ vaginal discharge	Normal		Abnormal	

Remark (if any):

Describe if abnormality detected: _____

Examined by: _____
(Medical Officer) (Signature and Date)Reviewed by: _____
(Medical Officer) (Signature and Date)

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

Volunteer Reg. No.	BEQ-	Initial	

INVESTIGATION REPORT

Parameter	Clinically acceptable	Clinically not acceptable
ECG		
X-Ray		
Remark (if any):		

I) Pathology laboratory investigations:

Parameters	WNL	WAL	OAL
Hematology			
Biochemistry			
Urine Analysis			

WNL-Within Normal Limit,

WAL- Within Acceptable Limit,

OAL- Outside Acceptable Limit.

II). Infectious Diseases	Positive	Negative

The pathology lab. Parameters are:

Normal	Clinically Not significant	Clinically significant	Repeat test

Note: For acceptable limits of laboratory parameter, refer Annexure No. ANX/CL/SOP-003-02, 'Definition of Abnormal Test Values When Baseline Values is Normal or Missing'

Remark: _____

Reports Reviewed by: _____

(Medical Officer) (Signature and Date)

If repeat test required (Name of test) _____

Advised by: _____

(Medical Officer) (Signature and Date)

Repeat test report dated ____/____/____ is/are reviewed and

Normal	Clinically Not significant	Clinically significant

Remark: _____

 Repeat test report Reviewed by: _____
 (Medical Officer) (Signature and Date)

ANX/CL/SOP-003-03



Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO. : BEQ/CL/SOP-003/18

LABORATORY PARAMETERS ACCEPTABLE RANGE

Parameter	Normal Range	Clinically Relevant Direction with Abnormality %	Decrease	Increase
Haemoglobin (g/dL)	M: 13.00-17.00	10% Decrease	M: 11.7	-
Hematocrit (%)	M: 40.00-50.00	10% Decrease	M: 36.00	-
Erythrocyte Count (mil/uL)	M: 4.50-5.50	10% Either	M: 4.05	M: 6.05
Platelets (thou/uL)	150-410	10% Decrease	135	-
Leucocyte Count (thou/uL)	4.00-10.00	10% Either	3.60	11.00
Neutrophils	40.00-80.00%	10% Either	36.00	88.00
Eosinophil	1.00-6.00%	25% Increase	-	7.5
Basophil	< 1-2.00%	25% Increase	-	2.5
Lymphocytes	20.00-40.00%	10% Either	18.00	44.00
Monocytes	2.00-10.00%	25% Increase	-	12.50
ESR	(Below 50 Yrs) M: < 15mm/hr	10% Increase	-	16.50
	(Below 50 Yrs) F: < 20mm/hr		-	22.0
	(50-85 Yrs) M: < 20mm/hr		-	22.0
	(50-85 Yrs) F: < 30 mm/hr		-	33.0
T Bili (mg/dL)	0.10 – 1.20	10% Increase	-	1.32
D Bili (mg/dL)	Less than 0.30	10% Increase	-	0.33
ID Bili (mg/dL)	0.10-1.00	10% Increase	-	1.10
SGOT (U/L)	Male 15.0 – 40.0	10% Increase	-	M: 44
SGPT (U/L)	Male 16.0- 63.0	10% Increase	-	M: 69.3
GGT (U/L)	M:15.00-85.00	10% Increase	-	M: 93.5
Alkaline Phosphatase (U/L)	46.00-116.00	10% Increase	-	127.6
BUN (mg/dL)	7.00-18.00	10% Increase	-	19.8
Creatinine (mg/dL)	M: 0.70-1.30	10% Increase	-	1.43
Sodium (mmol/L)	136.00-145.00	5% Either	129.20	152.25
Potassium (mmol/L)	3.50-5.10	5% Either	3.33	5.36
Chloride (mmol/L)	98.00-107.00	5% Either	93.10	112.35
Calcium (mg/dL)	8.50-10.10	5% Either	8.08	10.61
Blood Sugar (mg/dL)	Fasting: 70.0 – 110.0	10% Either	63.00	121.00
	Random: 70.0 – 150.0	10% Either	63.00	165.00
	Post Prandial Less than 140.0	10% Increase	-	154.0
Triglyceride (mg/dL)	Less than 150	10% Increase	-	165.00
Cholesterol (mg/dL)	Less than 200	10% Increase	-	220.00

Note:

- In case any of the above tests are done by sub contracted lab of Pathology Laboratory of Macleods Pharmaceuticals, the Normal range for the respective test, of the Contractual Laboratory should be considered.
- In case of any change in normal range by pathology laboratory of Macleod's pharmaceuticals, the clinical relevant direction with abnormality % will be with respective normal range.



Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP NO. : BEQ/CL/SOP-003/18	

Volunteer Reg. No	Initial	Date of Screening
BEQ-		

CRITERIA CHECK

The volunteer will be included in the study if the answers to all the statements are yes.

Criteria Check		Yes	No
1.	The volunteer is fulfilling the demographic criteria.		
2.	The volunteer is not having present history of tobacco use, intake of abusive /recreational drug and alcoholism.		
3.	No history of blood donation more than 350 mL of blood in the past 90 days.		
4.	The volunteer has not participated in a clinical drug trial in the past 90 days.		
5.	After assessment of vitals, medical history & examination, pathology laboratory parameters, ECG and X-ray the volunteer has no clinically significant illness and can be considered normal.		

Conclusion: The volunteer is **Eligible** ☐ **Not Eligible** ☐ to be included in the study.

Compiled by: _____
(Medical Officer) (Signature and Date)

Reviewed by _____
(Medical Officer) (Signature and Date)

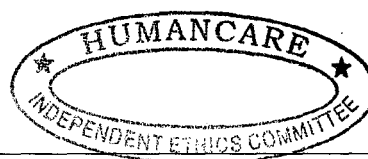
Verified by: _____
(Principal Investigator/Co-Investigator) (Signature and Date)





STUDY SPECIFIC CRF	Vol. Reg. Number : BEQ-
	Subject Number :
	Subject Initials :

STUDY SPECIFIC CRF



INCLUSION CRITERIA CHECKLIST	Vol. Reg. Number	:	BEQ-
	Period	:	I
	Date	:	

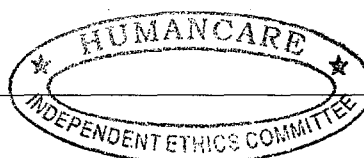
Sr. No.	INCLUSION CRITERIA	Yes	No
1.	Healthy volunteers within the age range of 18 to 45 years.		
2.	Presently non-tobacco users (smokers and chewers).		
3.	Willingness to provide written informed consent to participate in the study.		
4.	Body-mass index (BMI) between 18.50 kg/m ² and 29.99 kg/m ² (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).		
5.	Absence of significant disease or clinically significant abnormal laboratory values or laboratory evaluation, medical history or physical examination during the screening.		
6.	Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.		
7.	Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.		
8.	Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.		
9.	Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).		
10.	Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm, and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).		

Note: Tick '✓' for Yes and cross 'x' for No and Not Applicable

Remark (if any):

Compiled by: _____
MO (Sign/ Date)

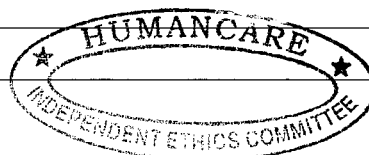
Checked by: _____
PI/ MO (Sign/ Date)





EXCLUSION CRITERIA CHECKLIST	Vol. Reg. Number	:	BEQ-
	Period	:	I
	Date	:	

Sr. No.	EXCLUSION CRITERIA	Yes	No
1.	Personal history of allergy or hypersensitivity to Levothyroxine or excipients (Magnesium stearate (E 572), Maize starch, Croscarmellose sodium (E 468), Gelatin (E 441), Lactose monohydrate.) or allied drugs.		
2.	Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure, Hepatitis, Hypotensive episodes, Hyperglycemia etc.		
3.	Presence of any clinically significant abnormal laboratory values during screening e.g. significant abnormality of liver function test, renal function test etc.		
4.	Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.		
5.	History of seizures, epilepsy or any kind of Neurological disorders.		
6.	Past history of Anaphylaxis or angioedema.		
7.	Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.		
8.	History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to dosing.		
9.	Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.		
10.	Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.		
11.	Use of any recreational drug or a history of drug addiction.		
12.	Participation in any clinical trial within the past 90 days.		
13.	History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.		
14.	Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.		





EXCLUSION CRITERIA CHECKLIST	Vol. Reg. Number	:	BEQ-
	Period	:	I
	Date	:	

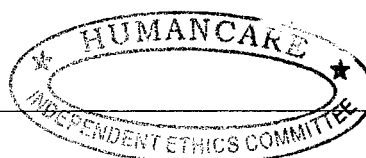
Sr. No.	EXCLUSION CRITERIA	Yes	No
15.	Consumption of any other prescription drug or over the counter (OTC) drugs [including vitamins and medicinal products from natural origin] within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study.		
16.	An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.		
17.	Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.		
18.	Use of oral contraceptive in last 90 days (for females).		
19.	Pregnant / lactating volunteers (for females).		
20.	Abnormal serum T ₄ (total), serum T ₃ (total), serum thyroid-stimulating hormone (TSH) test values.		

Note: Tick '✓' for Yes and cross 'x' for No and Not Applicable

Remark (if any): _____

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)





INVESTIGATIONAL PRODUCT ADMINISTRATION RECORD	Subject Number	:	
	Period	:	I
	Date	:	

Container - tampered/ un-tampered	Scheduled time of dose administration:

Parameters	Remark	Parameters	Remark
Dosing container checked for number of IP as per label		Subject dosed at scheduled time	
Subject seated comfortably		Actual time of dose administered (hrs)	
Identity of subject verified with identity card and wristband		Number of IP units administered	
Subject number checked on dosing container and form		240 mL of water taken with the IP	
Instructions regarding restriction (posture, water etc) given		Water consumed completely	
Instructed to swallow the dose with the provided volume of water given		Mouth checked with tongue depressor and torch	
IP administered in fasting condition		IP administered completely	
IP administered in upright sitting posture		Dosing activity performed under supervision of PI/MO	
Environmental Condition (YML)		Deviation (If any)	

Note: Tick '✓' for Yes and cross 'x' for No, N/AP: Not Applicable, YML: Yellow Monochromatic light

Stick label here

Remark (if any): _____

Done by: _____
(Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)





BLOOD COLLECTION RECORD (BLEED SHEET)	Subject Number	:	
	Period	:	I
	Date of Dosing	:	

Scheduled Time of Dosing	:	Volume of Blood/ TP	:	6 mL

- Instruction : A. **Blood sample withdrawn at -0.03 will be considered as collection at 0.00 hrs**
- B. Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light

Time point (hrs)	Date	Schedule Time (hrs)	Subject No. check	Tube ID check	Actual Time (hrs)	Deviation	Initial / Date
			Make (✓) mark				
-0.50							
-0.25							
Pre-dose (-0.03)							
0.50							
1.00							
1.50							
2.00							
2.50							
3.00							
3.50							
4.00							
4.50							
5.00							
5.50							
6.00							
8.00							
10.00							
12.00							
18.00							
24.00							
30.00							
36.00							
48.00							





BLOOD COLLECTION RECORD (BLEED SHEET)	Subject Number	:
	Period	:
	Date of Dosing	:

Time point (hrs)	Date	Schedule Time (hrs)	Subject No. check	Tube ID check	Actual Time (hrs)	Deviation	Initial / Date
			Make (✓) mark				
72.00							

Total number of samples to be collected: 24	Total number of samples collected:

Code for reasons for deviation:

A: cannula block

B: delay in previous sample collection

C: due to adverse event

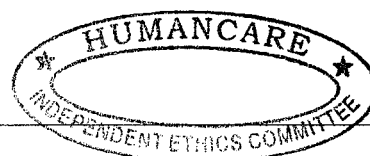
D: Not reported as per protocol
requirement

E: any other

Remark (if any):

Compiled by: _____
(Sign/ Date)

Checked by: _____
(Sign/ Date)





VITALS AND SUBJECT QUESTIONNAIRE	Vol. Reg. Number : BEQ-
	Subject Number :
	Period : I

Actual Time of Dosing:	Date of Dosing:

Time point (Hrs.)	Date	Start time of supine position	SQ		Posture (Supine)				Remark	Initial/ Date
			Well (✓)	Unwell (✓)	Pulse (Per min.)	Temp. (°F)	Start time of Blood Pressure	Blood pressure (mmHg)		
Check-in										
Pre-dose										
1.00										
3.00										
6.00										
9.00										
23.00										
29.00										
35.00										
48.00										
72.00										

SQ.: Subject Questionnaire Temp.: Temperature min.: minute Hrs.: Hours

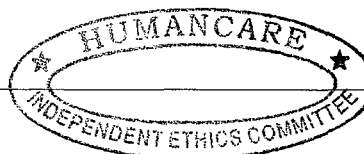
Reasons for not Recording Vitals and SQ:

- A: Drop out from the study B: Withdrawn from the study C: Not recorded start time of supine posture
D: any other

Remark (if any): _____

Compiled by: _____
Nurse/ MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



CLINICAL CASE RECORD (CCR)	Vol. Reg. Number	: BEQ-
	Day	: Check-in
	Date	:
Period: I		

CLINICAL CASE RECORD

Chief Complaints :

**General and Local (if
applicable) Examinations** :

Systemic Examinations

• Respiratory System :

• Cardio Vascular System :

• Central Nervous System :

• Per Abdomen :

Vein Puncture Site : Normal ☐ Abnormal ☐ Not Applicable ☐

Conclusion : Volunteer is Fit ☐ / Unfit ☐

(Mention 'NAD' for 'No Abnormality Detected')

Remark (if any):

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



CLINICAL CASE RECORD (CCR)	Subject Number	:	
	Day	:	Check-out
	Date	:	
Period: I			

CLINICAL CASE RECORD

Chief Complaints :

General (if applicable)

Examinations :

Systemic Examinations

• Respiratory System :

• Cardio Vascular System :

• Central Nervous System :

• Per Abdomen :

Vein Puncture Site : Normal ☐ Abnormal ☐ Not Applicable ☐

Conclusion : Subject is Fit ☐ / Unfit ☐

(Mention 'NAD' for 'No Abnormality Detected')

Remark (if any): _____

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)





EXCLUSION CRITERIA CHECKLIST	Subject Number	:	
	Period	:	II
	Date	:	

Sr. No.	EXCLUSION CRITERIA	Yes	No
1.	Any clinically significant abnormality reported/ detected.		
2.	Consumption of alcohol within 48 hours prior to dosing.		
3.	Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.		
4.	Consumption of any other prescription drug or over the counter (OTC) drugs [including vitamins and medicinal products from natural origin] within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study.		
5.	An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.		
6.	Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.		
7.	Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (e.g. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.		
8.	Use of any recreational drug or a history of drug addiction.		
9.	Participation in any clinical trial within the past 90 days.		
10.	Donation of blood (one unit or 350 mL) during washout period of the study.		
11.	Urine pregnancy test (UPT) is positive (for females).		

Note: Tick '√' for Yes and cross 'x' for No and Not Applicable

Remark (if any): _____

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



INVESTIGATIONAL PRODUCT ADMINISTRATION RECORD	Subject Number :
	Period : II
	Date :

Container - tampered/ un-tampered	Scheduled time of dose administration:

Parameters	Remark	Parameters	Remark
Dosing container checked for number of IP as per label		Subject dosed at scheduled time	
Subject seated comfortably		Actual time of dose administered (hrs)	
Identity of subject verified with identity card and wristband		Number of IP units administered	
Subject number checked on dosing container and form		240 mL of water taken with the IP	
Instructions regarding restriction (posture, water etc) given		Water consumed completely	
Instructed to swallow the dose with the provided volume of water given		Mouth checked with tongue depressor and torch	
IP administered in fasting condition		IP administered completely	
IP administered in upright sitting posture		Dosing activity performed under supervision of PI/MO	
Environmental Condition (YML)		Deviation (If any)	

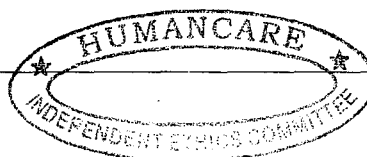
Note: Tick '✓' for Yes and cross 'x' for No, N/AP: Not Applicable, YML: Yellow Monochromatic light

Stick label here

Remark (if any):

Done by: _____
(Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



BLOOD COLLECTION RECORD (BLEED SHEET)	Subject Number	:
	Period	: II
	Date of Dosing	:

Scheduled Time of Dosing	:	Volume of Blood/ TP	:	6 mL

Instruction : A. **Blood sample withdrawn at -0.03 will be considered as collection at 0.00 hrs**

B. Owing to the sensitivity of Levothyroxine to light, samples will be collected and processed under yellow monochromatic light

Time point (hrs)	Date	Schedule Time (hrs)	Subject No. check	Tube ID check	Actual Time (hrs)	Deviation	Initial / Date
			Make (✓) mark				
-0.50							
-0.25							
Pre-dose (-0.03)							
0.50							
1.00							
1.50							
2.00							
2.50							
3.00							
3.50							
4.00							
4.50							
5.00							
5.50							
6.00							
8.00							
10.00							
12.00							
18.00							
24.00							
30.00							
36.00							
48.00							





BLOOD COLLECTION RECORD (BLEED SHEET)	Subject Number	:	
	Period	:	II
	Date of Dosing	:	

Time point (hrs)	Date	Schedule Time (hrs)	Subject No. check	Tube ID check	Actual Time (hrs)	Deviation	Initial / Date
			Make (✓) mark				
72.00							

Total number of samples to be collected: 24	Total number of samples collected:

Code for reasons for deviation:

A: cannula block

B: delay in previous sample collection

C: due to adverse event

D: Not reported as per protocol requirement

E: any other

Remark (if any):

Compiled by: _____
(Sign/ Date)

Checked by: _____
(Sign/ Date)





VITALS AND SUBJECT QUESTIONNAIRE

Subject Number : _____

Period : II

Scheduled Time of Dosing: _____

Date of Dosing: _____

Time point (Hrs.)	Date	Start time of supine position	SQ		Posture (Supine)				Remark	Initial/ Date
			Well (√)	Unwell (√)	Pulse (Per min.)	Temp. (°F)	Start time of Blood Pressure	Blood pressure (mmHg)		
Check-in										
Pre-dose										
1.00										
3.00										
6.00										
9.00										
23.00										
29.00										
35.00										
48.00										
72.00										

SQ.: Subject Questionnaire

Temp.: Temperature

min.: minute

Hrs.: Hours

Reasons for not Recording Vitals and SQ:

A: Drop out from the study

B: Withdrawn from the study

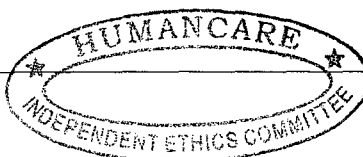
C: Not recorded start time of supine posture

D: any other

Remark (if any): _____

Compiled by: _____
Nurse/ MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



CLINICAL CASE RECORD (CCR)	Subject Number	:
	Day	: Check-in
	Date	:

CLINICAL CASE RECORD

Chief Complaints

General and Local (if applicable) Examinations

Systemic Examinations

- Respiratory System :

- Cardio Vascular System :

- Central Nervous System :

- Per Abdomen :

Vein Puncture Site : Normal ☐ Abnormal ☐ Not Applicable ☐

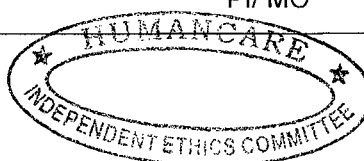
Conclusion : Subject is Fit ☐ / Unfit ☐

(Mention 'NAD' for 'No Abnormality Detected')

Remark (if any):

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



CLINICAL CASE RECORD (CCR)	Subject Number	:	
	Day	:	Check-out/Safety assessment
	Period: II	Date	:

CLINICAL CASE RECORD

Chief Complaints

General and Local (if applicable) Examinations

Systemic Examinations

- Respiratory System :

- Cardio Vascular System :

- Central Nervous System :

- Per Abdomen :

Vein Puncture Site : Normal ☐ Abnormal ☐ Not Applicable ☐

Conclusion : Subject is Fit ☐ / Unfit ☐

(Mention 'NAD' for 'No Abnormality Detected')

Remark (if any):

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)

ANX/CL/SOP-039-01

Page 20 of 24





POST STUDY SAFETY ASSESSMENT CRF	Vol. Reg. Number	:	BEQ-
	Subject Number	:	
	Subject Initials	:	

POST STUDY SAFETY ASSESSMENT CRF





SAFETY LABORATORY PARAMETER INVESTIGATION RECORD	Subject Number :
	Date of safety assessment :

Reference source no. for pathology report : _____

LABORATORY INVESTIGATIONS			
Parameter	WNL	WAL	OAL
Hematology			
Biochemistry			
Any Other			

DETAILS OF PARAMETERS OUTSIDE ACCEPTABLE LIMIT		
Laboratory Parameter	OAL	Reference Range

WNL: Within Normal Limit

WAL: Within Acceptable Limit

OAL: Outside Acceptable Limit

(Note: For acceptable limits of laboratory parameter, refer Protocol 'Laboratory Parameters Acceptable Range')

**Remark
(if any):**

Electrocardiogram (ECG): Normal ☐ Clinically acceptable ☐ Clinically not acceptable ☐

Conclusion: Normal ☐ Clinically acceptable ☐ Clinically significant ☐

Note: Tick '✓' the appropriate and Cross 'x' the not appropriate

(Attach Laboratory reports and ECG after this page)

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



SUBJECT WITHDRAWAL/ DROPOUT RECORD OR STUDY COMPLETION CERTIFICATE	Subject Number :
	Subject Initials :

SUBJECT WITHDRAWAL RECORD	
Did the subject withdrawn from the study? : Yes ☐ / No ☐	
Reason for withdrawal : (AE/ Protocol non compliance/ Uncooperative/ Others)	
Date of withdrawal :	Time of withdrawal

Medical Officer Report:

SUBJECT DROPOUT RECORD	
Did the subject dropped-out from the study? : Yes ☐ / No ☐	
Reason for dropped-out : (Personal/ Others)	
Date of dropped-out :	Time of dropped-out:

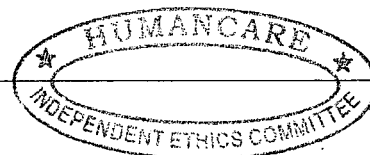
Medical Officer Report:

STUDY COMPLETION CERTIFICATE

Did the subject complete the study? Yes ☐ / No ☐

Compiled by: _____
MO (Sign/ Date)

Checked by: _____
PI/ MO (Sign/ Date)



CASE RECORD FORM REVIEW	Vol. Reg. Number : BEQ-
	Subject Number :
	Subject Initials :

CASE RECORD FORM REVIEW

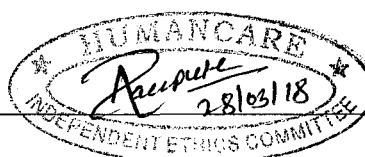
This is to certify that, all the data contained in this case record form are consistent with observations and source records. They accurately reflect the condition of the subject during the study.

List of documents attached		
Sr. No.	Document	Number of Document
1.	Screening Record	
2.	Adverse Event (AE) Form	
3.	Serious Adverse Event (SAE) Form	
4.	Follow-up conversation form	
5.	Note to File	
6.	Laboratory Report	
7.	ECG Report along with photocopy	
8.	X-Ray Report	
9.	Others (specify, if any)	

Compiled by: _____
(CRA) (Sign/Date)

Reviewed by: _____
(Medical Officer) (Sign/Date)

Verified by: _____
(Principal Investigator / Co-investigator) (Sign/Date)



APPENDIX 16.1.3

IEC CONSULTED AND IEC APPROVED INFORMED CONSENT FORM

HumanCare Independent Ethics Committee

- Dr. Pachpute Amol P.
(Chairperson)
- Mrs. Raje Gauri S.
(Member Secretary)

Shop No. 4, Chandresh Krishna,
Near Nilje Railway Station,
Kalyan Shil Road, Lodha Heaven
Dombivali (East), Thane - 421204
Mobile: +91 7738360789



HumanCare

INDEPENDENT ETHICS COMMITTEE

OHRP No.: IORG0009358

DCG(I) Regd. No.: ECR/276/Indt/MH/2017

28/03/2018

“Decision Letter”

To,
Dr. Rajendra Sonde
Principal Investigator
Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India

Subject: Decision for below mentioned research project submitted to the HumanCare Independent Ethics Committee.

Protocol No.	:	BEQ-2321-LEVT-2017
Version No.	:	02
Dated	:	19/03/2018

Dear Dr. Rajendra Sonde,

The HumanCare Independent Ethics Committee reviewed and discussed your research project entitled “Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects” on 28/03/2018 during the meeting. The following documents were reviewed and discussed;

1. Protocol No.: BEQ-2321-LEVT-2017; Version No.: 02, Dated: 19/03/2018
2. Informed Consent Form: Version No.: 02, Dated: 19/03/2018 – English
3. Informed Consent Form: Version No.: 01, Dated: 19/03/2018 – Hindi & Marathi

Confidential and Restricted Documents

Page 1 of 4

Shop No. 04, Chandresh Krishna, Near Nilje Railway Station, Kalyan-Shil Road,
Lodha Heaven, Dombivali (E) 421204
Contact - +917738360789 Email : humancareethics@gmail.com



HumanCare

INDEPENDENT ETHICS COMMITTEE

OHRP No.: IORG0009358

DCG(I) Regd. No.: ECR/276/Indt/MH/2017

4. Case Record Form: Version No. 01; Dated: 19/03/2018
5. Questionnaire for Subject: Version No. 01
6. References:
 - Summary of Product Characteristics of Euthyrox[®] (levothyroxine sodium) Tablets 200 mcg, Last update on 15/10/2017. Cited on 18/03/2018, Available from:
<https://db.cbg-meb.nl/IB-teksten/h09009.pdf>
 - Public Assessment Report for levothyroxine sodium, NL/H/2700/001-011/DC dated 30/11/2015. Cited on 22/11/2017, Available from:
https://mri.cts-mrp.eu/download/NL_H_2700_004_PAR.pdf
7. Proposed Methods for Patient accrual including advertisement(s) etc proposed to be used for purpose (SOP “Recruitment and Enrolment of Volunteers”)
8. Principal Investigator’s current CV
9. Insurance Policy

The following members of Ethics Committee were present at the Meeting held on 28/03/2018 at 08.20 pm.

Sr. No.	Name of Members	IEC Designation
1.	Dr. Pachpute Amol P.	Chairperson
2.	Mrs. Raje Gauri S.	Member Secretary
3.	Dr. Sharma Atul	Clinician
4.	Dr. Kamle Mangesh S.	Basic Medical Scientist
5.	Dr. Salunke Balwant P.	Basic Medical Scientist
6.	Dr. Tembhare Meena N.	Basic Medical Scientist
7.	Mrs. Kashid Priyadarshani	Legal Expert
8.	Mr. More Kiran S.	Social Scientist
9.	Mr. Pande Girish D.	Lay Person
10.	Mrs. Visapure Ashwini R.	Lay Person



HumanCare

INDEPENDENT ETHICS COMMITTEE

OHRP No.: IORG0009358

DCG(I) Regd. No.: ECR/276/Indt/MH/2017

“Levothyroxine” is an old drug in India was discussed by Member Secretary.

IEC is constituted and functions as per the ICH- GCP, Good Clinical Practices guidelines issued by Central Drugs Standard Control Organisation (CDSCO), Schedule Y of the Drugs and Cosmetics Act 1940, as amended from time to time, The Ethics guidelines for Biomedical research on Human Subjects, issued by Indian Council of Research and Declaration of Helsinki, 1964 as modified by World Medical Association, Brazil 2013, updated/amended from time to time.

Decision of HumanCare Independent Ethics Committee

On reviewing the documents send by the Investigator, vide letter dated 23/03/2018, for Protocol No.: BEQ-2321-LEVT-2017; Version No.: 02; dated 19/03/2018, the HumanCare Independent Ethics Committee concluded the decision that the research project submitted is Approved as presented.

The Investigator has to update HumanCare Independent Ethics Committee about;

1. Commencement date in advance and subsequent progress of the research project on regular basis.
2. Report serious and unexpected adverse events within 24 hours of their occurrence and subsequent follow up report after due analysis within 14 days of occurrence of event.
3. Any changes in the protocol, subject information sheet / ICF.
4. Immediately report the significant protocol deviation.
5. Submit the copy of final report on completion of the research project.

Note:

1. Appropriate regulatory permission to be obtained prior to commencement of the research project wherever applicable.

Confidential and Restricted Documents

Page 3 of 4



HumanCare

INDEPENDENT ETHICS COMMITTEE

OHRP No.: IORG0009358

DCG(I) Regd. No.: ECR/276/Indt/MH/2017

2. The validity of this decision is till the completion of the research project or one year from the date of decision, whichever is earlier.
3. No subject should be enrolled or admitted in the study before receiving written approval or favorable opinion of IEC.

Yours sincerely,



Chairperson / ~~Member Secretary~~

HumanCare Independent Ethics Committee



Informed Consent Form

Study Title:

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design:

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

ICF Version No.: 02

Status: Final

Date: 19th March 2018

Supersedes: 01

Date: 23rd November 2017

Volunteer's Registration No.	Volunteer's Initial	Sex: Male / Female	Subject No.
BEQ -			

Note: It is important to read carefully and understand the information given in this document before agreeing to participate in the study. You must sign this form with date. You will be provided with a copy of this form for your reference. Any clarifications and questions can be discussed during the oral presentation of this document and at any time during the course of study.

The purpose of this document is to clearly state the procedures of the study and to ensure that you enter the study only after knowing the relevant information about it. The informed consent form describes the purpose of the study, possible benefits, risks or discomfort, alternative treatment and confidentiality. It also bears the declaration of your voluntary participation in the study.

The informed consent is not a contract and you can withdraw from the study at any time, at your own will, without having to give any reasons for doing so.

Principal Investigator : Dr. Rajendra Sonde



[4] How many people will take part in the study?

30 healthy, adult, human subjects will be taking part in the study.

[5] What is the procedure of this study?

Your inclusion in the study will be based on a preliminary screening and certain exclusion criteria.

You will be eligible only if you satisfy the following requirements:

- Medical examinations
- Laboratory examinations
- Exclusion criteria

❖ **Screening:**

The following screening tests were performed to assess your health status:

1. Demographic data, including sex, completed age, height and weight, BMI, diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation and history of participation in a drug research study.
2. Medical history, including relevant past medical/surgical history, family history, history of allergies (food/drug/any other), past medication history in the last 90 days.
3. Present complaints (if any), medical examination including recording of vital signs (B.P, Pulse, Temperature and Respiration), general examination, physical and systemic examination.
4. Obstetrics and Gynecological History (only for females).
5. 12-lead ECG for heart rate, rhythm and specific finding (if any).
6. Blood and Urine analysis.
7. Chest X-ray (PA view).
8. Urine Pregnancy Test (only for females).
9. Serology Test {HIV (human immunodeficiency virus), HbsAg [hepatitis B (inflammation of liver) surface antigen], HCV (hepatitis C virus that primarily affects the liver)}.

Note: As you have passed all the screening parameters, following laboratory test were performed: Serum T₄ (total), serum T₃ (total), serum thyroid-stimulating hormone (TSH).

❖ **Exclusion Criteria:**

You will be ineligible to participate in the study if you have:

1. Personal history of allergy or hypersensitivity to Levothyroxine or excipients (inactive substances in medicine) (Magnesium stearate (E 572), maize starch, Croscarmellose sodium (E 468), Gelatin (E 441), Lactose monohydrate) or allied drugs.
2. Any major illness in the past 90 days or any clinically significant ongoing chronic (long-lasting medical condition) medical illness e.g. Congestive Cardiac Failure (Heart failure), Hepatitis (Inflammation of the liver), Hypotensive (low blood pressure) episodes, Hyperglycemia (high blood sugar) etc.





❖ **Procedures:**

1. In this study, you will be required to stay within clinical facility of Bioequivalence center for two study periods, i.e. Period I and Period II.
2. In each period you will receive any one treatment i.e., Treatment 'T' consisting of three tablets as single dose of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Ltd., India) or Treatment 'R' consisting of three tablets as single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands). The order in which you receive study medication will be decided randomly but by the end of study, you would have received both the treatments.
3. Between two consecutive periods there will be an interval of at least 35 days from the completion of dosing. If Period II is scheduled later the duration and compensation may change accordingly.
4. In each period you will be required to check-in at bioequivalence center sufficient time before to maintain 10 hours fasting condition before the administration of Investigational Product and until 72 hours post-dose.
5. In each period at the time of check-in urine test for drugs of abuse will be carried out.
6. In each period at the time of check-in your breath will be checked whether you have consumed alcohol or not through breath alcohol analyzer.
7. Urine pregnancy test (for females only) will be carried out at the time of check-in of period I and period II.
8. Your activity will be monitored through circuit camera system.
9. Medical examination will be carried out during check-in and check-out of each period of the study and whenever attending medical officer thinks necessary.
10. A dinner will be provided at 2200 hours on the day of check-in.
11. An overnight fast of at least 10 hours will be maintained.
12. In each study period, after an overnight fast of at least 10 hours you will receive orally, test or reference product with 240 mL of drinking water at the scheduled time.
13. Your investigational product dosing will be in upright sitting posture. You will remain seated or be ambulatory (avoiding any strenuous activity) for first two hours following the investigational product administration (except during recording of vitals and blood sample collection time point). During this interval, under supervision, you will be permitted to use the washroom facilities. Thereafter you will be allowed to engage only in normal activities while avoiding severe physical exertion.
14. Drinking water will not be allowed 1 hour pre and 1 hour post dosing.
15. No food will be allowed for at least 4 hours post dose, then standardized meals will be provided at 4.00 hours after the investigational product administration and at specified interval thereafter snacks at 8.00 hours and dinner at 13.00 hours post dose on dosing day (day 1) and approximately at 24.50, 28.00, 32.00 and 37.00 hours post dose on day 2 (i.e. breakfast, lunch, snacks and dinner) and approximately at 48.50, 52.00, 56.00 and 61.00 hours post dose on day 3 (i.e. breakfast, lunch, snacks and dinner) as per the meal plan in the study period. In case the



Skin and subcutaneous tissue disorders	Hyperhidrosis (abnormally increased sweating / perspiration.)
Musculoskeletal and connective tissue disorders	Muscle weakness Muscle spasms
General disorders and administration site conditions	Excessive flushing (skin redness usually of the face) Pyrexia (raised body temperature)
To investigate	Weight reduced

Reference:

1. Summary of Product Characteristics of Euthyrox® (levothyroxine sodium) Tablets 200 mcg, Last update on 15/10/2017. Cited on 18/03/2018, Available from:
<https://db.cbg-meb.nl/IB-teksten/h09009.pdf>

Possible risks due to cannulation and blood collection

During procedure of cannulation or blood collection through indwelling cannula you may be suffer from pain, swelling, infection at the cannulation site, Haemorrhage (Bleeding), Haematoma (A localized swelling that is filled with blood caused by a break in the wall of a blood vessel), Vaso-vagal episode (The brain is deprived of oxygen and the fainting episode occurs), Needle phobias (fear of needles), Catheter embolism (coiled worm-shaped platelet and fibrin aggregates), Transfixation (piercing through the vein wall), Nerve damage, Arterial puncture (rupture of arteries), Allergies, Needlestick injury (A penetrating stab wound from a needle that may result in exposure to blood or other body fluids), Thrombophlebitis (inflammation of the wall of a vein with associated thrombosis).

Note:

- This is not a complete list of side effect, this being a clinical study using an investigational product, so some unforeseeable risk or discomfort may occur that not yet known to us.
- Treatment may involve risks to you (or to the embryo or fetus, if you [female volunteer] become pregnant), which are currently unforeseeable.

[8] Are there benefits of taking part in the study?

As such, you will not derive any direct medical benefit from taking part because you are healthy but by participating in this study you will get a free medical check-up.

[9] Termination of the Study?

The principal investigator reserves the right to terminate the study at any time for safety reasons or in the best interest of the subject's welfare. The ethics committee can also cancel the study for major ethical violations. You would be briefed on the reasons for the termination and compensated adequately.



[10] What are the other options?

This study is purely for research purpose towards submission of results to the regulatory authorities and the only alternative for you would be not to participate.

[11] What is the financial compensation?

You will be compensated for the overall inconvenience borne during the study. The total compensation for participation in all aspects of study would be Rs.14400/-. If due to unexpected circumstances period II is scheduled later then the compensation will be given as rupees 75/- for each day. You will be also covered by an appropriate insurance policy up to last follow up.

During check out Rs 500 /- will be given as a part compensation to you or as per principle investigator's decision.

If required more blood is withdrawn after your consent and you will be compensated for each mL blood as per mention in below table.

Sr. No.	Purpose	Compensation (Rs.)
1.	Compensation for each mL of blood collected. Rs. 25/mL	325 × 25 = 8125
2.	Conveyance allowance for each check-in to the facility. Rs. 200/visit	2 × 200 = 400
3.	Compensation for each day stay (for stay of 8 hrs. and above). Rs. 400/day	6 × 400 = 2400
4.	Compensation for each night stay. Rs. 200/night	8 × 200 = 1600
5.	Wash out more than 10 days, Rs 75/day	25 × 75 = 1875
	Total	14400/-

In case of dropout/withdrawal of you before completion of the study, you will be entitled to the following proportionate compensation.

Sr. No.	Reasons of Withdrawal from the Study	Compensation
1.	Principal Investigator/ Medical Officer withdraws the subject from the study based on medical decision or due to any adverse event	Proportionate participation up to the entire period in which subject is withdrawn
2.	After the initiation of the study, subject drop out on his own free will.	Proportionate participation dues
3.	If subject is withdrawn from the study on humanitarian grounds, with the permission of the Principal Investigator/Medical Officer.	Proportionate participation dues
4.	If subject is withdrawn from the study due to violation of requirements of the study by the Principal Investigator/Medical Officer after signing the Informed Consent Form but before receiving any medications.	Proportionate participation dues
5.	If subject is withdrawn from the study by the Principal Investigator/Medical Officer because of willful misinformation on present and /or past medical illness/history.	Proportionate participation dues
6.	If subject is withdrawn from the study due to any serious adverse event	Full





Compensation in case of injury or death during clinical study:

- a) In case of an injury occurring to you, you shall be given free medical management as long as required.
- b) In case of an injury occurring to you related to the clinical study, you shall also be entitled for financial compensation as per order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of yours.
- c) In case of clinical study related death, your nominee(s) would be entitled for financial compensation as per order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of yours.
- d) The financial compensation for clinical study related injury or death could be in the form of :
 - i) payment for medical management;
 - ii) financial compensation for study related injury;
 - iii) financial compensation to nominee(s) of the study subject in case of death;
- e) The sponsor (M/s Macleods Pharmaceuticals Ltd., Mumbai) will provide financial compensation, if the injury or death has occurred because of any of following reasons, namely:
 - i) adverse effect of Investigational Product(s);
 - ii) Any study procedures involved in the study;
 - iii) violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the investigator;
 - iv) failure of Investigational Product to provide intended therapeutic effect;
 - v) adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol;
- f) The sponsor (M/s Macleods Pharmaceuticals Ltd., Mumbai) will pay the quantum of compensation decided by Licensing Authority in case of clinical study related injury or death within thirty days of the receipt of order from Licensing Authority.

[12] What is expected from me?

- 1. You are requested to co-operate with the Bioequivalence center staff and adhere to the study related procedures.
- 2. You will be checked personally and your belongings will be checked for any prohibited items prior to check-in and checkout of each study period.
- 3. You are expected to reply to the calls, SMS or post/courier, if you do not report for check-in
- 4. You should not make any noise in the study center.
- 5. In case emergency, you should press emergency bell, which is located at your bed and at wash room area.
- 6. Abusive language or behavior towards staff or fellow participants will not be tolerated.
- 7. You should not abuse and/or damage to any property of Bioequivalence Department of Macleods Pharmaceuticals Ltd., or that of fellow participants.
- 8. You will be provided with separate locker to keep your belongings.





9. You should use the recreational things (carom board, television, and cards) carefully without causing any damage.
10. The use and/or possession of any prohibited items or illicit drugs are strictly forbidden in the center.
11. You should provide your current address proof.
12. You must provide emergency contact number, e-mail I.D. (if available)
13. You should follow the diet restrictions as per the requirement of the study. You should not bring any outside food in the center.
14. Post dosing, you should be in upright sitting position for at least 2 hours.
15. You should not drink water at least for 1 hour pre and 1 hour post dosing.
16. You are not allowed to take any prescription / Over the Counter medicines (OTC) drugs (including vitamins and medicinal products from natural origin) while participating in the study without the approval of Principal Investigator / Medical Officer except in case of any emergency and you must inform the same to Principal Investigator / Medical Officer.
17. If you are unable to visit the facility for safety, you will be contacted through calls, SMS and post/courier.
18. If you could not visit the facility for follow-up of adverse event (during study or abnormal laboratory parameters during post study safety) you may be contacted telephonically, through SMS, post/courier if there is no response and as per the medical officer the adverse event or abnormal laboratory value during post study safety is considered severe visit can be given to the current address provided by you.
19. You should go to bed early at night.
20. You are instructed to abstain from products containing xanthine derivatives (chocolates, tea, coffee or cola drinks), tobacco products and alcohol for at least 48 hours prior to dosing and during your participation in the study.
21. You are instructed to abstain from grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration and during your participation in the study
22. You are instructed to abstain from an unusual diet for whatever reason e.g. low sodium (salt) diet, for two weeks prior to receiving first dose of investigational product and during your participation in the study.
23. Any adverse event occurred after last Investigational Product Administration up to 35 days, you will report to the facility for further management.
24. For female subjects you have to use a suitable barrier method of contraceptive to avoid pregnancy during the study period and up to 35 days after the last dosing of Investigational product. In case you get pregnant during this period, you need to report to study center for further management till outcome of pregnancy. This is because there may be risk to embryo or fetus due to drug which are not known to us.



[13] What about confidentiality?

Your original medical records or study data (like Informed Consent Form, etc.) obtained during the study will be maintained in confidentiality and will be directly accessible to:

- Independent ethics committee / Institutional review board
- Concerned regulatory authority not limited to but includes DCGI (Drug Controller General of India), CDSCO (Central Drugs Standard Control Organization), EMA (European Medicines Agency)
- Monitor(s)
- Auditor(s)
- Sponsor whose product is being tested
- Designated personnel of Bioequivalence center of Macleods Pharmaceuticals Ltd.

Published reports will however not disclose any information that allows revealing the identity of any specific volunteer in this study.

[14] What is the alternative procedure of medical treatment for study related injury?

Free medical treatment will be provided at Bioequivalence center of M/s Macleods Pharmaceuticals Ltd., and in case of any emergency you will be treated at a nearby hospital at no cost to you as long as required.

[15] What are my rights as I participate?

Your participation in the study is voluntary and you have all rights to withdraw at any time during study without giving any reason for doing so and that refusal to participate will not involve any penalty in terms of medical care and subsequent participation in any research studies.

You or your representative will be informed in a timely manner if information becomes available about significant new findings that develop during the course of the research which may be relevant to the subject's willingness to continue participation in the study.

You or your nominee(s) have right to claim compensation in case of study related injury or death, and to contact the sponsor representative (M/s Macleods Pharmaceuticals Ltd., Mumbai) directly for any claim related queries.





- If you have any claim related queries (in case of study related injury or death) you or your nominee(s) are free to call the Sponsor representative on the following address:

Ms. Shalmali Ambekar (Medical Services)

Macleods Pharmaceuticals Ltd.,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India.
Tel.: 91-22-61132900
Ext. No.: 133
Fax: 91-22-28304641

[17] When I should visit the facility?

Period-I	Date	Period-II	Date
Check-in		Check-in	

[18] How Ethics Committee helps?

The Ethics Committee is a group of people such as physicians, social workers, lay person and others and members of the community who are available to receive, initiate and investigate complaints of unethical conduct. They also protect your dignity, rights, safety and well being. They ensure universal ethical values in terms of local community values & customs and they also ensure that international scientific standards are followed by researchers.





[19] My Personal information:

Details of Volunteer:

Volunteer's Name:			
	First Name	Middle Name	Surname
Volunteer's Address:			
Qualification:			
Occupation:			
Student / Self-Employed / Service / Housewife / Others			
(Please tick as appropriate)			
Annual Income:			
Contact Number: Resi.: Mob.: PP:			
Emergency Contact		Email I.D. :	
Number : (Resi./Mob.)			
Date of Birth: DD / MM / YY		Age of the volunteer (completed years):	

Details of Nominee:

Name of Nominee:			
	First Name	Middle Name	Surname
Relation:			
Address of Nominee:			
(Mention, if not same as above)			
Contact Number: Resi.: Mob.: PP:			



SUBJECT'S CONSENT AND DECLARATION FOR PARTICIPATION IN THE STUDY

Languages Known	Read	Write	Speak	Understand
Hindi				
English				
Marathi				
Any other language (please specify): _____				

SR. No.	DECLARATION BY THE SUBJECT	PLEASE SIGN IN BOX (SUBJECT)
1.	I confirm that I have read and understood the information sheet (Informed Consent Form) dated 19 th March 2018 for the above study and have had the opportunity to ask questions.	
2.	I confirm that I don't have personal history of allergy or hypersensitivity to any of the excipients listed in exclusion criteria.	
3.	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4.	I understand that the Sponsor of the clinical study, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities like (DCGI) Drug Controller General of India and EMA (European Medicines Agency) will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	
5.	I agree not to restrict the use of any data or results that arise from this study provided such a use is only scientific purpose (s).	
6.	I agree to take part in the above study.	



**Signature (or thumb impression) of the Volunteer/ Legally Acceptable Representative (LAR):**

Note: Left hand thumb impression in case of female volunteer and right hand thumb impression in case of male volunteer

Date: ____/____/____
DD MM YYYY

****Signature of impartial witness is required if volunteer/ LAR is illiterate. Impartial witness will read the Informed Consent Form in a language known to the volunteer/LAR.**

Name of impartial witness:			
	First Name	Middle Name	Surname
Address of impartial witness:			
Contact Number: Resi.: _____ Mob.: _____ PP: _____			
Signature: _____		Date: ____/____/____ DD MM YYYY	

Signature and name of the Principal Investigator/ Co-investigator taking written informed consent form:

Name: _____
Signature: _____ Date: ____/____/____ DD MM YYYY

Signature and name of the Principal Investigator

(If written informed consent form taken by Co-investigator)

Name of the Principal Investigator: _____
Signature: _____ Date: ____/____/____ DD MM YYYY

Note: Copy of the signed and dated written informed consent form to be handed over to the volunteer.



सूचित सहमती पत्र

अध्ययन शीर्षक:

सेहतमंद, वयस्क, मानवी स्वेच्छार्थियों को उपवास की स्थिति में तीन गोलियों की एक ही मात्रा की लीवोथायरोक्सीन सोडियम २०० एमसीजी की गोलियों (मॅक्लीओड्स फार्मास्युटीकल्स लिमिटेड, इंडिया) का, यूथ्रोक्स® (लीवोथायरोक्सीन सोडियम) २०० एमसीजी की गोलियों (मर्क बी.वी., स्विफोल-रिज्क, नेदरलैंड्स) के साथ शरीर के अंदर की तीन गोलियों के एक ही मात्रा का जैव समानता अध्ययन।

अध्ययन रचना:

३० सेहतमंद, वयस्क, मानवी स्वेच्छार्थियों पर उपवास की स्थिति में किया जाने वाला खुला शीर्षक, संतुलित, विश्लेषक के लिए अनजान, अनियत बेतारिब ढंग से, दो उपचारोंका, दो कालावधियोंका, दो क्रमों का, एक ही मात्रा का, अदल बदल जैव समानता अध्ययन।

सूचित सहमती पत्र संस्करण क्र: ०१

स्थिति: सुनिश्चित

तारीख: १९ मार्च २०१८

पिछला क्र: अनावश्यक

तारीख: अनावश्यक

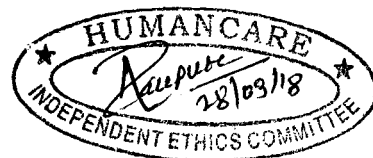
स्वेच्छार्थी पंजीकरण क्र.	स्वेच्छार्थी प्रथमाक्षर	लिंग: पुरुष / स्त्री	पात्र क्र.
बीईक्यू-			

सूचना: इस अध्ययन में भाग लेने के लिए सहमत होने से पहले इस दस्तावेज़ में दी गई जानकारी को ध्यान से पढ़ना और समझना महत्वपूर्ण है। आपको इस फॉर्म पर तारीख के साथ हस्ताक्षर करना होगा। आपको अपने संदर्भ के लिए इस पत्र की एक प्रति प्रदान की जाएगी। इस दस्तावेज़ की मौखिक प्रस्तुति के दौरान और अध्ययन के दौरान किसी भी समय किसी भी स्पष्टीकरण और प्रश्न पर चर्चा की जा सकती है।

इस दस्तावेज़ का उद्देश्य अध्ययन की प्रक्रियाओं को स्पष्ट रूप से बताता है और यह सुनिश्चित करने के लिए कि आप इसके बारे में उचित जानकारी जानने के बाद ही अध्ययन में प्रवेश करें। यह सूचित सहमती पत्र अध्ययन के उद्देश्य, संभावित लाभ, खतरे या तकलीफें, वैचारिक उपचार और गोपनीयता का वर्णन करता है। यह अध्ययन में आपके स्वेच्छिक सहभाग की घोषणा को भी सम्मिलित करता है।

यह सूचित सहमती पत्र कोई करार नहीं है और अध्ययन से आप किसी भी समय बिना कोई कारण दिए स्वेच्छा से हट सकते हैं।

प्रमुख अन्वेषक: डॉ. राजेंद्र सौंडे



१. बायोअॅव्हेलेबिलिटी / बायोइक्वीवॅलेंस का अर्थ क्या है ?

❖ बायोअॅव्हेलेबिलिटी

दवा लेने के बाद मानव की सुरक्षीतता और क्षमता का अंदाज लेने के लिए, शरीर में दवा का अवशोषण किस गति से होता है और किस हद तक होता है यह निश्चित करने के लिए बायोअॅव्हेलेबिलिटी अध्ययन की रचना की जाती है।

❖ बायोइक्वीवॅलेंस

जब दवा के दो सूत्र, दवा लेने के बाद किस गति से और किस हद तक शरीर की इन्द्रिय व्यवस्था के अभिसरण में घुल जाते हैं, और संख्याशास्त्र के अनुसार तूलना करने के लिए योग्य होते हैं तब एक ही दवा के दो सूत्रों को बायोइक्वीवॅलेंट कहा जाता है।

दो सूत्र (अन्वेषणात्मक उत्पाद) निम्नलिखित प्रकार से संबंधित किए गए हैं,

‘अध्ययन सूत्र’ – जिसका बायोइक्वीवॅलेंस के लिए सन्दर्भ सूत्र के साथ अध्ययन किया जाता है।

‘सन्दर्भ सूत्र’ – जो दवा पहले से ही बाजार में उपलब्ध है और उसका नाम है यूथोक्स® (लीवोथायरॉक्झीन सोडियम) २०० एमसीजी की गोलियां।

२. अध्ययन दवा की सामान्य जानकारी:

अध्ययन और संदर्भ सूत्रीकरण में लिवोथायरॉक्झीन सोडियम इसका समावेश हैं जो इसके लिए संकेतिक हैं: लीवोथायरॉक्झीन सोडियम २५-२०० माइक्रोग्राम :

- जब आयोडीन दर्शाये नहीं होते हैं तब, विशेषतः वयस्कों में थायरॉइड गॉइटर (थायरॉइड ग्रंथी का विस्तार) इसका उपचार
- पुनर्विभाजन के बाद प्रॉफिलैक्सिस की पुनरावृत्ति (अंग का हिस्सा निकालने के बाद) क्रियाशील पश्चात संप्रेरक स्थितीपर निर्भर हैं।
- हायपोथायरॉइडीज़म में प्रतिस्थापन (एक सिंड्रोम जो थायरॉइड ग्रंथी से थायरॉइड संप्रेरक के असाधारण कम स्राव के वजह से होता है)
- थायरॉइड कार्सिनोमा (कैंसर) के लिए अवरोधक उपचार

लीवोथायरॉक्झीन सोडियम २५-१०० माइक्रोग्राम :

- प्रतिस्थापन दौरान हायपरथायरॉइडीज़म में (थायरॉइड ग्रंथी से थायरॉइड संप्रेरक का अतिस्रावण होना) थायरोस्टैटिक्स (थायरॉइड संप्रेरक के निर्मिती को अवरोधक दवाई) इसके साथ सहवर्ती उपचार।

लीवोथायरॉक्झीन सोडियम १००/१५०/२०० माइक्रोग्राम :

- थायरॉइड अवरोधक जाँच में निदान इस्तेमाल

३. यह अध्ययन क्यों किया जा रहा है ?

इस अध्ययन में अनुसन्धान सम्मिलित है।

इस अध्ययन के उद्देश्य हैं:

१. उपवास की स्थिति में मुहद्वारा तीन गोलीयों की एक ही मात्रा की लीवोथायरॉक्झीन सोडियम २०० एमसीजी की गोलियां देने के बाद खून में लीवोथायरॉक्झीन की उपलब्धता का मूल्यमापन करना।



२. सेहतमंद, वयस्क, मानवी स्वेच्छार्थियों को उपवास स्थिति में मुहद्वारा तीन गोलियों की एक ही मात्रा की लीवोथायरॉक्झीन सोडियम २०० एमसीजी की गोलिया देने के बाद सुरक्षितता और सहनशीलता का मूल्यमापन करना।

४. इस अध्ययन में कितने लोग हिस्सा लेंगे ?

३० सेहतमंद, वयस्क, मानवी स्वेच्छार्थी इस अध्ययन में हिस्सा लेंगे ।

५. इस अध्ययन में क्या शामिल है ?

इस अध्ययन में आपका प्रवेश एक प्राथमिक जाँचकीय परीक्षण और कुछ निष्कासन मापदंडों पर आधारित है । निम्नलिखित जरूरतों को पूरा करने पर ही आप शामिल होने योग्य होंगे :

- वैद्यकीय जांच
- प्रयोग शालेय जाँच
- निष्कासन मापदंड

❖ परीक्षण :

आपके स्वास्थ्य की स्थिति का आकलन करने के लिए निम्नलिखित परीक्षण जांच किए गए हैं:

१. संपूर्ण जानकारी जिसमें लिंग, संपूर्ण आयु, लम्बाई और वजन, बीएमआई, आहार, तम्बाकू के उपयोग का इतिहास, निषिद्ध किए गए पदार्थ / नशीले पदार्थ सेवन किया हो, मद्यपान का सेवन किया हो, रक्तदान का इतिहास और अध्ययन में दवा के अनुसंधान सहभाग का इतिहास, ये जानकारी शामिल होगी ।
२. वैद्यकीय इतिहास और उससे संबंधित पिछला वैद्यकीय / शस्त्रक्रिया का इतिहास, पारिवारिक इतिहास, एलर्जी का इतिहास (खाद्यपदार्थ / दवा / अन्य), पिछला ९० दिनों का दवाईयों का इतिहास ।
३. वर्तमान स्वास्थ्य विषयक शिकायते (अगर हैं), वैद्यकीय परीक्षण जिसमें महत्वपूर्ण संकेतों को मापना (रक्तचाप, नाडी, तापमान और श्वसन क्रिया), सामान्य परीक्षण, शारीरिक और शरीर क्रिया का परीक्षण ।
४. प्रसव संबंधी और महिला रोग चिकित्सा का इतिहास (सिर्फ महिलाओं के लिए) ।
५. हृदय की गति, लय और विशिष्ट तथ्य (अगर हैं) के लिए १२-लीड ई. सी. जी. ।
६. खून और मूत्र विश्लेषण ।
७. छाती का एक्स-रे (पीए व्ह्यू)।
८. गर्भधारण की जाँच के लिए मूत्र का परीक्षण (सिर्फ महिलाओं के लिए) ।
९. सिरोलॉजी जाँच (एचाआयव्ही (मानवी इम्युनोडेफिशियन्सी विषाणू), एचबीसएजी [हिपैटेटिस बी (यकृत कि सृजन) सर्फेस एंटीजन], एचसीव्ही (हिपैटेटिस सी विषाणू जिनका मुख्य रूप से यकृत पर परिणाम होता है)) ।

नोट : जैसे की आप सब परीक्षण मापदंड पास किए हो तो, स्वयंसहभागीयों को निछले प्रयोगशालीय जाँच के अंतर्गत गुजरना होगा: सीरम टि_१ (कुल), सीरम टि_३ (कुल), सीरम थायरॉईड- उत्तेजक संप्रेरक (टिएएसएच)

❖ निष्कासन के मापदंड

इस अध्ययन में सहभागी होने के लिए आप अयोग्य हो जाएंगे यदि :

१. लीवोथायरॉक्झीन या संबंधित दवाओं की अलर्जी या एक्सिपीएंट्स (दवाई में होने वाले निष्क्रिय पदार्थ) [मैग्नेशियम स्टेरेट (ई ५७२), मेज स्टार्च, क्रोसकारमेल्लोस सोडियम (ई ४६८), जेलेटिन (ई ४४१), लैक्टोज मोनोहाइड्रेट] या अतिसंवेदनशीलता का निजी इतिहास है ।



२. पिछले ९० दिनों में कोई बड़ी बीमारी या चिकित्सकीय महत्वपूर्ण चल रही कोई पुरानी चिकित्सकीय बीमारी (लंबे समय तक चलनेवाली चिकित्सकीय स्थिती) उदा. हृदय की कार्यक्षमता में बाधा आना (हार्ट फेल्युअर), पीलिया (यकृत में सुजन), कम रक्तचाप के प्रसंग (रक्तचाप बहुत कम होना), हायपरग्लायसेमिया (खून में शक्कर की मात्रा बहुत ज्यादा होना) इत्यादि ।
३. परिक्षण के दौरान कोई भी चिकित्सकीय महत्वपूर्ण असामान्य प्रयोगशालाय मूल्यों का पाया जाना। उदा. महत्वपूर्ण असामान्य यकृत की कार्यक्षमता का परिक्षण, गुर्दों की कार्यक्षमता का परिक्षण इत्यादि ।
४. गंभीर रूप से हृदय ,गुर्दों और यकृत की दुर्बलता ,जठर-आंतों की बिमारी या अन्य तकलीफ ,अन्य किसी इन्द्रिय या व्यवस्था की दुर्बलता (विकलांगता) ।
५. आकडी (मस्तिष्क में अनियंत्रित विद्युत् गतिबंध जिससे शरीर में अनियंत्रित कंपना, छोटे मोटे शारीरिक लक्षण, वैचारिक गड़बड़ी या संयुक्त लक्षण), मिर्गी (मस्तिष्क की विकृति जिससे बेहोश होना और अनियंत्रित शारीरिक कंपन आना) या किसी भी प्रकार के मस्तिष्क संबंधी विकार (तंत्रिका तंत्र का विकार) का इतिहास हो ।
६. ऐंफिलेक्सीस (तीव्र ऐंलर्जिक प्रतिक्रिया) या ऐंजीओईडीमा (त्वचा पर जल्दी से सुजन आना) का पुराना इतिहास।
७. एच.आय.व्ही.या बी प्रकार के पीलिया या सी प्रकार के पीलिया के विषाणु के निशान की बिमारी की उपस्थिती पाए जाना ।
८. दो वर्षों से अधिक समय से बहुत अधिक मात्रा में किसी भी प्रकार का मद्यपान करने का इतिहास हो या दवा की मात्रा लेने से पहले ४८ घंटों में मद्यपान किया हो ।
९. दवा की मात्रा लेने से पहले ४८ घंटों में झान्थाईनयुक्त पदार्थ (चोकलेट, चाय, कोफी, या कोला पेय) या तंबाकू पदार्थ का सेवन किया गया हो ।
१०. पपनस या पपनसयुक्त पदार्थ या किसी भी कृसिफेरस सब्जी (उदा ब्रोकोली, ब्रुसेल्स स्प्राऊटस (अंकुरित कोबी) इ.) या कोयले में सिका हुआ मांस इनका अन्वेषणात्मक उत्पाद की मात्रा लेने के ७ दिन पहले सेवन किया गया हो ।
११. किसी भी मनोरंजक दवा का उपयोग (रासायनिक पदार्थ जो मस्तिष्क के कार्य को प्रभावित करता है जो व्यवहार, मन और चेतना में परिवर्तन करता है, मनोरंजन प्रयोजनों के लिए दवाओं) या मादक पदार्थों की लत का इतिहास ।
१२. पिछले ९० दिनों में किसी भी चिकित्सीय अध्ययन में भाग लिया हो ।
१३. रक्तदान में तकलीफ या फिर रक्तदान करने के लिए दाए या बाए हाथ की योग्य नस पाई जाने में कठिनाई होने का इतिहास ।
१४. रक्तदान (१ यूनिट या ३५० मी.ली.) अध्ययन के लिए दवा की पहली मात्रा लेने के पहले ९० दिनों में किया हो ।
१५. किसी भी दवा का नुस्खा लिया हो (वैद्यकीय अधिकारी के सलाह से) या काउंटर पर (ओटीसी) दवाई (जिसमे जीवनसत्त्व की दवा या प्राकृतिक दवा का उत्पाद है), दवा की पहली मात्रा लेने के पहले २ हफ्तों में आसानी से पाए जाने वाली दवा का सेवन किया गया हो या किसी भी दवा का पिछले ४ हफ्तों में बार बार सेवन या स्वयंसहभागियों की इस भागीदारी के दौरान किया गया है ।
१६. किसी भी कारणवश असामान्य आहार लिया हो, उदा. कोई भी दवा लेने से २ हफ्ते पहले और पूर्ण अध्ययन काल में कम सोडियम (नमक) वाला भोजन लेना ।
१७. अध्ययन से पहले ४८ घंटों के भीतर जुलाब, उलटी या किसी भी कारण निर्जलीकरण होने का ताजा इतिहास ।
१८. मुह से लेने वाले गर्भनिरोधक गोलियों का सेवन पिछले ९० दिनों में किया हो (महिलाओं के लिए) ।

१९. गर्भवती / स्तनपान कराने वाली स्वयंसेविका (महिलाओं के लिए) ।
२०. असामान्य सीरम टि_४ (कुल), सीरम टि_३ (कुल), सीरम थायरॉइड-उत्तेजक संप्रेरक (टिएसएच) परीक्षण मूल्य।

❖ कृति योजना:

१. इस अध्ययन में आपको बायोइक्वीवैलेंस केन्द्र की नैदानिक सुविधा में २ कालावधीओं के लिए रहना पड़ेगा, याने की कालावधी १ और कालावधी २ ।
२. हर एक कालावधि में आपको किसी भी एक प्रकार का उपचार दिया जाएगा, याने की उपचार 'T' तीन गोलियों की एक ही मात्रा की लीवोथायरॉक्सीन सोडियम २०० एमसीजी की गोलिया (मॅक्लीओड्स फार्मास्यूटीकल्स लिमिटेड, इंडिया) या उपचार 'R' तीन गोलियों के एक ही मात्रा का यूथ्रोक्स® (लीवोथायरॉक्सीन सोडियम) २०० एमसीजी की गोलिया (मर्के बी.वी., स्विफोल-रिज्क, नेदरलैंड्स) । किस क्रम से अध्ययन की दवा दी जाएगी वह अनियत रूप से निश्चित किया जाएगा, लेकिन अध्ययन के अंत तक आपको दोनों उपचार दिए जाएँगे।
३. क्रम से आनेवाले दो कालावधीयों में दवा की मात्रा लेने के बाद कम से कम ३५ दिन का मध्यांतर रहेगा । अगर किसी कारणवश कालावधी २ बाद में निश्चित हो तो अध्ययन काल और मुआवजे की रकम उस प्रकार बदल सकती है ।
४. हर कालावधी के दौरान दवा के मात्रा लेने से पहले आपको १० घंटे उपवास की स्थिति में रहने के लिए पर्याप्त समय पहले बायोइक्वीवैलेंस केंद्र में दाखिल होना पड़ेगा और अन्वेषणात्मक उत्पाद की मात्रा लेने के बाद ७२ घंटे तक रहना पड़ेगा ।
५. हर कालावधी में दाखिल होते समय नशीले दवाईयों का सेवन किया है के नही ये जांच के लिए मूत्र परिक्षण किया जाएगा ।
६. हर कालावधी में दाखिल होते समय सांस परिक्षण यंत्र द्वारा आपके सांस का परिक्षण किया जाएगा, जिससे पता चलेगा की अपने मद्यपान किया है या नहीं ।
७. कालावधी १ और कालावधी २ में दाखिल होने के समय मूत्र की गर्भधारणा जाँच की जाएगी (सिर्फ महिलाओं के लिए) ।
८. सर्किट कैमरा सिस्टम से आपकी हरकत पर निगरानी रखी जाएगी ।
९. हर अध्ययन कालावधी में दाखिल होते समय, जाते समय और निगरानी करने वाले उपस्थित वैद्यकीय अधिकारी के अनुसार आवश्यक उस समय वैद्यकीय परिक्षण किया जाएगा ।
१०. दाखिल होने के दिन, २२०० बजे रात का भोजन दिया जाएगा ।
११. रातभर कम से कम १० घंटे की उपवास की स्थिति में रहेना पड़ेगा ।
१२. हर अध्ययन कालावधी में, रातभर के कम से कम १० घंटे की उपवास के बाद आपको अध्ययन या सन्दर्भ उत्पाद मुह से २४० मी. ली. पानी के साथ निर्धारित समय पर दिया जाएगा ।
१३. सीधे बैठी हुई स्थिति में आपको अन्वेषणात्मक उत्पाद दी जाएगी । अन्वेषणात्मक उत्पाद की मात्रा लेने के बाद आपको पहले दो घंटे बैठने के या चलते फिरते रहने के (थकावट के काम के बिना) आदेश दिए जाएँगे (महत्वपूर्ण संकेतों के समय और खून संकलन समय के अंकों के अतिरिक्त) । इस समय के दौरान निगरानी में आपको स्वच्छता कक्ष का उपयोग करने के लिए अनुमति दी जाएगी । उसके बाद बिना शारीरिक थकान के सामान्य गतिविधियों में शामिल होने की इजाजत दी जाएगी ।
१४. दवा की मात्रा लेने से १ घंटे पहले और १ घंटे बाद तक पानी पीना मना रहेगा ।
१५. दवा की मात्रा लेने से कम से कम ४ घंटे बाद तक कुछ भी खाना मना रहेगा, हर अध्ययन कालावधि में, अन्वेषणात्मक उत्पाद की मात्रा देने के ४.०० घंटे बाद प्रमाणित भोजन और विशिष्ट मध्यांतर ८.०० घंटे

बाद नाश्ता और १३.०० घंटे बाद रात का भोजन दवा की मात्रा देने के बाद के दिन १ में, दवा की मात्रा देने के दिन २ में लगभग २४.५०, २८.००, ३२.०० और ३६.०० घंटे बाद (नाश्ता, दोपहर का भोजन, शाम का नाश्ता और रात का भोजन) और दवा की मात्रा देने के दिन ३ में लगभग ४८.५०, ५२.००, ५६.०० और ६१.०० घंटे बाद (नाश्ता, दोपहर का भोजन, शाम का नाश्ता और रात का भोजन) भोजन, भोजन योजना अनुसार दिया जाएगा। इस मामले में खाने का समय, यह खून का नमूना संग्रह करने का समय, महत्वपूर्ण संकेत और स्वेच्छार्थी प्रभावली के साथ मेल खाता है तो घटनाओं का क्रम खून का नमूना संग्रह करना, महत्वपूर्ण संकेत और स्वेच्छार्थी प्रभावली और भोजन इस प्रकार रहेगा।

१६. हर कालावधि में खून के नमूने (१ x ६ मी. ली.) के खून लेने की नली में लिए जाएंगे। नस में से खून के नमूने दवा की मात्रा देने के बाद में -०.५०, -०.२५, -०.०३, ०.५०, १.००, १.५०, २.००, २.५०, ३.००, ३.५०, ४.००, ४.५०, ५.००, ५.५०, ६.००, ८.००, १०.००, १२.००, १८.००, २४.००, ३०.००, ३६.००, ४८.०० और ७२.०० घंटों के समय पर लिए जाएंगे (अन्वेषणात्मक उत्पाद की मात्रा लेने के समय से ये समय सापेक्ष हैं)। यह घटक प्रकाश के प्रति संवेदनशील होने के कारण प्रकाश में जलद गती से इसका नाश होता है, इसके कारण खून का नमूना और दवाई की खुराक लेने और संबंधित सभी क्रियाएँ पिले मोनोक्रोमैटिक रोशनी में किए जाएगी।
१७. खून के नमूने आपके हाथ के नस में लगाई गई कैंन्यूला से लिए जाएंगे।
१८. हर एक व्यक्ति से कुल मिलकर ४८ बार (२४ प्रति कालावधि) खून निकला जाएगा। कुल मिलाकर निकले गए खून की मात्रा ३२५ मी.ली. से ज्यादा नहीं होगी (जिसमें सुरक्षितता मुल्यमापन के लिए निकला गया १३ मी.ली. और २४ मी.ली. नॉर्मल सलाइन खून जो फेक दिया जाएगा का समावेश है)।
१९. कुछ कारणवश, जहां अधिक रक्त को वापस लेने की जरूरत है, जैसे खून लेने के बाद नली का टूटना, विपरीत परिणाम (जिनमें असामान्य प्रयोगशाला तत्वों का समावेश है) हो तो आपकी सहमती लेने के बाद आपका अतिरिक्त खून लिया जाएगा और उसके साथ योग्य मुआवजा दिया जाएगा।
२०. केंद्र में रहने के कालावधि में खून के नमूने लेते समय, नस में लगे गया कैंन्यूला, ०.५ मी. ली. नॉर्मल सलाइन से इंजेक्ट करने के बाद आवश्यक उतने समय रखा जाएगा।
२१. कैंन्यूला से नार्मल सलाइन खून ०.५ मी. ली. खून फेक देने के बाद खून का नमूना लिया जाएगा।
२२. किसी कारणवश कैंन्यूला अवरुद्ध हो या कैंन्यूला निकला गया हो तो हाथ के नस में से एकही बार इस्तमाल किए जाने वाली सिरिंज और सुई से खून निकला जाएगा।
२३. हर कालावधि के ७२ घंटे बाद में अगर आपका स्वास्थ्य अच्छा है और विपरीत परिणाम नहीं हुए हो तो आपको घर जाने की इजाजत मिलेगी। अगर विपरीत परिणाम दिखाई दी तो औषधोपचार करके आप स्वस्थ होने तक आपको निगरानी में रखा जाएगा।
२४. सभी दवाईयों और / या अध्ययन संबंधी विपरीत परिणाम दिखाई दी तो बायोइक्वीवेलंस केंद्र के उपस्थित वैद्यकीय अधिकारी से या पास के योग्य रुग्णालय में मुफ्त उपचार करेंगे और जिसका खर्चा मॅक्लीओड्स फार्मास्युटीकल्स लि. के बायोइक्वीवेलंस विभाग से किया जाएगा।
२५. आपको योग्य बिमा की सुविधा भी उपलब्ध है।
२६. हर कालावधि में, स्वेच्छार्थी प्रभावली और महत्वपूर्ण संकेत (रक्तचाप, तापमान और नाडी की गति) दाखिल होने के समय, दवा की मात्रा लेने के पहले और दवा के मात्रा लेने के बाद १.००, ३.००, ६.००, ९.००, २३.००, २९.००, ३५.००, ४८.०० और ७२.०० घंटों के समय पर किए जाएंगे (अन्वेषणात्मक उत्पाद की मात्रा लेने के समय से ये समय सापेक्ष हैं)।
२७. कालावधि २ में, आखिरी खून का नमूना लेने के बाद, अध्ययन के बाद के सुरक्षा आकलन के लिए वैद्यकीय परीक्षा, ईसीजी और नैदानिक प्रयोगशाला परीक्षण किया जाएगा।

६. इस अध्ययन के लिए मुझे यहां कितने दिन रहना पड़ेगा ?

अध्ययन की कालावधि करीबन ४० दिन है जिसमें ३५ दिन का मध्यांतर है। अगर कालावधि २ बाद में निर्धारित किये गये तो अध्ययन की कालावधि उसके अनुसार बदलेगी और बायोइक्वीवैलेंस केंद्र में आपको हर कालावधि में करीबन ८२ से ८७ घंटे रहना पड़ेगा।

७. इस अध्ययन में संभाव्य जोखिम, दुष्प्रभाव और बैचनी क्या हो सकती है ?

संभावित दुष्प्रभाव

अन्य सभी दवाइयों की तरह लिक्वोथायरॉक्झीन के वजह से भी दुष्प्रभाव हो सकते हैं, लेकिन यह सभी में नहीं दिखाई देते हैं। निम्नलिखित दुष्प्रभाव इस दवाई के वजह से हो सकते हैं।

दुष्प्रभाव

निम्न दुष्प्रभावों के लिए बारंबारता की श्रेणी ज्ञात नहीं है (उपलब्ध जानकारी के साथ निर्धारित नहीं हो सकता है)

प्रतिरक्षा प्रणाली विकार	अतिसंवेदनशीलता (एलर्जि) अंजिओएडिमा (यह त्वचा का निचला स्तर और त्वचा के नीचे होनेवाले ऊतकों की या श्लेष्म त्वचा के क्षेत्र की सूजन)

यदि जर सोडियम लिक्वोथायरॉक्झीन के वैयक्तिक सहनशीलता की मर्यादा या दवाई की खुराक प्रमाण के बाहर गया तो निम्न चिकित्सकिय लक्षण होते हैं, हायपरथायरॉइडीझम के वैशिष्ट्य (थायरॉइड ग्रंथी से थायरॉइड संप्रेरक का अतिस्रावण होना), उत्पन्न हो सकता है, मुख्य रूप से अगर शुरुवाती के उपचार पर दवाई की खुराक ज्यादा जल्दी बढ़ गई तो। इस मामले में हररोज की खुराक कम करना चाहिए या दिन में बहुत बार दवाई लेना रोकना चाहिए। यह प्रभाव गये तो यह उपचार ध्यान से वापस शुरू किया जा सकता है।

अंतःस्रावी विकार	हायपरथायरॉइडीझम (थायरॉइड ग्रंथी से थायरॉइड संप्रेरक का अतिस्रावण होना) अनियमित मासिक धर्म
चेतासंस्था प्रणाली विकार	सिरदर्द सौम्य अंतःस्राहोग्य (एक ऐसी स्थिती जो भी उत्पन्न होती है जब खोपड़ी के अंदर का दबाव किसी भी कारण के बिना बढ़ता है) उच्च रक्तचाप (रक्तचाप में वृद्धि) कंपन (अनैच्छिक शरीर की या निचले अंग कप कपाना) बेचैनी अनिद्रा (नींद आना)
हृदयसंबंधित विकार	अरेथमीया (अनियमित या असामान्य लय के साथ दिल कि अनियमित धडकन) एट्रीयल फिब्रीलेशन (अनियमित हृदय का लय) एक्सासिस्टोल्स (हृदय का समय से पहले हि होनेवाला संकुचन)

	टैकीकार्डिआ (तीव्र दिल की धड़कन) पल्पीटेशन अन्जायना पेक्टोरिस (एक हृदय का विकार जिसमें सीने में तीव्र दर्द उत्पन्न होता है)
जठरांत्रिय विकार	उल्टी दस्त (लगातार बढना या आंतों की हलचल की कम सुसंगतता)
त्वचा और त्वचा के निचले ऊर्ती के विकार	हाइपरहाइड्रोसिस (असामान्य रूप से पसीना / स्वेद बढना)
मांसपेशी और संयोजी ऊतक के विकार	मांसपेशी में कमजोरी मांसपेशियों की ऐंठन
सामान्य विकार और दवाई देने के जगह कि स्थिति:	अत्यधिक फ्लेशिंग (आमतौर पर चेहरे की त्वचा लालिमा) पायरेक्झिया (शरीर का तापमान बढना)
जाँच के लिए	वजन कम होना

संदर्भ:

यूथोक्स[®] (लीवोथायरॉक्झीन सोडियम) २०० एमसीजी की गोलियों के उत्पाद के लक्षणों का सारांश,
१५/१०/२०१७ को अंतिम अपडेट, १८/०३/२०१८ को उद्धृत,
<https://db.cbg-meb.nl/IB-teksten/h09009.pdf> से उपलब्ध

कैन्सूलेशन और रक्त संग्रह की वजह से संभावित जोखिम

निबाह प्रवेशानी माध्यम से कैन्सूलेशन और रक्त संग्रह की प्रक्रिया के दौरान आप कैन्सूलेशन की जगह पर दर्द, सुजन, संक्रमण, रक्तस्राव (रक्तस्राव), हिमेटोमा (एक स्थानीय सुजन जो रक्तवाहिका की दीवार में तोड़ के कारन रक्त से भरी हुई होती है), वासो – वेगल एपिसोड (मस्तिष्क प्राणवायु से वंचित होता है और बेहोशी आती है), सुई भय (सुई का डर), कैथेटर एम्बोलीज़म (गोलाकार कीड़े के आकर का प्लेटलेट और फाइब्रिन का समुच्चय), ट्रांसफीक्सेशन (नस दीवार के माध्यम से भेदना), तंत्रिका तंत्र को हानी, धमनी पंचर (धमनियों का टूटना), एलर्जी निडलास्टिक चोट (सुई से या तीक्ष्ण चाकू के घाव से रक्त या शरीर के अन्य तरल पदार्थ के लिए जोखिम हो सकता है), थ्रोम्बोफ्लेबीटीस (किसी रक्तवाहिका की दीवार की सुजन के साथ थ्रोम्बोसिस) से पिडीत हो सकते हैं।

सुचना:

- यह दुष्प्रभावो की पूरी सूची नहीं है, यह एक नैदानिक अध्ययन है जिसमें अन्वेषणात्मक उत्पाद का उपयोग किया है, तो कुछ अनदेखी खतरा या असुविधा हो सकती है जिसका ज्ञान नहीं है।
- उपचारों से आपको खतरा होने की संभावना है, (भ्रूण या गर्भ को, अगर आप [महिला स्वयंसेवकी] गर्भवती हो तो) जो फिलहाल अनदेखी है।

८. इस अध्ययन में सहभागी होने के क्या फायदे हैं ?

इस अध्ययन में सहभागी होने के कारण आपको सीधा वैद्यकीय लाभ नहीं मिलेगा क्योंकि आप पहले से ही स्वस्थ हैं लेकिन अध्ययन में सहभागी होने से आपका मुफ्त वैद्यकीय परिक्षण किया जाएगा।



९. अध्ययन बंद करना ?

सुरक्षितता के कारणों के लिए या स्वेच्छार्थी का हित ध्यान में रखते हुए किसी भी समय अध्ययन बंद करने का हक प्रमुख निरीक्षक को होता है। अगर महत्वपूर्ण अनैतिकता दिखाई दी तो नीति समिति भी अध्ययन बंद कर सकती है। आपको अध्ययन बंद होने के कारणों की संक्षिप्त जानकारी दी जाएगी और योग्य मुआवजा दिया जाएगा।

१०. और विकल्प क्या हो सकते हैं ?

यह अध्ययन अनुसंधान के उद्देश्य में नियामक संस्था को नतीजे से प्राप्त करने के लिए है और इस अध्ययन में सहभागी न होना यही एक और विकल्प हो सकता है।

११. इसमें आर्थिक क्षतिपूर्ति कितनी है ?

अध्ययन काल में आपको होने वाली असुविधा के लिए आपको भुगतान दिया जाएगा। अध्ययन संबंधी सभी प्रक्रियाओं में सहभागी होने के लिए आपको रु. १४४००/- का भुगतान दिया जाएगा। अगर अनपेक्षित परिस्थितियों में कालावधि २, बाद में निश्चित हो तो मुआवजा एक दिन के लिए रु. ७५/- दिया जाएगा। आपको योग्य बिमा सुविधा अंतिम अनुसरण तक दी जाएगी।

बाहर जाने के दौरान रु. ५००/- आप के लिए एक भाग मुआवजे के रूप में या प्रमुख अन्वेषक के फैसले के अनुसार दिया जाएगा।

अगर जरूरत होने पर आपके सहमती के बाद ज्यादा खून लिया जाएगा और आपको प्रत्येक मि.ली. खून के लिए निचे दिए गए तालिका के अनुसार मुआवजा दिया जाएगा।

क्र.	उद्देश्य	क्षतिपूर्ति (रु.)
१.	प्रत्येक मिली खून लेने के लिए मुआवजा, रु.२५/ मिली	३२५ X २५ = ८१२५
२.	हर कालावधि में दाखिल होते समय वाहन भत्ता रु.२००/ मुलाकात	२ X २०० = ४००
३.	हर एक दिन रुकने के लिए मुआवजा (८ घंटे और उससे ज्यादा रुकने के लिए), रु.४००/ दिन	६ X ४०० = २४००
४.	हर एक रात रुकने के लिए मुआवजा, रु.२००/ रात	८ X २०० = १६००
५.	१० दिन के मध्यांतर से अधिक, रु.७५/ दिन	२५ X ७५ = १८७५
	कुल	१४४००/-

नियत अवधि पूर्व अध्ययन से हटने / हटाए जाने पर आप निम्नलिखित आनुपातिक सहभाग देय के अधिकारी होंगे।

क्र.	अध्ययन से हटने का कारण	क्षतिपूर्ति
१.	वैद्यकीय निर्णय के आधार पर या किसी भी प्रतिकूल घटना के कारण प्रमुख अन्वेषक / वैद्यकीय अधिकारी द्वारा स्वेच्छार्थी को अध्ययन से हटाया जाता है।	जिस कालावधि में स्वेच्छार्थी को निकाला है उस सम्पूर्ण कालावधि तक का आनुपातिक सहभाग देय
२.	अध्ययन शुरू होने के बाद आप स्वेच्छा से हट जाता है।	आनुपातिक सहभाग देय

३.	अगर आप मानवतावादी कारणों के लिए आपको प्रमुख निरीक्षक / वैद्यकीय अधिकारी की अनियमित से हटाया जाता है।	आनुपातिक सहभाग देय
४.	अगर आप द्वारा अध्ययन की आवश्यकताओं का उल्लंघन करने के कारण सहमती पत्र पर हस्ताक्षर करने के बाद किन्तु कोई उपचार लेने से पूर्व आपको प्रमुख निरीक्षक / वैद्यकीय अधिकारिद्वारा हटाया जाता है।	आनुपातिक सहभाग देय
५.	अगर आपके द्वारा वर्तमान और पिछली बीमारी / इतिहास के बारे में जानबूझकर गलत जानकारी देने पर प्रमुख निरीक्षक / वैद्यकीय अधिकारी आपको अध्ययन से हटा देते हैं।	आनुपातिक सहभाग देय
६.	किसी भी गंभीर प्रतिकूल घटना की वजह से स्वेच्छार्थी अध्ययन से हटा देते हैं।	पूरा

नैदानिक अध्ययन के दौरान जख्म या मृत्यु होने के मामले में भुगतान :

अ) आपको होने वाली जख्म के मामले में, आपको जब तक अपेक्षित होगा मुफ्त चिकित्सा प्रबंधन दी जाएगी।

आ) नैदानिक अध्ययन से संबंधी आपको होने वाली जख्म के मामले में, आपको लाइसेंसिंग प्राधिकरण के आदेश और वित्तीय मुआवजे पर और तुम्हारी नैदानिक प्रबंधन पर किए गए खर्च के ऊपर हो जाएगा के अनुसार वित्तीय मुआवजे के लिए पात्र होंगे।

इ) नैदानिक अध्ययन से संबंधित मृत्यु के मामले में, आपकी (नामनिर्देशितियों) के लाइसेंसिंग प्राधिकरण के आदेश के अनुसार वित्तीय मुआवजे पर और तुम्हारी चिकित्सा प्रबंधन पर किए गए किसी भी खर्च के अतिरिक्त होगा।

ई) नैदानिक अध्ययन से संबंधित जख्म या मृत्यु के लिए वित्तीय मुआवजा के रूप में हो सकता है:

- नैदानिक प्रबंधन के लिए भुगतान
- अध्ययन से संबंधित जख्म के लिए वित्तीय मुआवजा
- मृत्यु के मामले में अध्ययन विषय नामनिर्देशित (नामनिर्देशितियों) के लिए वित्तीय मुआवजा

उ) अगर निम्नलिखित कारणों में से किसी की भी जख्म या मृत्यु हुई तो प्रायोजक (एम / एस मॅक्लीओड्स फार्मास्युटीकल्स लिमिटेड, मुंबई) वित्तीय मुआवजा प्रदान करेगा :

- अन्वेषणात्मक उत्पाद के संभाव्य दुष्प्रभाव
- अध्ययन में शामिल कोई भी अध्ययन प्रक्रिया
- अनुमोदित प्रोटोकॉल का उल्लंघन, वैद्व्यानिक दुराचार या प्रायोजक या उनके प्रतिनिधि या अन्वेषक द्वारा लापरवाही
- इरादा उपचारात्मक प्रभाव प्रदान करने के लिए अन्वेषणात्मक उत्पाद की असफलता
- मानक की देखभाल को छोड़कर सहवर्ती दवा की वजह से प्रतिकूल प्रभाव को, अनुमोदित प्रोटोकॉल के हिस्से के रूप में आवश्यक हो

ऊ) प्रायोजक (एम / एस मॅक्लीओड्स फार्मास्युटीकल्स लिमिटेड, मुंबई) से संबंधित जख्म या मृत्यु नैदानिक अध्ययन के मामले में लाइसेंसिंग प्राधिकरण के द्वारा तय मुआवजा की मात्रा का भुगतान करना होगा लाइसेंसिंग प्राधिकरण देने से आदेश प्राप्त होने के तीस दिनों के भीतर होना चाहिए।



१२. मुझसे क्या अपेक्षा की गई है ?

१. बायोइक्वीवैलेंस सेंटर के कर्मचारियों के साथ सहयोग करने का और अध्ययन संबंधी सब प्रक्रियों से सलंगन रहने का निवेदन आपसे किया जाता है ।
२. हर कालावधीयों में दाखिल होते समय और जाते समय निषिद्ध किए गए वस्तुएं का पता लगाने के लिए आपकी और आपके सामान की तलाशी ली जाएगी ।
३. अगर दाखिल होते समय में आपने रिपोर्ट नहीं किया तो कॉल, एसएमएस या टपाल / कुरियर द्वारा जवाब अपेक्षित है ।
४. आपको अध्ययन केंद्र में शांतता रखनी होगी ।
५. आपातकालीन परिस्थिति में, आपको आपातकालीन घंटी दबानी पड़ेगी, जो आपके बिस्तर के और शौचालय के क्षेत्र में स्थित होगी ।
६. कर्मचारी या अन्य सहभागियों के साथ बुरे बर्ताव का निषेध किया जाएगा ।
७. मॅक्लीओड्स फार्मास्युटीकल्स, बायोइक्वीवैलेंस विभाग / अन्य अध्ययन में भाग लेने वालों की वस्तुओं का दुरुपयोग और / या खराबी का निषेध किया जाएगा ।
८. आपको आपका सामान रखने के लिए स्वतंत्र सामान कक्ष दिया जाएगा ।
९. मनोरंजन की वस्तुएं (कैरम बोर्ड, टी व्ही और ताश) इनको हानि न पहुंचाते हुए सावधानी से उपयोग करना चाहिए ।
१०. विभाग में निषिद्ध की गई वस्तुएं या अवैध की गई दवाओं का उपयोग और / या अपने पास रखना इसका कड़ा निषेध किया जाता है ।
११. आपको आपका वर्तमान पता प्रमाण प्रदान करना चाहिए ।
१२. आपको आपातकालीन संपर्क नंबर, ई-मेल आईडी प्रदान करना चाहिए (यदि उपलब्ध है) ।
१३. अध्ययन की जरूरतों के मुताबिक आपको खान पान का पालन करना पड़ेगा । बाहर का खाना अंदर लाना मना है ।
१४. दवा की मात्रा लेने के बाद आपको कम से कम २ घंटों तक आपको बैठी हुई स्थिति में रहना पड़ेगा ।
१५. आपको दवा की मात्रा लेने के पहले १ घंटा और बाद में १ घंटा पानी पीना मना रहेगा ।
१६. आपातकालीन घटना के सिवा प्रमुख अन्वेषक / वैद्यकीय अधिकारी के अनुमति के बिना अध्ययन में भाग लेने के दौरान आपको किसी भी दवा का नुस्खा / दुकान में आसानी से मिलने वाली (ओटीसी) दवाएं (जिसमें जीवनसत्त्व की दवा या प्राकृतिक दवा उत्पाद हैं) लेना मना रहेगा और उसकी आपकी प्रमुख अन्वेषक / वैद्यकीय अधिकारी को सूचना देनी पड़ेगी ।
१७. अगर आप सुरक्षा के लिए सुविधा में आने में असमर्थ हो तो आपको कॉल, एसएमएस, टपाल, कुरियर, द्वारा संपर्क किया जाएगा ।
१८. अगर आप प्रतिकूल घटना (अध्ययन के दौरान या असामान्य प्रयोगशालेय मापदंड के बाद की सुरक्षा के दौरान) की अनुवर्ती के लिए केंद्र की यात्रा नहीं कर सकते हैं तो आपको दूरध्वनीद्वारा या एसएमएस, टपाल, कुरियर, द्वारा संपर्क किया जाएगा अगर कोई जवाब न मिले तो और वैद्यकीय अधिकारी के अनुसार अध्ययन के बाद की सुरक्षा के दौरान प्रतिकूल घटना या असामान्य प्रयोगशालेय मापदंड पाया तो उसे गंभीर मान लिए जाते हुए आपके द्वारा दी गई वर्तमान पते पर यात्रा प्रदान की जाएगी ।
१९. आपको रात में जल्दी सोना पड़ेगा ।



२०. अध्ययन काल में दवा की मात्रा लेने के कम से कम ४८ घंटे पहले, और अध्ययन में आपके सहभाग की अवधि में झान्थाइनयुक्त खाद्य (चोकलेट, चाय कॉफी या कोला पेय), तम्बाखू के पदार्थ और मद्यपान से परहेज रखना पड़ेगा।
२१. अध्ययन काल में आपको अन्वेषणात्मक उत्पाद की मात्रा लेने के ७ दिन पहले और अध्ययन में आपके सहभाग की अवधि में पपनस या पपनसयुक्त पदार्थ या किसी भी क्रुसिफेरस सब्जी (उदा. ब्रोकली, ब्रुसेल्स स्प्राउट्स (अंकुरित कोबी) ई.) या कोयले में सिका हुआ मांस से परहेज रखना पड़ेगा।
२२. अध्ययन काल में आपको किसी भी कारणवश असामान्य आहार लेना मना है, उदा. अन्वेषणात्मक उत्पाद की मात्रा लेने से पहले २ हफ्ते और पूरे अध्ययन काल में कम सोडियम (नमक) वाला भोजन लेना।
२३. अंतिम अन्वेषणात्मक उत्पाद देने के बाद कोई भी प्रतिकूल घटना ३५ दिन तक होती है, तो आप को आगे के प्रबंधन के लिए सुविधा में सुचना देनी पड़ेगी।
२४. महिला स्वयंसेवीकाओं अंतिम अन्वेषणात्मक उत्पादन के बाद, अध्ययन कालावधी के दौरान और ३५ दिन तक आपको गर्भवस्था से बचने के लिए गर्भनिरोधक का एक उचित अवरोध पद्धती का इस्तेमाल करना पड़ेगा। इस कालावधी के दौरान अगर आप गर्भवती हो तो आपकी गर्भावस्था के परिणाम तक अध्ययन केंद्र में आगे के प्रबंधन के लिए सुचना देनी पड़ेगी। इसका कारण यह है की दवा की वजह से भ्रूण या गर्भ को खतरा हो सकता है जिसका हमें ज्ञान नहीं है।

१३. गोपनीयता के बारे में क्या होगा ?

अध्ययन के दौरान का आपका मूल वैद्यकीय रिकॉर्ड और अध्ययन की जानकारी (जैसे की सूचित सहमती पत्र इ.) गोपनीय रखी जाएगी और निम्नलिखित लोगों को ही जानकारी प्राप्त कि जाएगी।

- इंडिपेंडेंट एथिक्स कमिटी / इनस्टीट्यूशनल रीव्यू बोर्ड
- संबंधित नियामक संस्था जैसे डीसीजीआय (ड्रग कंट्रोलर जनरल ऑफ इंडिया), सीडीएससीओ (सेन्ट्रल ड्रग स्टैंडर्ड कंट्रोल ऑर्गेनाइजेशन), ईएमए (यूरोपियन मेडिसिन्स एजेंसी)
- मॉनिटर
- ऑडिटर
- प्रायोजक जिनकी दवा अध्ययन हो रहा है
- मॅक्लीओड्स फार्मास्यूटीकल्स लि. के बायोइक्वीवैलेंस सेंटर के नियुक्त अधिकारी

प्रकाशित जानकारी से अध्ययन में भाग लेने वाले किसी भी विशिष्ट स्वेच्छार्थी का परिचय नहीं दिया जाएगा।

१४. अध्ययन से संबंधित जख्म या तकलीफ के लिए क्या वैकल्पिक योजना है ?

मुफ्त वैद्यकीय उपचार मॅक्लीओड्स फार्मास्यूटीकल्स लि. के बायोइक्वीवैलेंस सेंटर में दिए जाएंगे और आपातकालीन स्थिति में पास के अस्पताल में उपचार आपको जब तक अपेक्षित होगा तब तक किये जाएंगे और जिनका भुगतान आपको नहीं करना होगा।

१५. मेरे सहभागी होने पर मेरे अधिकार क्या है ?

इस अध्ययन में आपका सहभाग स्वेच्छा से होगा और आपको अध्ययन से किसी भी समय बिना कारण देते हुए हटने का अधिकार है और अध्ययन में सहभागी होने से आपने इन्कार किया तो भी आपकी वैद्यकीय देखभाल या अन्य अनुसन्धान अध्ययन में सहभाग लेने में कोई दंडरूप परिणाम नहीं होगा।

यदि शोध के दौरान कोई ऐसी नई जानकारी प्राप्त होती है जो की आपके इस अध्ययन में आगे भी सहभागी होने की इच्छा से संबंधित है इस अवस्था में आपको अथवा आपके प्रतिनिधि को समय - समय पर अवगत कराया जाएगा ।

आप या आपके नामांकित व्यक्ति (अधिकारियों) को अध्ययन से संबंधित चोट या मृत्यु के मामले में मुआवजे का दावा करने का अधिकार है और सीधे किसी दावे से संबंधित प्रश्नों के लिए प्रायोजक प्रतिनिधि (एम/एस मैक्लीओड्स फार्मास्युटिकल्स लि., मुंबई) से संपर्क करें।

१६. यदि मुझे कोई सवाल या समस्या है तो मे किस से बात करू ?

- इस अध्ययन की अवधि के दौरान आप अध्ययन के बारे में अधिक जानकारी पाने के लिए मुक्त है । अध्ययन के दौरान आपत्काल चिकित्सा सम्बन्धि संकट आने पर या अध्ययन से जुड़े किसी महत्वपूर्ण सवाल पर सलाह चाहते हैं तो आप निम्नलिखित बायोइक्विव्हेलंस सेंटर के अधिकारियों से संपर्क कर सकते हैं ।

१. डॉ. राजेंद्र सोंडे (प्रमुख अन्वेषक)	+९१-८२९१०२८७२१
२. डॉ. एस. विजय कुमार (वैद्यकीय अधिकारी)	+९१-८२९१०८३४८२
३. डॉ. अतुल पाटील (वैद्यकीय अधिकारी)	+९१-८२९१०२८७३१
४. डॉ. मिलिंद अ. जाधव (वैद्यकीय अधिकारी)	+९१-२२-६११३२९००
५. डॉ. प्रतीप सेन (वैद्यकीय अधिकारी)	+९१-८२९१०३६४४२
६. डॉ. आशिष मुनगंटीवार (प्रमुख- बायोइक्विव्हेलंस)	+९१-९८६७०२३९१४

पता (नैदानिक अध्ययन सुविधा):

मैक्लीओड्स फार्मास्युटिकल्स लि.

बायोइक्विव्हेलंस डिपार्टमेंट,

आर एंड डी - २, प्लॉट नं ९५,

रोड नं १६, सनसिटी होटल के सामने,

एम्आयडीसी, अंधेरी - (पूर्व),

मुंबई ४०००९३, भारत,

दूरध्वनी क्रमांक : ९१-२२-६७२५८४१२

- मानवी स्वेच्छार्थी के रूप में यदि अपने अधिकारों को लेकर आपके पास प्रश्न है तो आप निम्नलिखित पते पर एथिक्स कमिटी को संपर्क करे ।

डॉ. अमोल पाचपुते (अध्यक्ष)

ह्यूमनकेअर इंडिपेंडेंट इथिक्स कमिटी

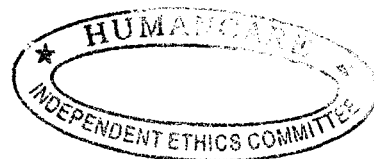
दुकान क्रमांक. ४, चंद्रेश कृष्णा,

निळजे रेल्वे स्टेशन के पास,

कल्याण-शीळ रोड, लोढा हेवन ,

डोंबिवली (पूर्व), ठाणे -४२१२०४,

मोबाइल: +९१ ७७३८३६०७८९



- आपके किसी भी दावे से संबंधित प्रश्न (अध्ययन से संबंधित चोट या मौत के मामले में) है, तो आप या आपके नामनिर्देशनी निम्न पते पर प्रायोजक के प्रतिनिधि फ़ोन करने के लिए स्वतंत्र है।

कु. शालमली आंबेकर (वैद्यकीय सेवा)

मैक्लीओड्स फार्मास्यूटीकल्स ली.

जी-२ महाकाली केव्हज रोड, शांति नगर,

अंधेरी -(पूर्व), मुंबई - ४०००९३, इंडिया

दूरध्वनी क्र: ९१-२२-६११३२९००

विस्तृत क्र: १३३

फैक्स: ९१-२२-२८३०४६४१

१७. मुझे कब सुविधा की यात्रा करनी चाहिए ?

कालावधी - १	दिनांक	कालावधी - २	दिनांक
दाखिल होने के समय		दाखिल होने के समय	

१८. इथिक्स कमिटी कीस प्रकार से मदद करती है ?

नीतिशास्त्र समिती यह चिकित्सक, सामाजिक कार्यकर्ता, व्यक्ती और अन्य जैसे लोगों का समुह हैं और समुदाय में होनेवाले सदस्यों का समूह हैं जो अनैतिक वर्तन की शिकायत प्राप्त करने में, प्रारंभ करने में और उसकी जाँच करने के लिए उपलब्ध होते हैं। और वह आपकी प्रतिष्ठा, अधिकार, सुरक्षा और स्वास्थ्य की रक्षा भी करते हैं। स्थानिक समुदाय मूल्य और प्रचलन रूप से सार्वभौमिक नैतिक मूल्यों को सुनिश्चित किया जाता है और संशोधक द्वारा आंतरराष्ट्रीय वैज्ञानिक मानक का पालन होता है इसको भी सुनिश्चित किया जाता।



१९. मेरी निजी जानकारी:

स्वेच्छार्थी की जानकारी

स्वेच्छार्थी का नाम:			
	पहला नाम	बिच का नाम	उपनाम
स्वेच्छार्थी का पता:			
योग्यता:			
व्यवसाय	छात्र / स्वनियोजित / नोकरी / गृहिणी / अन्य (कृपया उचित रूप से निशान लगाए)		
वार्षिक उत्पन्न:			
संपर्क क्र :	घर:	मोबा.:	पीपी:
आपातकालीन संपर्क क्र :			
(घर/ मोबाईल)	ई-मेल आय डी:		
जन्मतारीख: _____/_____/_____	स्वेच्छार्थीकी आयु (पूरी वर्ष): _____		
दिन महिना साल			

नामनिर्दिशित की जानकारी

नामनिर्दिशित का नाम:			
	पहला नाम	बिच का नाम	उपनाम
संबंध:			
नामनिर्दिशित का पता:			
(अगर ऊपर उल्लेख एक ही नहीं है)			
संपर्क क्र:	घर .:	मोबाइल .:	पीपी

स्वेच्छार्थी की सहमती और अध्ययन में सहभाग लेने की घोषणा

ज्ञात होने वाली भाषाएँ	पढ़ना	लिखना	बोलना	समझना
हिंदी				
अंग्रेजी				
मराठी				
कोई अन्य भाषा (कृपया निर्देशित करें)				

क्र.	स्वेच्छार्थीद्वारा घोषणापत्र	कृपया बक्से में हस्ताक्षर करें (स्वेच्छार्थी)
१.	मैं पुष्टि करता / करती हूँ की, उपरोक्त अध्ययन के लिए १९ मार्च २०१८ की जानकारी पत्रिका (सूचित सहमती पत्र) मैंने पढ़ा/पढ़ी और समझ कर ली है और सवाल पूछने का अवसर मिला है।	
२.	मैं पुष्टि करता हूँ की मुझे कोई भी वैयक्तिक अंश या जो निष्कासन के मापदंड में नमूद किए गए एक्सपीएण्ट्स की अतिसंवेदनशीलता का इतिहास नहीं है।	
३.	मैं यह समझता / समझती हूँ की, मेरी अध्ययन में भागीदारी स्वैच्छिक है और मैं कोई भी कारण दिए बिना, किसी भी समय में वापस लेने के लिए स्वतंत्र हूँ जिसमें नैदानिक देखभाल या कानूनी अधिकारों के बिना प्रभावित, शामिल है।	
४.	मैं यह समझता / समझती हूँ की नैदानिक अध्ययन के प्रायोजक अन्य कार्यरत प्रायोजक के व्यक्ति निम्न समिति तथा नियामक संस्था जैसे डीसीजीआय (ड्रग कंट्रोलर जनरल ऑफ़ इंडिया) और ईएमए (यूरोपियन मेडिसिन्स एजेंसी) को मेरे स्वस्थ की जानकारी देने वाली पत्रिका देखने के लिए मेरी आज्ञा की आवश्यकता नहीं होगी। यह तत्काल अध्ययन या इससे संबंधित बाद में होने वाले अनुसन्धान दोनों के सन्दर्भ में है यदि मैं अध्ययन से निष्कासित हूँ फिर भी। मैं समझता / समझती हूँ की मेरी पहचान किसी भी तीसरे व्यक्ति को बताई नहीं जाएगी या प्रकाशित नहीं की जाएगी।	
५.	मैं इस तरह के प्रयोग केवल वैज्ञानिक उद्देश्य को प्रदान की जाती है की इस अध्ययन से उत्पन्न होने वाली कोई भी आंकड़ों या परिणाम के इस्तमाल को प्रतिबंधित करने के लिए सहमत नहीं हूँ।	
६.	मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूँ।	

स्वेच्छार्थी के हस्ताक्षर (या अंगूठे का निशान) / कानूनी तौर पर स्वीकार्य प्रतिनिधि (एलएआर):

सूचना: महिला स्वेच्छार्थियों के लिए बाएं हाथ के अंगूठे का निशान और पुरुष स्वेच्छार्थियों के लिए दाएं हाथ के अंगूठे का निशान का प्रयोग करें।

तारीख: ____/____/____
दिन महिना साल

**** स्वेच्छार्थी / एलएआर अशिक्षित हो तो निष्पक्ष गवाह का हस्ताक्षर जरूरी है। निष्पक्ष गवाह, उस भाषा में सूचित सहमती पत्र पड़ेगा जो स्वेच्छार्थी / एलएआर को ज्ञात है।**

निष्पक्ष गवाह का नाम:	_____	_____	_____
	पहला नाम	बिच का नाम	उपनाम
निष्पक्ष गवाह का पता:	_____	_____	_____
	_____	_____	_____
संपर्क क्र.:	घर: _____	मोबाइल: _____	पीपी: _____
हस्ताक्षर: _____	तारीख: _____/_____/_____ दिन महिना साल		

लिखित सूचित सहमती पत्र लेनेवाले प्रमुख अन्वेषक / सह - अन्वेषक का हस्ताक्षर और नाम :

नाम: _____	
हस्ताक्षर: _____	तारीख: _____/_____/_____ दिन महिना साल

प्रमुख अन्वेषक का हस्ताक्षर और नाम
(अगर सह - अन्वेषक द्वारा लिखित सूचित सहमती पत्र लिया गया)

प्रमुख अन्वेषक का नाम: _____	
हस्ताक्षर: _____	तारीख : _____/_____/_____ दिन महिना साल

सूचना: हस्ताक्षर और दिनांकित लिखित सूचित सहमती पत्र की नकल स्वेच्छार्थी को सौंप दी जाएगी।

सूचित संमती पत्र

अभ्यास शीर्षक :

सुट्ट, प्रौढ, मानवी स्वेच्छार्थीना उपाशी अवस्थेत तीन गोळ्यांच्या एकाच मात्रेच्या लीवोथायराॅक्झीन सोडियम २०० एमसीजी (मॅक्लिओडस फार्मास्युटिकल्स लिमिटेड, इंडिया) च्या गोळ्यांची, यूथ्रोक्स® (लीवोथायराॅक्झीन सोडियम) २०० एमसीजी च्या (मर्क बी.वी., स्विफोल-रिज्क, नेदरलँड्स) गोळ्यांबरोबर शरीरात तीन गोळ्यांच्या एकाच मात्रेचा जैवसमानता अभ्यास.

अभ्यास रचना

३० सुट्ट, प्रौढ, मानवी स्वेच्छार्थीवर उपाशी अवस्थेत होणारा खुले शीर्षक, संतुलित, विश्लेषकाच्या माहिती शिवाय, नेमावाचून, दोन उपचारांचा, दोन कालावधींचा, दोन क्रमांचा, एकाच मात्रेचा, अदल बदल जैवसमानता अभ्यास.

सूचित संमती पत्र संस्करण क्र: ०१

स्थिती: सुनिश्चित

दिनांक: १९ मार्च २०१८

मागील क्रमांक: अनावश्यक

दिनांक: अनावश्यक

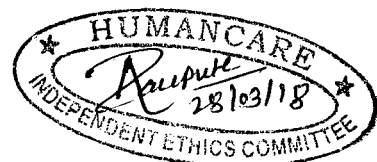
स्वेच्छार्थी नोंदणी क्र.	स्वेच्छार्थी प्रथमाक्षर	लिंग: पुरुष / स्त्री	स्वेच्छार्थी क्र.
बीईक्यू -			

सूचना : या अभ्यासात भाग घेण्याची मान्यता देण्यापूर्वी या दस्तऐवजात दिलेली माहिती काळजीपूर्वक वाचून समजून घेणे महत्वाचे आहे. तुम्हाला या फॉर्मवर दिनांकाबरोबर सही करावी लागेल तुम्हाला संदर्भासाठी या फॉर्मची एक प्रत दिली जाईल. या दस्तऐवजाच्या तोंडी सादरीकरणादरम्यान आणि अभ्यासक्रमादरम्यान कोणत्याही वेळी स्पष्टीकरण आणि प्रश्नांची चर्चा करता येईल.

या दस्तऐवजाचा उद्देश या अभ्यासाची कार्यपद्धती समजावून देणे आणि हे सुनिश्चित करण्यासाठी तुम्ही वस्तुस्थिती जाणून घेतल्यानंतर अभ्यासात प्रवेश करा. या सूचित संमती पत्राच्या अभ्यासाचा उद्देश, संभाव्य फायदे, जोखीम किंवा अस्वस्थता, पर्यायी उपचार आणि गोपनीयता यांची माहिती दिली आहे. या अभ्यासात आपण स्वेच्छापूर्वक भाग घेत आहात अशी जाहीर घोषणाही आहे.

हे सूचित संमती पत्र म्हणजे कुठलाही करार नाही आणि तुम्ही इच्छेनुसार केव्हाही, कोणतेही कारण न देता ह्या अभ्यासातून तुम्ही बाहेर पडू शकता.

प्रमुख अन्वेषक : डॉ. राजेंद्र सोंडे



१. बायोअॅव्हॅलेबिलिटी / बायोइक्विव्हॅलन्सचा अर्थ काय आहे ?

❖ बायोअॅव्हॅलेबिलिटी

औषध घेतल्यानंतर औषधाची मानवामध्ये सुरक्षितता आणि क्षमता यांचा अंदाज घेण्यासाठी शरीरात औषधाचे अभिशोषण किती वेळेत आणि किती प्रमाणात होते हे निश्चित करण्यासाठी बायोअॅव्हॅलेबिलिटी अभ्यासाची रचना केली जाते.

❖ बायोइक्विव्हॅलन्स

जेव्हा औषधाचे दोन सूत्र, औषध घेतल्यानंतर किती वेळात आणि किती प्रमाणात शरीराच्या इंद्रिय व्यवस्थेत अभिसरण होते, यांची संख्याशास्त्राच्या अनुसार तुलना करण्यास योग्य असतात तेव्हा एकाच औषधाच्या दोन प्रमाणित सूत्रांना बायोइक्विव्हॅलन्ट म्हटले जाते.

दोन सूत्रांना (अन्वेषणात्मक उत्पादन) खालीलप्रमाणे संबोधित केले आहे.

‘अभ्यास सूत्र’ : ज्याचा बायोइक्विव्हॅलन्ससाठी संदर्भ सूत्राशी तुलना करून अभ्यास केला जातो.

‘संदर्भ सूत्र’ : जे औषध पहिल्यापासूनच बाजारात उपलब्ध आहे आणि त्याचे नाव आहे यूथ्रोक्स® (लीवोथायरॉक्झीन सोडियम) २०० एमसीजी च्या गोळ्या.

२. अभ्यासाच्या औषधाची सामान्य माहिती:

अभ्यास आणि संदर्भ सूत्रीकरणामध्ये लिवोथायरॉक्झीन सोडियम समाविष्टित आहे जे यासाठी संकेतिक आहे लीवोथायरॉक्झीन सोडियम २५-२०० माइक्रोग्राम :

- जेव्हा आयोडीन दर्शविलेले नसतात तेव्हा, विशेषतः प्रौढांमध्ये युथायरॉइड गोंडर (थायरॉइड ग्रंथीचा विस्तार) याचा उपचार
- पुनर्विभाजननंतर प्रॉफिलॅक्सिसची पुनरावृत्ती (अंगाचा भाग काढून टाकल्यानंतर) क्रियाशील पश्चात संप्रेरक स्थितीवर अवलंबून.
- हायपोथायरॉइडीझम मध्ये प्रतिस्थापन (एक सिंड्रोम जो थायरॉइड ग्रंथीपासून थायरॉइड संप्रेरकांच्या असाधारण कमी सावामुळे होतो)
- थायरॉइड कार्सिनोमा (कॅन्सर) साठी अवरोधक उपचार

लीवोथायरॉक्झीन सोडियम २५-१०० माइक्रोग्राम :

- प्रतिस्थापन दरम्यान हायपरथायरॉइडीझममध्ये (थायरॉइड ग्रंथीपासून थायरॉइड संप्रेरकाचे अतिसावण होणे) थायरोस्टॅटिक्स (थायरॉइड संप्रेरकांच्या निर्मितीस अवरोधक औषधे) यासह सहवर्ती उपचार.

लीवोथायरॉक्झीन सोडियम १००/१५०/२०० माइक्रोग्राम :

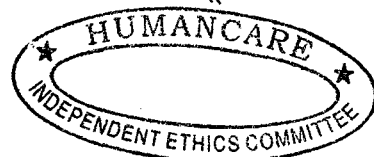
- थायरॉइड अवरोधक चाचणीत निदान वापर

३. हा अभ्यास का केला जातो ?

या अभ्यासात संशोधन अंतर्भूत आहे.

या अभ्यासाचे उद्देश आहेत:

- १) उपाशी अवस्थेत तोंडावाटे तीन गोळ्यांच्या एकाच मात्रेच्या लीवोथायरॉक्झीन सोडियम २०० एमसीजी च्या गोळ्या दिल्यानंतर रक्तातील लीवोथायरॉक्झीन च्या उपलब्धतेचे मूल्यमापन करणे.



२) सुदृढ, प्रौढ, मानवी स्वेच्छार्थीना उपाशी अवस्थेत तोंडावाटे तीन गोळ्यांच्या एकाच मात्रेच्या लीवोथायरोक्झीन सोडियम २०० एमसीजी च्या गोळ्या दिल्यानंतर सुरक्षिततेचे आणि सहनशीलतेचे मूल्यमापन करणे.

४. या अभ्यासात किती व्यक्ती भाग घेतील ?

३० सुदृढ, प्रौढ, मानवी स्वेच्छार्थी ह्या अभ्यासात भाग घेतील.

५. या अभ्यासात कशाचा समावेश आहे ?

या अभ्यासातील तुमचा समावेश प्राथमिक परीक्षण तसेच वगळण्याच्या निकषांवर आधारलेला असेल. जर तुम्ही खालील निकषांची पूर्ती केलीत तरच भाग घेण्यास पात्र ठरू शकाल :

- वैद्यकीय तपासणी
- प्रयोगशालेय तपासणी
- वगळण्या संबंधीचे निकष

❖ परीक्षण :

तुमच्या आरोग्य स्थितीचे मूल्यांकन करण्यासाठी खालील परीक्षण चाचण्या पार पाडल्या गेल्या आहेत :

१. संपूर्ण माहिती ज्यात लिंग, पूर्ण वय, उंची आणि वजन, बीएमआय, आहार, तंबाखूच्या वापराचा इतिहास, निषिद्ध केलेले पदार्थ / नशील्य पदार्थांचे सेवन केले असल्यास, मद्यपानचे सेवन केले असल्यास, रक्तदानाचा इतिहास आणि अभ्यास औषधांच्या संशोधनात भाग घेतल्याचा इतिहास या सर्व माहितीचा समावेश असेल.
 २. वैद्यकीय इतिहास, त्यांच्याशी संबंधित मागील वैद्यकीय / शस्त्रक्रियेचा इतिहास, कौटुंबिक इतिहास, अलर्जीचा इतिहास (खाद्यपदार्थ / औषध / अन्य), मागील ९० दिवसांमधील घेतलेल्या औषधाचा इतिहास.
 ३. सध्या असलेल्या तब्येतीच्या तक्रारी (जर असतील तर), वैद्यकीय परीक्षण ज्यात महत्वपूर्ण संकेतची नोंद करणे (रक्तदाब, नाडी, तापमान, आणि श्वसन क्रिया), सामान्य परीक्षण, शारीरिक आणि शरीर व्यवस्थेची तपासणी.
 ४. प्रसव संबंधी आणि महिला रोग चिकित्सेचा इतिहास (फक्त महिलांसाठी).
 ५. हृदयाची गती, लय आणि विशिष्ट लक्षणांसाठी (जर असतील तर) १२-लीड इ. सी. जी.
 ६. रक्त आणि लघवीचे विश्लेषण.
 ७. छातीचा एक्स-रे (पीए व्ह्यू).
 ८. गर्भधारणा आहे की नाही हे पाहण्यासाठी लघवीची तपासणी (फक्त महिलांसाठी).
 ९. सिरोलॉजी चाचणी {एचाआयव्ही (मानवी इम्युनोडेफिशियन्सी विषाणू), एचबीसएजी [हिपेटेटिस बी (यकृत सुजणे) सर्फेस एंटीजन], एचसीव्ही (हिपेटेटिस सी विषाणू ज्याचा प्रामुख्याने यकृतावर परिणाम होतो)}.
- नोंद : जसे की तुम्ही सर्व परीक्षण मापदंड पास केले असल्यास, स्वयंसहभागीना खालील प्रयोगशालेय चाचण्यांच्या अंतर्गत जावे लागेल: सीरम टि_१ (एकूण), सीरम टि_२ (एकूण), सीरम थायरॉईड- उत्तेजक संप्रेरक (टिएसएच)



❖ वगळण्या संबंधीचे निकष:

खालील गोष्टींमुळे तुम्ही या अभ्यासाला अपात्र ठरू शकता:

१. लीवोथायराॅक्झीन किंवा संबंधित औषधांची अॅलर्जी किंवा एक्सिपीएंट्स (औषधातील निष्क्रिय घटक) [मॅग्नेशियम स्टॅरेट (ई ५७२), मेज स्टार्च, क्रोसकारमेल्लोस सोडिअम (ई ४६८), जेलेटीन (ई ४४१), लॅक्टोज मोनोहाइड्रेट] किंवा अतिसंवेदनशीलतेचा वैयक्तिक इतिहास असल्यास.
२. मागील ९० दिवसात झालेला कोणताही मोठा आजार किंवा वैद्यकीय महत्वपूर्ण चालू कोणताही जुनाट वैद्यकीय आजार (दिर्घकाळापासून असणारी वैद्यकीय स्थिती) उदा. हृदयाच्या कार्यक्षमतेत बाधा येणे (हार्ट फेल्युअर), कावीळ (यकृताला सूज), कमी रक्तदाबाचे प्रसंग (कमी रक्त दाब), हायपरग्लायसेमिया (रक्तातील साखर खूप वाढणे) वगैरे.
३. परीक्षणा दरम्यान कोणतेही वैद्यकीय महत्वपूर्ण असामान्य प्रयोगशाळेय मुल्ये आढळणे, उदा. महत्वपूर्ण असामान्य यकृत कार्यक्षमता परीक्षण व मूत्रपिंडाच्या कार्यक्षमता परीक्षण इ.
४. हृदय, मूत्रपिंड किंवा यकृताची गंभीर दुर्बलता, जठर व आतड्याचा आजार किंवा अन्य त्रास, इतर कोणतेही इंद्रिय किंवा व्यवस्था यांची दुर्बलता (अपंगत्व).
५. आकडी (मेंदूतील अनियंत्रित विद्युत कार्य ज्यामुळे शरीरात अनियंत्रित थरथर, सौम्य अशी शारीरिक लक्षणे, वैचारीक गडबड, किंवा संयुक्त लक्षणे), अपस्मार (मेंदूमध्ये विकृती ज्यामुळे बेशुद्ध होणे आणि अनियंत्रित शारीरिक थरथर होणे) किंवा अन्य प्रकारच्या मज्जासंस्थेच्या विकृतीचा (चेतासंस्थासंबंधीत विकार) इतिहास असल्यास.
६. ऍनफीलॅक्सीस (तीव्र अलर्जीची प्रतिक्रिया) किंवा ऍजीओईडीमा (त्वचेवर जलदरित्या सूज येणे) यांचा पूर्व इतिहास.
७. एच. आय. व्ही. किंवा बी प्रकारच्या कावीळीच्या किंवा सी प्रकारच्या कावीळीच्या विषाणूच्या खुणांच्या आजाराची उपस्थिती आढळल्यास.
८. दोन वर्षांपेक्षा जास्त काळ सतत कोणत्याही प्रकारच्या मद्यपानाचा इतिहास असल्यास किंवा औषधाची मात्रा घेण्याअगोदर ४८ तासात मद्यपान केले असल्यास.
९. औषधाची मात्रा घेण्याअगोदर ४८ तासात झाल्याइनयुक्त पदार्थांचे (चॉकलेट, चहा, कॉफी किंवा कोला पेय) किंवा तंबाखूचे पदार्थ यांचे सेवन केल्यास.
१०. पपनस किंवा पपनस युक्त पदार्थ किंवा कोणत्याही कुसीफेरस भाज्या (उदा. ब्रोकोली, ब्रुसेल्स स्प्राऊट्स (अंकुरित कोबी) इ.) किंवा कोळश्यात भाजलेले मांस यांचे अन्वेषणात्मक उत्पादनाची मात्रा घेण्याच्या ७ दिवसांपूर्वी सेवन केले असल्यास.
११. कोणत्याही नशील्या पदार्थांच्या (रासायनिक पदार्थ ज्यामुळे मेंदूच्या कार्यपद्धतीवर परिणाम होतो ज्यामुळे त्याच्या वागणुकीवर आणि मानसिक अवस्थेत व त्याच्या जागरूकतेत बदल होतो, स्वतःच्या करमणुकीसाठी घेतलेली औषधे) वापर केल्यास किंवा औषधांवर अवलंबून असल्याचा इतिहास.
१२. गेल्या ९० दिवसात कोणत्याही चिकित्सक अभ्यासात भाग घेतल्यास.
१३. रक्तदान करण्यास कठीण असल्यास किंवा डाव्या किंवा उजव्या हातातील योग्य शीर सापडण्यास कठीण असल्याचा इतिहास.
१४. अभ्यासासाठी औषधाची पहिली मात्रा घेण्या अगोदर ९० दिवसात रक्तदान (१ युनिट किंवा ३५० मि.लि.) केले असल्यास.



१५. कुठल्याही अन्य औषधाची शिफारस (वैद्यकीय अधिकार्याच्या सल्ल्याने) झाली असल्यास किंवा काऊन्टर वर (ओटीसी) औषध (ज्यात जीवनसत्व आणि नैसर्गिक औषधी उत्पादन आहेत), अभ्यास औषधाची पहिली मात्रा घेण्या अगोदर २ आठवड्यात, सहजपणे उपलब्ध होणारे कुठलेही औषध किंवा मागील ४ आठवड्यात वारंवार कोणतेही औषध किंवा संपूर्ण अभ्यासात सहभाग घेतले असल्यास.
१६. कोणत्याही कारणांसाठी असामान्य आहार घेतल्यास उदा. औषध घेण्यापूर्वी २ आठवडे आणि अभ्यास काळातील पूर्ण कालावधीत कमी सोडियम (मीठ) चा आहार घेणे.
१७. अभ्यास सुरु होण्यापूर्वीच्या ४८ तासात अतिसार, उलट्या किंवा अन्य कारणांमुळे शरीरात निर्जलीकरण झाल्याचा ताजा इतिहास.
१८. तोंडावाटे घेतले जाणारे गर्भनिरोधक गोळ्या मागील ९० दिवसात घेतल्यास (महिलांसाठी)
१९. गर्भवती / स्तनपान करत असणाऱ्या स्वयंसेविका (महिलांसाठी).
२०. असामान्य सीरम टि_४ (एकूण), सीरम टि_३(एकूण), सीरम थायरोईड- उत्तेजक संप्रेरक (टिएसएच) चाचणी मूल्य.

❖ कृती योजना:

१. या अभ्यासात तुम्हाला बायोइक्विव्हॅलन्स केंद्राच्या चिकित्सकिय सुविधेमध्ये दोन कालावधीमध्ये राहावे लागेल, म्हणजे कालावधी १ आणि कालावधी २.
२. प्रत्येक कालावधीत तुमच्यावर कोणत्याही एक प्रकारचा उपचार केला जाईल, ज्यात उपचार 'I' तीन गोळ्यांच्या एकाच मात्रेच्या लीवोथायरोक्झीन सोडियम २०० एमसीजी (मॅक्लिओडस फार्मास्युटिकल्स लिमिटेड, इंडिया) च्या गोळ्या किंवा उपचार 'R' तीन गोळ्यांच्या एकाच मात्रेच्या यूथोक्स® (लीवोथायरोक्झीन सोडियम) २०० एमसीजी च्या (मर्क बी.वी., स्विफोल-रिज्क, नेदरलँड्स) गोळ्या. कोणत्या क्रमाने अभ्यासाचे औषध दिले जाईल ते नेमावाचून ठरविले जाईल, परंतु अभ्यासाच्या शेवट पर्यंत तुम्हाला दोन्ही उपचार दिले गेले असतील.
३. क्रमाने येणाऱ्या कालावधींच्या मध्ये औषधाची मात्रा घेतल्यानंतर कमीत कमी ३५ दिवसांचा मध्यंतर असेल. जर काही कारणास्तव कालावधी २ नंतर निश्चित करण्यात आला तर अभ्यास कालावधी आणि सहभागाची रक्कम त्याप्रमाणे बदलेल.
४. प्रत्येक कालावधीत औषधाची मात्रा घेण्यापूर्वी तुम्हाला १० तास उपवासाची स्थिती बनवून ठेवण्यासाठी पुरेश्या वेळे आधी, बायोइक्विव्हॅलन्स केंद्रामध्ये दाखल व्हावे लागेल आणि अन्वेषणात्मक उत्पादनाची मात्रा घेतल्या नंतर ७२ तासापर्यंत राहावे लागेल.
५. प्रत्येक कालावधीत दाखल होण्याच्या वेळेस नशील्या औषधांचा वापर केला आहे की नाही हे पाहण्यासाठी लघवीची तपासणी केली जाईल.
६. प्रत्येक कालावधीत दाखल होण्यापूर्वी तुम्ही मद्यपान केले आहे की नाही हे पाहण्यासाठी श्वास परीक्षण यंत्राद्वारे तुमच्या श्वासाचे परीक्षण केले जाईल.
७. कालावधी १ आणि कालावधी २ मध्ये दाखल होण्याच्या वेळेस गर्भधारणा तपासणीसाठी लघवीची तपासणी केली जाईल (फक्त महिलांसाठी).
८. सर्किट कॅमेरा सिस्टीमने तुमच्या हालचालींवर लक्ष ठेवले जाईल.
९. प्रत्येक अभ्यास कालावधीसाठी दाखल होण्याच्या वेळेस, जाण्याच्या वेळेस आणि उपस्थित वैद्यकीय अधिकार्याला आवश्यक वाटेल त्यावेळी वैद्यकीय तपासणी केली जाईल.
१०. दाखल होण्याच्या दिवशी २२०० वाजता रात्रीचे जेवण दिले जाईल.



११. रात्री कमीत कमी १० तास उपवासाच्या स्थितीत राहावे लागेल.
१२. प्रत्येक अभ्यास कालावधीत, रात्री कमीत कमी १० तासाच्या उपवासानंतर, अभ्यास किंवा संदर्भ उत्पादन तोंडावाटे २४० मिली पिण्याच्या पाण्याबरोबर अनुसूचित वेळेवर दिले जाईल.
१३. सरळ बसून राहण्याच्या स्थितीमध्ये तुम्हाला अन्वेषणात्मक उत्पादन दिले जाईल. अन्वेषणात्मक उत्पादनाची मात्रा दिल्यानंतर तुम्हाला पहिले दोन तास बसून राहण्याचे किंवा थकवा न आणता (थकवा आणणार्या कामाव्यतिरिक्त) चालते फिरते राहण्याचे आदेश दिले जातील (महत्वपूर्ण संकेत तपासण्याच्या आणि रक्त संकलनाच्या वेळेच्या अंकाव्यतिरिक्त). मध्यंतरीच्या काळात तुम्हाला निरीक्षणाखाली स्वच्छता गृहाचा उपयोग करण्याची परवानगी दिली जाईल. नंतरच शारीरिक थकवा न आणता तुमची सामान्य कामे करण्यास परवानगी दिली जाईल.
१४. औषधाची मात्रा देण्याअगोदर १ तास व मात्रा दिल्यानंतर १ तासापर्यंत पाणी पिण्यास मनाई असेल.
१५. औषधाची मात्रा दिल्यानंतर कमीतकमी ४ तास काहीही खाण्यास मनाई असेल, त्यानंतर प्रत्येक अभ्यास कालावधीत अन्वेषणात्मक उत्पादनाची मात्रा दिल्यावर ४.०० तासांनी प्रमाणित जेवण आणि औषधाची मात्रा देण्याच्या दिवशी दिवस १ मध्ये विशिष्ट मध्यंतरानंतर ८.०० तासांनी नाश्ता आणि १३.०० तासांनी रात्रीचे जेवण, औषधाची मात्रा दिल्यानंतर दिवस २ मध्ये अंदाजे २४.५०, २८.००, ३२.०० आणि ३७.०० तासानंतर (नाश्ता, दुपारचे जेवण, संध्याकाळचा नाश्ता आणि रात्रीचे जेवण) आणि औषधाची मात्रा दिल्यानंतर दिवस ३ मध्ये अंदाजे ४८.५०, ५२.००, ५६.०० आणि ६१.०० तासानंतर (नाश्ता, दुपारचे जेवण, संध्याकाळचा नाश्ता आणि रात्रीचे जेवण) जेवण, जेवण योजने नुसार दिले जाईल. जर जेवणाची वेळ नमुना गोळा करण्याच्या वेळेशी, महत्वपूर्ण संकेत, स्वेच्छार्थी प्रश्नावली घेण्याच्या वेळीच एकत्र आल्या तर या घटनांचा अनुक्रम असा असेल अनुक्रमे रक्ताचा नमुना घेतल्यानंतर महत्वपूर्ण संकेत, स्वेच्छार्थी प्रश्नावली आणि जेवणे.
१६. प्रत्येक कालावधीत रक्ताचे नमुने (१ X ६ मि.ली.) रक्त घेण्याच्या नळीत घेतले जाईल. शिरेतून रक्ताचे नमुने औषधाची मात्रा दिल्यानंतर -०.५०, -०.२५, -०.०३, ०.५०, १.००, १.५०, २.००, २.५०, ३.००, ३.५०, ४.००, ४.५०, ५.००, ५.५०, ६.००, ८.००, १०.००, १२.००, १८.००, २४.००, ३०.००, ३६.००, ४८.०० आणि ७२.०० तासांच्या वेळी घेतले जाईल (अन्वेषणात्मक उत्पादनाची मात्रा घेण्याच्या वेळेशी या वेळा सापेक्ष असतील). हा घटक प्रकाश संवेदनशील असल्याने प्रकाशात जलदरीत्या नाश पावतो. त्यामुळे रक्ताचे नमुने आणि औषधाची मात्रा घेण्याच्या वेळेशी संबंधित सर्व क्रिया पिवळ्या मोनोक्रोमॅटिक प्रकाशात केल्या जातील.
१७. हाताच्या शिरेमध्ये बसविलेल्या कॅन्युलामधून रक्ताचे नमुने घेतले जातील.
१८. प्रत्येक व्यक्तीकडून एकूण ४८ वेळा (प्रत्येक कालावधीमध्ये २४ वेळा) रक्त काढले जाईल. आणि एकूण काढलेले रक्त हे ३२५ मि.लि. पेक्षा जास्त नसेल (यात सुरक्षितता मूल्यमापनासाठी काढलेले १३ आणि २४ मि.लि. नॉर्मल सलाईन रक्त जे टाकून दिले जाते यांचा समावेश होतो).
१९. काही कारणास्तव, जिथे जास्त रक्त काढण्याची गरज भासल्यास, जसे रक्त काढल्यावर नळी तुटणे, विपरीत परिणाम (ज्यात असामान्य प्रयोगशाळा मूल्ये) असल्यास तुमच्या संमती नंतर तुमचे अतिरिक्त रक्त काढले जाईल आणि त्यानुसार तुम्हाला योग्य मोबदला दिला जाईल.
२०. केंद्रामध्ये राहण्याच्या कालावधीत रक्ताचे नमुने घेताना शिरेत लावलेली कॅन्युला, ०.५ मि.लि. नॉर्मल सलाईन इंजेक्ट केल्यानंतर आवश्यक तेवढा वेळ ठेवला जाईल.
२१. कॅन्यूलामधील पहिले ०.५ मि.लि. नॉर्मल सलाईन रक्त फेकून दिल्यानंतर रक्ताचे नमुने घेतले जातील.
२२. कॅन्युलातून रक्त घेण्यास अडथळा आल्यास किंवा अन्य काही कारणांमुळे कॅन्युला काढल्यास रक्ताचे नमुने हातातील शिरेतून एकदाच वापरल्या जाणार्या सिरीज व सुईने काढले जातील.



२३. प्रत्येक कालावधीत अन्वेषणात्मक उत्पादन दिल्यानंतर ७२ तासानंतर तुमची प्रकृती चांगली असेल आणि तुमच्यावर कोणतेही विपरीत परिणाम झाले नसतील तर तुम्हाला घरी पाठविले जाईल. जर विपरीत परिणाम दिसले तर औषधोपचार करून आणि गरज भासल्यास तुम्हाला पूर्ण बरे होईपर्यंत निरीक्षणाखाली ठेवले जाईल.
२४. सर्व औषध आणि / किंवा अभ्यासाच्या संबंधित विपरीत परिणाम आढळल्यास उपस्थित वैद्यकीय अधिकारी बायोइक्विव्हॅलंस केंद्रात किंवा जवळच्या योग्य रुग्णालयात तुमच्यावर मोफत उपचार करतील आणि तो खर्च मॅक्लिओडस फार्मास्युटिकल्स लि. च्या बायोइक्विव्हॅलंस विभागाकडून केला जाईल.
२५. तुम्हाला योग्य विमा सुविधा पण उपलब्ध असेल.
२६. प्रत्येक कालावधीत स्वेच्छार्थी प्रभावली आणि महत्वपूर्ण संकेत (रक्तदाब, तापमान आणि नाडीच्या ठोक्यांचा दर) दाखल होण्याच्या वेळेस, औषधाची मात्रा घेण्याअगोदर आणि औषधाची मात्रा दिल्यानंतर १.००, ३.००, ६.००, ९.००, २३.००, २९.००, ३५.००, ४८.०० आणि ७२.०० तासांच्यावेळी केले जाईल (अन्वेषणात्मक उत्पादनाची मात्रा घेण्याच्या वेळेशी या वेळा सापेक्ष असतील).
२७. कालावधी- २ मध्ये, शेवटचा रक्ताचा नमुना घेतल्यानंतर, अध्ययनानंतरच्या सुरक्षा परीक्षणासाठी, वैद्यकीय परीक्षण, ईसीजी आणि चिकित्सा विषयक प्रयोगशालेय परीक्षण केले जाईल.

६. या अभ्यासात मला किती दिवस राहावे लागेल ?

संपूर्ण अभ्यास काल अंदाजे ४० दिवसांचा आहे ज्यामध्ये ३५ दिवसांचा मध्यंतर आहे. जर कालावधी २ नंतर निश्चित केला गेला तर त्याप्रमाणे अभ्यास काळ बदलेल आणि तुम्हाला प्रत्येक कालावधीत बायोइक्विव्हॅलंस केंद्रामध्ये अंदाजे ८२ ते ८७ तास राहावे लागेल.

७. या अभ्यासात संभाव्य धोके, दुष्परिणाम आणि बेचैनी काय असू शकते ?

संभावनीय दुष्परिणाम

इतर सर्व औषधांप्रमाणेच, लिक्वोथायरोक्झीनमुळे देखील दुष्परिणाम होऊ शकतात, सर्वांना ते होतीलच असे नाही.

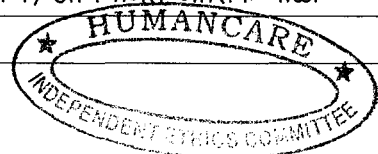
दुष्परिणाम

खालील दुष्परिणामांसाठी वारंवारता श्रेणी जात नाही (उपलब्ध माहितीसह निर्धारितअसू शकत नाही)

रोगप्रतिकार प्रणाली विकार	अतिसंवेदनशीलता (एलर्जी) अॅन्जिओएडिमा(हा त्वचेच्या खालच्या स्तर आणि त्वचेखाली असलेल्या ऊतींचीकिंवा श्लेष्म त्वचेच्या क्षेत्राची सूज)

जर सोडियम लिक्वोथायरोक्झीनच्या वैयक्तिक सहनशीलतेची मर्यादा किंवा औषधाची मात्रा प्रमाणाबाहेर गेल्यावर खालील चिकित्सकिय लक्षणे होतात, हायपरथायरोइडीझमचे वैशिष्ट्य (थायरोइड ग्रंथीपासून थायरोइड संप्रेरकाचे अतिस्रावण होणे), उद्भवू शकते, प्रामुख्याने जर सुरुवातीच्या उपचारावर औषधाची मात्रा खूप लवकर वाढली तर. अशा प्रकरणांमध्ये दररोजची मात्रा कमी केले पाहिजे किंवा दिवसातून अनेक वेळा औषध घेण्याबरोबर पाहिजे. हे परिणाम गेले कि हा उपचार काळजीपूर्वक पुन्हा सुरु केला जाऊ शकतो.

अंतःस्रावी विकार	हायपरथायरोइडीझम (थायरोइड ग्रंथीपासून थायरोइड संप्रेरकाचे अतिस्रावण होणे) अनियमित मासिक पाळी
चेतासंस्था प्रणाली विकार	डोकेदुखी



	सौम्य अंतःसाहोर्ग्य (एखादी अशी परिस्थिती जी तेव्हाच उद्भवते जेव्हा कवटीच्या आतमध्ये दबाव कोणत्याही कारणाशिवाय वाढतो) उच्च रक्तदाब (रक्तदाब वाढणे) थरकाप (अनैच्छिक शरीराची किंवा खालील अवयवांची थरकाप होणे) अस्वस्थता निद्रानाश (झोपयेणे)
हृदयसंबंधित विकार	अरेथमीया (अनियमित किंवा असामान्य लय यासह हृदयाचे अनियमित ठोके) एट्रीयल फिब्रिलेशन (अनियमित हृदयाची लय) एक्ससिस्टोल्स (हृदयाचे वेळेच्या अगोदर होणारे संकुचन) टेंकीकार्डिआ (तीव्र हृदयाचे ठोके) पाल्पीटेशन अन्जायना पेक्टोरिस (एक हृदयाचा विकार ज्यामध्ये छातीत तीव्र वेदना उत्पन्न होतात)
जठरांत्रिय विकार	उल्टी अतिसार (वारंवारता वाढणे किंवा आतड्यांच्या हालचाली कमी सुसंगतता)
त्वचा आणि त्वचेखालील ऊतींचे विकार	हायपरहाइड्रोसिस (असामान्यपणे घाम / स्वेदवाढणे)
स्नायू अस्थी आणि संयोजी ऊतीचा विकार	स्नायू कमकुवतपणा स्नायूंचे अकडणे
सामान्य विकार आणि औषध देण्याच्या जागेची स्थिती	अत्याधिक फ्लशिंग (त्वचेचा लालसरपणा सामान्यता: चेहऱ्यावर) पायरेडिझिया (शरीराचे तापमान वाढणे)
तपास करण्यास	वजन कमीहोणे

संदर्भ:

यूथोक्स® (लीवोथायरोक्झीन सोडियम) २०० एमसीजी च्या गोळ्या च्या उत्पादनांचे सारांश, १५/१०/२०१७ रोजी अंतिम अद्यतन, १८/०३/२०१८ रोजी नमूद, <https://db.cbg-meb.nl/IB-teksten/h09009.pdf> पासून उपलब्ध.

कॅन्यूलेशन आणि रक्त संकलनामुळे संभाव्य धोके

कॅन्युला घालण्याच्या कार्यपद्धती दरम्यान किंवा रक्तवाहिनीत घातल्या जाणाऱ्या इनड्वेलिंग कॅन्युलामार्फत रक्त गोळा करण्या दरम्यान आपणास कॅन्युला घातलेल्या जागी वेदना होवू शकते, सूज, संक्रमण होऊ शकते. रक्तस्त्राव, हिमाटोमा (त्या जागी सूज येणे ज्यात रक्त भरलेले असते जे एखाद्या रक्त वाहिनीच्या भिंतीमध्ये अडथळा आल्यामुळे होते), व्हेसो-व्हेगल एपिसोड (मेंदू मध्ये प्राणवायू नसणे आणि वारंवार बेशुद्ध होणे), नीडल फोबिया (सुईची भीती वाटणे), कॅथेटर एम्बोलीझम (वर्तुळाकार जंतांच्या आकाराच्या प्लेटलेट आणि फायब्रिन (रक्त गोठण्यास मदत करणारे तंतुमय प्रथिन) ची संख्या वाढते), ट्रान्सफिक्सेशन (रक्तवाहिनीच्या भिंतीतून टोचणे), मज्जातंतू हानी पोहोचणे, आर्टिरियल पंच्वर (धमनी फाटणे/ त्यास छिद्र पडणे), एलर्जी, सुई टोचल्यामुळे इजा होणे (सुईच्या तीक्ष्ण टोचण्याने झालेली एक जखम, त्याचा परिणाम म्हणून रक्त येते

किंवा शरीरातील इतर द्रव पदार्थ बाहेर पडतात), थ्रोम्बोफ्लेबीटीस (एखाद्या रक्तवाहिनीच्या भिंतीचा दाह त्याचबरोबर थ्रोम्बोसीस (रक्तवाहिनीमध्ये रक्त गोठणे) होणे).

सूचना:

- हि पूर्ण दुष्परिणामांची यादी नाही आहे, हा एक चिकित्सकिय अभ्यास आहे ज्यात अन्वेषणात्मक उत्पादनाचा उपयोग केला आहे म्हणून काही अज्ञात धोका किंवा असुविधा होऊ शकते जी अजून जात नाही आहे.
- उपचारातून तुम्हाला धोका होण्याची संभावना आहे (किंवा गर्भास किंवा भ्रूण, जर तुम्ही [महिला स्वयंसेविका] गर्भवती असाल तर) जे सध्या अज्ञात आहे.

८. या अभ्यासात भाग घेण्याचे काही फायदे आहेत का ?

तुम्ही सुट्ट असल्यामुळे तुम्हाला या अभ्यासात भाग घेतल्यामुळे तसा फायदा होणार नाही, पण अभ्यासात भाग घेतल्यामुळे मोफत वैद्यकीय तपासणी करून मिळेल.

९. अभ्यास बंद करणे ?

सुरक्षिततेच्या कारणांमुळे किंवा स्वेच्छार्थीच्या हितासाठी अभ्यास कोणत्याही वेळी बंद करण्याचे अधिकार प्रमुख अन्वेषकाला असतात. गंभीर प्रकारच्या नैतिक उल्लंघनामुळे नीती समितीसुद्धा अभ्यास बंद करू शकते. तुम्हाला अभ्यास बंद होण्याची कारणे थोडक्यात सांगितली जातील आणि योग्य मोबदला दिला जाईल.

१०. अजून वेगळे पर्याय काय आहेत ?

हा अभ्यास संशोधनासाठी असून याचे निर्णय नियामक संस्थाना प्राप्त करून दिले जातात आणि यात भाग न घेणे एवढाच पर्याय असू शकतो.

११. यात आर्थिक भरपाई किती मिळते ?

या अभ्यासामध्ये तुम्हाला गैरसोयीबद्दल भरपाई दिली जाईल. अभ्यासातील सर्व प्रक्रियांमध्ये सहभागी झाल्याबद्दल तुम्हाला एकूण रु. १४४००/- भरपाई म्हणून दिले जातील. जर अनपेक्षित वस्तुस्थितीमुळे कालावधी २, नंतर निश्चित करण्यात आला तर भरपाई एका दिवसासाठी रु. ७५/- दिले जातील. तुम्हाला योग्य विम्याची सुविधा अंतिम अनुसरणपर्यंत मिळेल.

बाहेर जाण्याच्या दरम्यान रु. ५००/- आपल्याला एक भाग म्हणून भरपाई किंवा प्रमुख अन्वेषकाच्या निर्णयानुसार दिली जाईल.

जर आवश्यक असेल तर तुमच्या संमतीनंतर अधिक रक्त घेतले जाईल आणि तुम्हाला प्रत्येक मिली रक्तासाठी खाली दिलेल्या सारणीनुसार भरपाई मिळेल.

क्र.	उद्देश	भरपाई (रु.)
	प्रत्येक मिली रक्त घेण्यासाठी भरपाई, रु. २५/मिली	३२५ X २५ = ८१२५
	प्रत्येक कालावधीत दाखल होण्याच्या वेळेस वाहन भत्ता, रु. २००/ भेट	२ X २०० = ४००
	प्रत्येक दिवशी थांबविण्यासाठी भरपाई (८ तास आणि त्यापेक्षा अधिक) रु. ४००/दिवशी	६ X ४०० = २४००
	प्रत्येक रात्री थांबण्यासाठी भरपाई रु. २००/ रात्री	८ X २०० = १६००

१० दिवसांपेक्षा जास्त मध्यांतर असेल तर रु.७५/ दिवशी	२५ X ७५ = १८७५
एकूण	१४४००/-

अभ्यास अर्धवट सोडून गेल्यास /अभ्यासातून काढले गेल्यास, खालीलप्रमाणे भरपाई मिळवीण्याचा तुम्हाला अधिकार असेल.

क्र.	अभ्यास अर्धवट सोडण्याची कारणे	भरपाई
१.	प्रमुख अन्वेषक / वैद्यकीय अधिकार्याच्या वैद्यकीय निर्णयामुळे किंवा कोणत्याही प्रतिकूल घटनांमुळे अभ्यास सोडावा लागल्यास	संपूर्ण कालावधीपर्यंत जो की स्वेच्छार्थी घेण्यात आला आहे, त्यासाठी प्रमाणशीर सहभाग
२.	अभ्यास चालू झाल्यावर स्वेच्छेने अभ्यास सोडल्यास	प्रमाणशीर सहभागाची रक्कम
३.	जर तुम्हाला स्वेच्छार्थी मानवतावादी कारणांमुळे संशोधनातून प्रमुख अन्वेषक / वैद्यकीय अधिकारी यांच्या संमतीने माघार घ्यावी लागल्यास	प्रमाणशीर सहभागाची रक्कम
४.	जर तुम्हाला संमतीपत्रावर सही केल्यावर पण औषधाची मात्रा देण्यापूर्वी आवश्यक नियमांचा भंग केल्यामुळे स्वेच्छार्थीला प्रमुख अन्वेषक / वैद्यकीय अधिकार्याने काढून टाकल्यास	प्रमाणशीर सहभागाची रक्कम
५.	जर आताच्या / पूर्वीच्या वैद्यकीय इतिहासाची / आजाराची जाणूनबुजून चुकीची माहिती पुरविल्याबद्दल प्रमुख अन्वेषक / वैद्यकीय अधिकार्याने तुम्हाला काढून टाकल्यास	प्रमाणशीर सहभागाची रक्कम
६.	कोणत्याही गंभीर प्रतिकूल कारणांमुळे अभ्यासातून स्वेच्छार्थीला काढून टाकल्यास.	पूर्ण

चिकित्सकीय अभ्यासादरम्यान जखम किंवा मृत्यू झाल्यास भरपाई:

- तुम्हाला होणार्या जखमेच्या बाबतीत, तुम्हाला जोपर्यंत आवश्यक असेल तोपर्यंत मोफत वैद्यकीय व्यवस्थापन दिले जाईल.
- चिकित्सकीय अभ्यासासंबंधी तुम्हाला होणार्या जखमेच्या बाबतीत, तुम्हाला लाइसेंसिंग प्राधिकरणाचे आदेशानुसार आर्थिक नुकसान भरपाईसाठी हक्क असेल आणि आर्थिक भरपाईवर आणि तुमच्या चिकित्सा व्यवस्थापनावर केल्या गेलेल्या खर्चाच्या अतिरिक्त असेल
- चिकित्सकीय अभ्यासासंबंधी तुम्हाला होणार्या मृत्यूच्या बाबतीत, तुमच्या नामनिर्देशितच्या लाइसेंसिंग प्राधिकरणाच्या आदेशानुसार आर्थिक नुकसान भरपाईसाठी हक्क असेल आणि आर्थिक भरपाईवर आणि तुमच्या चिकित्सा व्यवस्थापनावर केल्या गेलेल्या खर्चाच्या अतिरिक्त असेल.
- चिकित्सकीय अभ्यासासंबंधी जखम किंवा मृत्यू झाल्यास आर्थिक भरपाई या स्वरूपात असू शकते:
 - चिकित्सकीय व्यवस्थापनासाठी भरपाई
 - अभ्यासासंबंधी जखमेच्या बाबतीत आर्थिक भरपाई
 - मृत्यू बाबतीत अभ्यास विषयाच्या नामनिर्देशितसाठी आर्थिक भरपाई
- जर खालील कोणत्याही कारणांसाठी जखम किंवा मृत्यू झाल्यास प्रायोजक (एम/एस मॅक्लिओड्स फार्मास्युटिकल्स लिमिटेड, मुंबई) आर्थिक भरपाई देतील:
 - अन्वेषणात्मक उत्पादनाचे दुष्परिणाम



- अभ्यासात समाविष्ट कोणतीही अभ्यास प्रक्रिया
- मंजूर प्रोटोकॉलचे उल्लंघन, वैज्ञानिक गैरवर्तन किंवा प्रायोजक किंवा त्यांचे प्रतिनिधी किंवा अन्वेषक द्वारा निष्काळजीपणा
- हेतू उपचारांचा परिणाम प्रदान करण्यासाठी अन्वेषणात्मक उत्पादनाचे अपयश
- मानक ची काळजी वगळून सहवर्ती औषधामुळे प्रतिकूल प्रभावाला, मंजूर प्रोटोकॉलच्या भागात आवश्यक आहे.

ऊ) प्रायोजक (एम/एस मॅक्लिओडस फार्मास्युटिकल्स लिमिटेड, मुंबई) चिकित्सकीय अभ्यासाशी संबंधित जखम किंवा मृत्यू लाइसेंसिंग प्राधिकरण द्वारा निश्चित भरपाईच्या प्रमाणानुसार देतील, जे लाइसेंसिंग प्राधिकरणाच्या आदेशानंतर ३० दिवसांच्या आत दिले जाईल.

१२. माझ्याकडून काय अपेक्षित आहे ?

- १) बायोइक्विव्हॅलेंस सेंटरच्या कर्मचार्यांना तुम्ही सहकार्य द्यावे आणि अभ्यास प्रक्रियेशी संलग्न रहावे.
- २) प्रत्येक कालावधीत दाखल होण्याच्यावेळी व जाण्याच्यावेळी निषिद्ध केलेल्या वस्तू शोधण्यासाठी तुमची व तुमच्या सामानाची झडती घेतली जाईल.
- ३) दाखल होण्याच्यावेळी जर तुम्ही रिपोर्ट केला नाही तर कॉल, एसएमएस किंवा टपाल / कुरियर द्वारे उत्तर अपेक्षित आहे
- ४) तुम्ही अभ्यास केंद्रात शांतता पाळावी.
- ५) आपात्कालीन परिस्थितीमध्ये, तुम्हाला आपात्कालीन घंटी दाबावी लागेल, जी तुमच्या पलंग आणि स्वच्छतागृहाच्या क्षेत्रावर स्थित असेल.
- ६) कर्मचारी आणि अन्य भाग घेणाऱ्या लोकांशी वाईट शब्द किंवा वाईट वागणे सहन केले जाणार नाही.
- ७) मॅक्लिओडस फार्मास्युटिकल्सच्या, बायोइक्विव्हॅलेंस विभागाच्या कोणत्याही मालमतेची हानी आणि / अन्य अभ्यासात भाग घेणाऱ्या वस्तूंची खराबी सहन केली जाणार नाही.
- ८) तुम्हाला तुमचे सामान ठेवण्यासाठी स्वतंत्र सामान कक्ष दिला जाईल.
- ९) मनोरंजनाच्या वस्तू (कॅरम बोर्ड, टीव्ही आणि पते) यांचा बिघाड होणार नाही अशा रीतीने काळजीपूर्वक उपयोग करावा.
- १०) केंद्रामध्ये निषिद्ध केलेल्या वस्तू किंवा अवैध औषधे यांचा उपयोग आणि / किंवा आपल्याजवळ बाळगण्यास मनाई आहे.
- ११) तुम्हाला तुमच्या वर्तमान पत्त्याचा पुरावा देणे आवश्यक आहे.
- १२) तुम्हाला आपत्कालीन संपर्क क्रमांक, ई-मेल आयडी प्रदान करणे आवश्यक आहे (उपलब्ध असल्यास).
- १३) अभ्यासाच्या आवश्यकतेनुसार तुम्हाला खाण्यापिण्याचे नियम पाळावे लागतील. बाहेरील खाद्यपदार्थ केंद्रात आणण्यास मनाई आहे.
- १४) औषधाची मात्रा घेतल्यानंतर तुम्हाला २ तासापर्यंत बसलेल्या स्थितीमध्ये राहावे लागेल.
- १५) तुम्हाला औषधाची मात्रा देण्या अगोदर कमीत कमी १ तास व मात्रा दिल्यानंतर १ तासापर्यंत पाणी पिण्यास मनाई असेल.
- १६) आपत्कालीन परिस्थिती शिवाय प्रमुख अन्वेषक / वैद्यकीय अधिकार्याच्या परवानगी शिवाय अभ्यासाच्या कालावधी दरम्यान कोणत्याही औषधाची शिफारस / दुकानात सहजपणे मिळणारे (ओटीसी) औषध (ज्यात जीवनसत्व आणि नैसर्गिक औषधी उत्पादन आहेत) घेण्यास मनाई असेल व त्याची तुम्हाला प्रमुख अन्वेषकाला / वैद्यकीय अधिकार्याला माहिती द्यावी लागेल.
- १७) जर तुम्ही सुरक्षिततेसाठी सुविधेत येण्यास असमर्थ असल्यास तुम्हाला कॉल, एसएमएस, टपाल / कुरियर द्वारे संपर्क साधला जाईल.



- १८) जर तुम्ही प्रतिकूल घटनेच्या (अभ्यासाच्या दरम्यान किंवा असामान्य प्रयोगशाळा मापदंड अभ्यासानंतरची सुरक्षा दरम्यान) पुढील कारवाईसाठी केंद्राची भेट देऊ शकला नाही तर तुम्हाला दूरध्वनीद्वारे किंवा एसएमएस, टपाल / कुरियर द्वारे संपर्क केला जाईल, जर कोणतेही उत्तर मिळाले नाही तर आणि प्रयोगशाळा मापदंड मिळाले तर त्याला गंभीर मानले जाईल त्याबरोबर तुमच्या द्वारे दिलेल्या वर्तमान पत्त्यावर भेट दिली जाईल.
- १९) तुम्हाला रात्री लवकर झोपावे लागेल.
- २०) अभ्यासात तुमच्या सहभागाच्या कालावधीत औषधाची मात्रा घेण्यापूर्वी कमीत कमी ४८ तास तुम्हाला झालेले खाद्य (चॉकलेट, चहा, कॉफी किंवा कोला पेय), तंबाखूचे पदार्थ आणि मद्यपान या पासून दूर राहावे लागेल.
- २१) तुम्हाला अन्वेषणात्मक उत्पादनाची मात्रा घेण्याच्या ७ दिवसांपूर्वी आणि अभ्यासात तुमच्या सहभागाच्या कालावधीसह पपनस किंवा पपनस युक्त पदार्थ किंवा कोणत्याही क्रुसीफेरस भाज्या (उदा. ब्रोकोली, ब्रुसेल्स स्प्राऊट्स (अंकुरित कोबी) इ.) किंवा कोळश्यात भाजलेले मांस यांच्या सेवनापासून दूर राहावे लागेल.
- २२) अभ्यास कालावधीत कोणत्याही कारणांसाठी असामान्य आहार घेण्यास मनाई आहे. उदा. अन्वेषणात्मक उत्पादनाची पहिली मात्रा घेण्यापूर्वी २ आठवडे आणि अभ्यासाच्या पूर्ण कालावधीत कमी सोडियम (मीठ) चा आहार घेण्यास मनाई आहे.
- २३) अंतिम अन्वेषणात्मक उत्पादन दिल्यानंतर कोणत्याही प्रतिकूल घटना ३५ दिवसांपर्यंत आहे, तर तुम्ही पुढील व्यवस्थापनासाठी सुविधेत तक्रार करा.
- २४) महिला स्वयंसेविकांना अंतिम अन्वेषणात्मक उत्पादन दिल्यानंतर, अभ्यास कालावधीच्या दरम्यान आणि ३५ दिवसांपर्यंत तुम्हाला गर्भावस्थेतून वाचविण्यासाठी गर्भनिरोधकाचे एक अनुरूप प्रतिबंध पद्धतीचा उपयोग करावा लागेल. या कालावधीच्या दरम्यान जर तुम्ही गर्भवती असाल तर तुम्हाला गर्भावस्थेच्या परिणामांपर्यंत अभ्यास केंद्रात पुढील व्यवस्थापनासाठी सुविधेत तक्रार करावी लागेल. याचे कारण हे आहे की गर्भ किंवा गर्भाला धोका होऊ शकतो ज्याचे आपल्याला ज्ञान नाही आहे.

१३. गोपनीयता किती असते ?

अभ्यासा दरम्यानचे तुमचे मूळ वैद्यकीय रेकॉर्ड्स आणि अभ्यास माहिती (जसे की सूचित संमती पत्र इ.) याबद्दल गोपनीयता बाळगली जाईल आणि खालील लोकांनाच माहिती दिली जाईल.

- इंडीपेंडंट एथिक्स कमिटी / इंस्टीट्यूशनल रिव्यू बोर्ड
- संबंधित नियामक संस्था जसे की डीसीजीआय (ड्रग कंट्रोलर जनरल ऑफ इंडिया), सीडीएससीओ (सेन्ट्रल ड्रग स्टॅण्डर्ड कंट्रोल ऑर्गनायझेशन), ईएमए (यूरोपियन मेडिसिन्स एजेंसी)
- मोनिटर
- ऑडीटर
- प्रायोजक ज्यांच्या औषधाचा अभ्यास केला जात आहे
- मॅक्लिओड्स फार्मास्युटिकल्स लि. च्या बायोइक्विव्हलेंस सेंटरचे नियुक्त कर्मचारी

परंतु, प्रसिद्ध करण्यात आलेल्या अहवालांमध्ये ह्या अभ्यासातील भाग घेतलेल्या कोणत्याही विशिष्ट स्वयंसेवकाचा परिचय असलेली कोणतीही माहिती उघड केली जाणार नाही.

१४. अभ्यासाशी संबंधित कुठली जखम झाल्यास त्याचे पर्यायी वैद्यकीय उपचार कोणते ?

मोफत वैद्यकीय उपचार मॅक्लिओडस फार्मास्युटिकल्स लि. च्या बायोइक्विव्हॅलंस सेंटरमध्ये केले जातील आणि आपत्कालीन परिस्थितीत तुमच्यावर जवळच्या रुग्णालयात उपचार केले जातील आणि त्याची भरपाई तुम्हाला करावी लागणार नाही.

१५. मी या अभ्यासात सहभागी झाल्यावर माझे हक्क काय आहेत ?

या अभ्यासात तुम्ही स्वेच्छेने भाग घेतला आहे आणि तुम्हाला अभ्यासातून कोणत्याही वेळी कारण न देता माघार घेण्याचा अधिकार आहे. असे केल्यामुळे तुमच्या वैद्यकीय देखभालीत आणि कोणत्याही अन्य संशोधनात सहभागी होण्यावर दंड स्वरूपी परिणाम होणार नाही.

संशोधनात तुमच्या स्वेच्छेने सहभागी होण्याशी निगडित असलेली कुठलीही महत्वाची माहिती, संशोधनाच्या वेळी आढळल्यास तुम्हाला किंवा तुमच्या प्रतिनिधीला वेळोवेळी कळविली जाईल.

आपण किंवा आपल्या नामनिर्देशिताला अभ्यासासंबंधी जखम किंवा मृत्यू बाबतीत भरपाईचा दावा करण्यासाठी आणि कोणत्याही ताबडतोब दाव्याशी संबंधी प्रश्नांसाठी प्रायोजक प्रतिनिधीला (एम/एस मॅक्लिओडस फार्मास्युटिकल्स लिमिटेड, मुंबई) संपर्क करण्याचा अधिकार आहे.

१६. मला काही शंका असल्यास मी कोणाशी संपर्क साधावा ?

- या अभ्यासाच्या कालावधीत तुम्हाला कुठलीही माहिती मिळविण्याची मुभा आहे. अभ्यास कालावधीत वैद्यकीय आणीबाणी उद्भविल्यास किंवा त्या संदर्भात सल्ला हवा असल्यास तुम्ही खालील बायोइक्विव्हॅलंस सेंटर अधिकार्यांशी संपर्क साधू शकाल.

१. डॉ. राजेंद्र सोंडे (प्रमुख अन्वेषक)	+९१-८२९१०२८७२१
२. डॉ. एस. विजय कुमार (वैद्यकीय अधिकारी)	+९१-८२९१०८३४८२
३. डॉ. अतुल पाटील (वैद्यकीय अधिकारी)	+९१-८२९१०२८७३१
४. डॉ. मिलिंद अ. जाधव (वैद्यकीय अधिकारी)	+९१-२२-६११३२९००
५. डॉ. प्रतीप सेन (वैद्यकीय अधिकारी)	+९१-८२९१०३६४४२
६. डॉ. आशिष मुनगंटीवार (प्रमुख- बायोइक्विव्हॅलंस)	+९१-९८६७०२३९१४

पत्ता (चिकित्सकीय अभ्यास सुविधा) :

मॅक्लिओडस फार्मास्युटिकल्स लि.

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आर एंड डी २, प्लॉट नंबर ९५

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एमआयडीसी, अंधेरी (पूर्व),

मुंबई - ४०० ०९३, भारत

टेलीफोन: ९१-२२-६७२५८४१२



- स्वेच्छेने भाग घेणारी व्यक्ती या नात्याने तुमच्या अधिकारांबद्दल प्रश्न विचारायचे असतील तर तुम्ही पुढील पत्त्यावर इथिक्स कमिटी ला संपर्क करू शकता.

डॉ. अमोल पाचपुते (अध्यक्ष)
ह्यूमनकेअर इंडिपेंडंट इथिक्स कमिटी
दुकान क्रमांक. ४, चंद्रेश कृष्ण,
निळजे रेल्वे स्थानकाजवळ,
कल्याण-शीळ रोड, लोढा हेवन,
डोंबिवली पूर्व, ठाणे-४२१ २०४
दूरध्वनी क्र.: +९१ ७७३८३६०७८९०

- तुमच्या कोणत्याही दाव्याशी संबंधी प्रश्न (अभ्यास संबंधित दुखापत किंवा मृत्यू झाल्यास) असतील तर तुम्ही किंवा तुमचे नामनिर्देशित व्यक्ती खालील पत्त्यावर प्रायोजकांचे प्रतिनिधी फोन करण्यासाठी स्वतंत्र आहेत.

कु. शालमली आंबेकर (वैद्यकीय सेवा)
मॅक्लिओड्स फार्मास्युटिकल्स लि.
जी - २, महाकाली केव्हज रोड, शांती नगर,
अंधेरी (पूर्व), मुंबई - ४०० ०९३, भारत
दूरध्वनी क्र: ९१-२२-६११३२९००
विस्तारित क्र.: १३३
फॅक्स.: ९१-२२-२८३० ४६४१

१७. मला सुविधेत कधी यावे लागेल ?

कालावधी -१	दिनांक	कालावधी -२	दिनांक
दाखल होण्याच्या वेळेस		दाखल होण्याच्या वेळेस	

१८. इथिक्स कमिटी कशी मदत करते?

इथिक्स कमिटी हा एक वैद्यकीय केंद्रातील कर्मचारी जसे वैद्य, सामाजिक कार्यकर्ते, अनभिज्ञ व्यक्ती व इतर आणि समाजातील सदस्यांचा एक समूह आहे जे अनैतिक वर्तनाच्या तक्रारी स्वीकारण्यास, सुरवात करण्यास आणि त्यांचा तपास करण्यास उपलब्ध आहेत. ते तुमची प्रतिष्ठा, अधिकार, सुरक्षा आणि आरोग्य यांचे सुद्धा रक्षण करतात. ते सार्वत्रिक स्थानिक समुदायाची मूल्ये आणि रुढींच्या दृष्टीने नैतिक मुल्यांची खात्री करतात आणि ते संशोधक आंतरराष्ट्रीय वैज्ञानिक मानकांचे अनुसरण करत आहेत का याची सुद्धा खात्री करतात.

१९. माझी वैयक्तिक माहिती:

स्वेच्छार्थीची माहिती:

स्वेच्छार्थीचे नाव:			
	पहिले नाव	मधले नाव	आडनाव
स्वेच्छार्थीचा पत्ता:			
योग्यता:			
व्यवसाय:	विद्यार्थी / स्वयंरोजगार / नोकरी / गृहिणी / इतर (कृपया योग्य निशाणी करा)		
वार्षिक उत्पन्न:			
संपर्क क्र:	घर:	मोबा.:	पीपी:
तत्काळ संपर्क क्र: (घर /मोबाईल)		ई-मेल आय डी:	
जन्मतारीख: ____/____/____ दिवस महिना वर्ष	स्वेच्छार्थीचे वय (पूर्ण वर्ष): ____		

नामनिर्देशित माहिती:

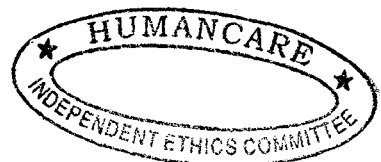
नामनिर्देशितचे नाव:			
	पहिले नाव	मधले नाव	आडनाव
संबंध:			
नामनिर्देशितचा पत्ता :			
(जर वरील उल्लेख एकच नाही आहे)			
संपर्क:	घर:	मोबा:	



स्वेच्छार्थीची संमती आणि अभ्यासात सहभागी होण्याची घोषणा

माहिती असलेल्या भाषा	वाचणे	लिहिणे	बोलणे	समजणे
हिंदी				
इंग्रजी				
मराठी				
कोणतीही इतर भाषा (कृपया निर्देश करून सांगणे): _____				

क्र.	स्वेच्छार्थीनुसार घोषणा पत्र	कृपया बॉक्समध्ये सही करा (स्वेच्छार्थी)
१.	मी खात्री करून देतो की वरील अभ्यास करण्यासाठी दिनांक १९ मार्च २०१८ चे माहिती पत्रक (सूचित संमती पत्र) मी वाचून आणि समजून घेतले आहे आणि प्रश्न विचारण्याची संधी मला मिळाली आहे.	
२.	मी खात्री करून देतो की माझा कोणताही वैयक्तिक ॲलर्जी किंवा जे वगळण्या संबंधीचे निकषामध्ये नमूद केलेल्या एक्सिपीएंट्सच्या अतिसंवेदनशीलतेचा इतिहास नाही आहे.	
३.	मी हे समजतो की, अभ्यासात माझा सहभाग स्वेच्छेने आहे आणि मी कोणतेही कारण न देता, कोणत्याही वेळी काढून घेण्याचे स्वातंत्र्य आहे ज्यामध्ये वैद्यकीय देखभाल किंवा कायदेशीर अधिकारांशिवाय प्रभावित, समाविष्ट आहे.	
४.	मी हे समजतो की, चिकित्सकीय अभ्यासाचे प्रायोजक, प्रायोजकांतर्षे काम करणारे, नीती समिती, आणि नियामक संस्था जसे की डीसीजीआय (ड्रग कंट्रोलर जनरल ऑफ इंडिया) आणि ईएमए (यूरोपियन मेडिसिन्स एजेंसी) यांना या अभ्यासाच्या संदर्भात आणि भविष्यातील संशोधनाच्या संबंधात माझ्या प्रकृतीची माहिती मिळविण्यास माझी अनुमती घ्यावी लागणार नाही, जरी मी या अभ्यासातून माघार घेतली तरी यासाठी मी सहमत आहे, तरी सुद्धा मी जाणतो की तिसरा पक्ष किंवा प्रकाशित केलेली माहिती यात माझा परिचय गुप्त ठेवला जाईल.	
५.	मी प्रयोग केवळ वैज्ञानिक उद्देशाला प्रदान केली जाते की या अभ्यासातून निर्माण होणाऱ्या अंक किंवा परिणामांचा वापर प्रतिबंधित करण्यासाठी सहमत नाही आहे.	
६.	मी अभ्यासात भाग घेण्यास सहमत आहे.	



स्वेच्छार्थीची सही (किंवा अंगठ्याचा ठसा)/ कायदेशीर स्वीकारण्यायोग्य प्रतिनिधी (एलएआर):

सूचना: महिला स्वेच्छार्थीसाठी डाव्या हाताच्या अंगठ्याच्या ठशाचा आणि पुरुष स्वेच्छार्थीसाठी उजव्या हाताच्या अंगठ्याच्या ठशाचा उपयोग करावा.

दिनांक: ____/____/____
दिवस महिने वर्ष

****स्वेच्छार्थी /एलएआर अशिक्षित असेल तर अपक्ष साक्षीदार ची सही गरजेची आहे .अपक्ष साक्षीदार ,त्या भाषेमध्ये सूचित संमती पत्र वाचून दाखवेल जी स्वेच्छार्थी /एलएआर ला माहित आहे.**

अपक्ष साक्षीदाराचे नाव:			
	पहिले नाव	मधले नाव	आडनाव
अपक्ष साक्षीदाराचा पत्ता:			
संपर्क:	घर: _____	मोबा.: _____	पीपी: _____
सही: _____		दिनांक: ____/____/____ दिवस महिने वर्ष	

लिखित सूचित संमती पत्र घेणाऱ्या प्रमुख अन्वेषकाची /सह अन्वेषकाची सही आणि नाव:

नाव: _____	
सही: _____	दिनांक: ____/____/____ दिवस महिने वर्ष

प्रमुख अन्वेषकाचे सही आणि नाव
(जर लिखित सूचित संमती पत्र सह-अन्वेषकाने घेतल्यास)

प्रमुख अन्वेषकाचे नाव: _____	
सही: _____	दिनांक: ____/____/____ दिवस महिने वर्ष

सूचना :सही आणि दिनांकासाहित लिखित सूचित संमती पत्राची प्रत स्वेच्छार्थीला दिली जाईल .

APPENDIX 16.1.4

LIST OF INVESTIGATORS AND IMPORTANT PARTICIPANTS IN THE STUDY

❖ **List of Investigator:**

1. Principal Investigator:

Dr. Rajendra Sonde

Qualification: (M.B.B.S., PGDHMM, D.PHARM.)

(CV enclosed).

2. Study Director:

Dr. Ashish Mungantiwar

Qualification: PhD in Pharmacology

(CV enclosed).

3. List of Co or Sub Investigators:

- Dr. S. Vijay Kumar – Medical Officer
- Dr. Atul Patil – Medical Officer
- Dr. Milind Jadhav – Medical Officer
- Dr. Pratip Sen – Medical Officer

4. Author(s) of the Report:

- Mr. Satyendra Varma – CRA, Clinical
- Mr. Pankaj Bhangale – Biostatistician

CURRICULUM VITAE

Address : 2, Jaoli Co-Op. Hgs. So. Ltd.
R. N. Narkar Marg, Rajawadi
Post Office, Ghatkopar,
Mumbai -400077
Contact No. : 9920678183
Date of Birth: 27th December 1963

DR. RAJENDRA SONDE

Designation / Section: Medical Officer / Clinical Section
Employee No.: H005353

QUALIFICATION: M.B.B.S. (Mumbai) 1993
Senior Management Program (IIM - Calcutta) (2013)
Post graduation of D. H. H. M. (IGNOU) 2006

Role Description: Principle investigator supervise activities and documentation, compliance to GCP, organise and conduct clinical phase of the biostudies.

Current Job Profile

Macleods Pharmaceuticals Limited, Mumbai. (June 2010 – Till Date)

Medical Officer - Clinical Section

- To organise and conduct clinical phase of the biostudies
- To liase with the Bioequivalence head, Section Head and group leaders in bioequivalence department Macleods Pharmaceuticals Limited
- To review medical records and ascertain suitability of subjects for participation in study
- To prepare protocols and informed consent forms for clinical studies

- To liaise with ethics committee for review of study protocols and informed consent forms
- To manage occurrence of adverse events (if any) during study
- To write and revise SOPs as per need and ensure implementation
- To maintain awareness in recent trends and newer guidelines in clinical research
- To conduct medical examination of subjects during screening and at the time of study
- To conduct pre HIV test counselling / Post Test HIV / HCV / HbsAg counselling
- To obtain informed consent from the subject
- To supervise the drug dosing activity
- To serve as Principal Investigator for assigned projects
- To vital monitoring and ECG monitoring
- To ICF presentation to volunteers
- To checking and recording of pathology reports and x-ray
- To provide medical care to all subjects admitted in clinical section
- To record the vital signs of the subject during study and assure subject's wellbeing
- To liaise with clinical pharmacologist in management of adverse event occurrence
- To carry out medical examination of the subjects during screening to ensure that healthy and eligible subjects are included in the study
- To compile raw data in data sheets
- To maintain awareness on all current SOPs
- To operate and maintain instruments used in clinical section
- To be able to provide medical care during emergencies or in ICU Preparation
- To conduct the audit of pathology lab as per guidelines

Previous professional experience:

Reliance Life Sciences (June 2009 – June 2010)

Principal Investigator / Clinical Investigator

Macleods Pharmaceuticals Limited (Feb 2007 – May 2009)

Medical Officer– Principal Investigator – Bioequivalence

Rajawadi Hospital (B.M.C.) (2000 – 2007)

- Management of Critically Ill / Accident / Medical Patients in Casualty Department

Health post (B.M.C.) (1995 – 2000)

- Organization Implementation Management Of Various National Programmes

Rular Hospital (Govt. of Maharashtra) (1994 – 1995)

- Incharge Medical Officer
- Clinical and Administration of Hospital

Dr. Rane's I.C.C.U. (1993 – 1994)

- Resident Medical Officer
- Management of Critically ill Patients

OTHER ACTIVITIES:

- Basic Life Support (BLS) Provider Programme in accordance with the curriculum of the American Heart Association at Mumbai (May 2016)
- Advanced Cardiovascular Life support (ACLS) Provider Programme in accordance with the curriculum of the American Heart Association at Mumbai (May 2016)
- Raigad Medical Association XVII – Annual Conference (07th - 08th Jan 2012)
- Advanced Good Clinical Practice (GCP) (26th April 2009)
- ECG Learning Course (03rd Jan 2009)
- HIV/AIDS Sensitization Programme (Feb 2008)
- Advanced Cardiovascular Life support (ACLS) Provider Course (26th – 27th April 2008)
- Basic Life Support (BLS) Provider Course (26th April 2008)
- Fundamentals of Good Clinical Practice (GCP) (20th April 2008)
- Best Slogan Award In 2001 By Deputy Mayor of Mumbai
- BD Vacationer Training
- Best Street Play Award In 1999 by Health Committee Chairman
- Best Orator Award in 1998 By Additional Commissioner of BMC.

Signature Of Employee

Initial	Full Signature	Date
<i>M</i>	<i>Rayjorde</i>	08/02/16

CURRICULUM VITAE

Address : 106 C, Sai - Kiran, Sai Aasha
Complex, Near Neelam Nagar,
Phase - II, Mulund (E),
Mumbai – 400 081.
Contact No. : +91-9867023914 / 67982109
E-mail : drashish@macleodspharma.com
Date of Birth : 28th September 1972

Dr. ASHISH MUNGANTIWAR

Designation / Department: Head Bioequivalence / President –Medical Services

Employee No.: H00111

QUALIFICATION: D.M.M., Passed with distinction at Somaiya College of Management Studies (Marketing), Mumbai University (1998).

Ph.D. (Tech) (Pharmacology), completed dissertation on 'Immunomodulatory Activity of Boerhaavia Diffusa', at Bombay College of Pharmacy, Mumbai University (1998).

M. Pharm., Passed with distinction at Bombay College of Pharmacy, Mumbai University (1996).

B. Pharm., Passed with distinction at Bombay College of Pharmacy, Mumbai University (1994).

Role Description: Overall control of functions of the Bioequivalence department.

Current Job Profile

Macleods Pharmaceuticals Limited, Mumbai, (Sep. 2004 – Till Date)

Head Bioequivalence

- To liaise with management
- To ensure all the projects are carried out under GCP/GLP guidelines
- To serve as a study director for BE study as follows:-

- To approve the study plan and any amendments to the study plan by sign and date
- To ensure that the raw data generated are fully documented and recorded and also ensures the computerised system used are validated
- To ensure that the procedures specified in study plan are followed and assessed and document the impact of any deviation from the study plan on quality and integrity of the study and take appropriate corrective action, if necessary. Acknowledge the deviation from SOP during the conduct of the study
- To ensure that after completion of the study, the study plan, final report, raw data and supporting material are archived
- To supervise the activities of clinical pharmacologist, biostatistician, quality assurance, group leaders and section head
- To assess the facility needs and seek budgetary support
- To recruit staff with requisite skills and experience
- To interact with ethics committee, National Drug Regulatory Authorities
- To authorise study plans
- To authorise release of SOPs and final reports
- To provide expert comments on final reports
- To provide technical assessments

Previous Experience at Macleods (Dec. 1998 – Sep. 2004)

- **Bioequivalence studies**
 - Audited various Bioequivalence centers as per ICH-GCP and GLP standards. Coordinated plethora of bioequivalence studies from outside laboratories required for DCGI and WHO requirements.
- **Clinical Trials**
 - Drafted protocol and successfully completed various multicentric clinical trials in Tuberculosis, Respiratory tract infections, Typhoid, BPH, Hypertension, Post-surgical infections, periodontal infection, Menorrhagia, Osteoarthritis, Non-Productive Cough, GERD, Hyperlipidemiae, Haemoptysis, Infected Dermatitis,

Intertrigo, CAP, Bronchitis, Urinary Tract Infections, Diabetic nephropathy, Nephrotic syndrome etc.

- Conducted clinical trials of different designs like open, comparative, placebo, double blind double dummy etc.
- **New products and DCGI activities**
 - Obtained various new drug approvals from DCGI.
- **New Product Search**
 - Evaluated new products through various databases, Internet search, Pharmaprojects, Scrip World Pharmaceutical News, Micromedex and R and D Insight, Micro patent Database.

Previous professional experience

Medley Pharmaceutical. (Jun. 1998 – Dec. 1998)

Assistant Manager Medical Services

- Conduct training of Medical Representative
- Prepare product manual
- Answer medical queries
- Monitor clinical trials

OTHER ACTIVITIES:

PUBLICATION (S):

- **International**

1. Mungantiwar A., et al, β - adrenoreceptor desensitization of the isolated rat trachea and its reversal by furosemide, Pharmaceutical Sciences 1997, 3; 93-97, 1997.
2. Mungantiwar A., et al, Effect of stress on plasma and adrenal cortisol levels and immune responsiveness in rats: modulation by alkaloidal fraction of Boerhavia diffusa, Fitoterapia Volume LXVIII No.6, 1997, 498-500.
3. Mungantiwar A., et al Membrane stabilizing activity – a possible mechanism of action for the anti-inflammatory activity of Cedrus deodar wood oil. Fitoterapia 70, 251,-257, 1999.

Version No.: 03

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Page 3 of 8

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5. Mungantiwar A. et al Studies on the immunomodulatory effects of Boerhaavia diffusa alkaloidal fraction, J. Ethnopharmacology, 1999, May; 65(2); 125-131.
6. Mungantiwar A. et al Human insulin genome sequence map, biochemical structure of insulin for recombinant DNA insulin, Mini Rev Med. Chem. 2003, Aug; 3(5); 375-385.
7. Mungantiwar A. et al Development and validation of a highly sensitive LC-MS/MS method for simultaneous quantification of ethionamide and ethionimide sulfoxide in human plasma: application to a study, Biomed Chromatogr. 2011 Sep; 25 (9):985-94 2126148.
8. Mungantiwar A. et al Tandem, mass spectrometric estimation of Efavirenz from human plasma and comparison of various statistical approaches for evaluation of incurred sample reanalysis, Annals of Biological Research, 2011,2 (4) : 126-135.

- **Indian**

1. Mungantiwar A., et al., Anti-allergic potential of furosemide, Indian J. Exp. Biol., 1997, May, 35(5); 466-469.
2. Mungantiwar A., et al., Modulation of invitro anaphylaxis by furosemide, Indian Journal of Pharmacology, 29, 182-186, 1997.
3. Mungantiwar A., et al., Mast cell stabilizing and lipooxygenase inhibitory activity of Cedrus deodar wood oil, Indian J. Exp. Biology, 1999, Mar., 37(3); 258-261.
4. Mungantiwar A., et al., Comparative evaluation of the efficacy and safety of valdecoxib 10 mg tablet versus Rofecoxib 25 mg in patients with osteoarthritis, Indian Practitioner, Vol. 56, 1, 2003.
5. Mungantiwar A., et al., Efficacy and safety of Quinapril versus Enalapril in the treatment of mild to moderate hypertension, cardiology Today, Vol. VI, No. 6, Nov. – Dec. 2002.
6. Mungantiwar A., et al., Ofloxacin – Tinidazole and Ciprofloxacin – Tinidazole in the patients with Odontogenic Infections, Indian Practitioner, Vol. 56. No. 2, Feb. 2003.

7. Mungantiwar A., et al., Evaluation of Efficacy and Safety of Tranexamic acid plus Mefenamic acid tablets versus Ethamsylate tablets in the treatment of Menorrhagia, Obst & Gynae, Vol. VIII No. 2, Feb. 2003.
8. Mungantiwar A., et al Bioequivalence study of Clopidogrel Indian Practitioner, March 2009, Vol 62. No. 3 141-146.
9. Mungantiwar A., et al Bioequivalence study of Carvedilol, Indian Practitioner, July 2009, Vol 62. No. 7 413-417.
10. Amol K C, Ashish A M and Meena C., A comparative, Bioequivalence study to evaluate the safety and pharmacokinetic profile of single dose Cinacalcet Hydrochloride Tablets in healthy, adult, human subjects under fed conditions. Annals of Biological Research. 2011; 2 (3): 35-50.
11. Amol K Choulwar, Ashish A Mungantiwar, Meena Chintamaneni. Comparison of Efficacy And Safety of Cinacalcet Versus Calcitriol In Patients of Secondary Hyperparathyroidism In Indian Population 'Journal of Pharmacy Research; Vol.5 Issue 1.January 2012.
12. A comparative, Bioequivalence study to evaluate the safety and pharmacokinetic profile of single dose Ivabradine 7.5mg Tablets in healthy, adult, human subjects under fasting conditions'. Communicated in Research Journal of Pharmacy and Technology. (Accepted).
13. Rajeev Nerurkar, Ashish Mungantiwar et. al., Cefixime with enhanced solubility, a better option in treatment of upper respiratory tract infection: A randomized controlled clinical study. Int. J. Res Med. 2013; 2(4); 95 – 99.
14. Arvind Vaish, Ashish Mungantiwar et. al., Cefixime with enhanced solubility, a better alternative in management of Typhoid fever: A randomized controlled clinical study. Am.J.PharmTech Res.2014; 4(2).
15. Prerana N. Shah, Vaibhao Dongre, Vijay Patil, Sarla Pandya, Ashish A Mungantiwar, Amol Choulwar Comparison of post-operative ICU sedation between dexmedetomidine and propofol in Indian population., Indian journal of critical care medicine, vol. 18 issue 5, 2014, 291-296.
16. Mungantiwar A. A., Chari S.V., Mayekar Rahul, et. al., An open comparative, Randomized, parallel, post marketing multicentric trial to compare the safety and efficacy of formula A (Ofloxacin + Ornidazole + Terbinafine + Hydrochloride + Clobetasol Propionate) versus Formula B (Clotrimazole + Beclometasone

Dipropionate + Neomycin sulphate), Formula C (Clotrimazole+ Beclometasone Dipropionate + Neomycin Sulphate) and Formula D (Clotrimazole + Beclometasone Dipropionate + Neomycin Sulphate) in the treatment of Patients with vaginitis. Indian medical gazette 2014 Aug; 148 (8): 288-296.

- **Book**

1. Mungantiwar A., "Immunomodulation: Therapeutic Strategy through Ayurveda" in Scientific Basis of Ayurvedic therapies, Ed. Dr. Mishra, CRC press, Washington, pg 63-81, 2004.

- **Patent**

1. Granted patent for "New improved dry powder inhaler" device, Patent no. 209920, Application no. 94/MUM/2006.
2. Granted patent for composition containing combination of proton pump inhibitor with modified release Domperidone, Patent No. 1N248777.
3. Patent applied for "Stable cefixime Formulation with Improved Bioavailability" has been filed with Mumbai Patent office on Aug 05, 2013. Patent Application no. 2570/MUM/2013.

- **Design Registration**

1. Granted design registration for new improved dry powder inhaler device.

- **Conference**

International

1. Presented a paper at Eastern Region IUATLD at Manila, Philippines, March 2001.
2. Attended Cphi, Tokyo, Japan, April 2002.
3. Attended Cphi World wide, Paris, October 2002.
4. Attended World Congress IUATLD, Montreal, Canada, November 2002.
5. Attended Cphi World wide, Brussels, Belgium, December 2004.
6. Invited as a speaker for Tuberculosis conference in Moscow, October 2005.
7. Invited as a speaker for MDR-Tuberculosis conference in Moscow, June 2006.
8. Invited as a speaker for "TB-HIV Double Trouble" in Moscow, June 2007.

9. Attended a close meeting with WHO assessors with Prequalification team in Copenhagen, Denmark, May 2007.
10. Attended seminar on Dissolution testing and Bioavailability and Bioequivalence studies, Informa Science, Berlin, Germany, November 2007.
11. Attended conference on Respiratory Drug Delivery, May 2009, Lisbon, Portugal.
12. Attended conference on inhalation conference, London, September 2010.
13. Attended CPW World Wide, Paris, October 2010.
14. Attended Conference on Canadian LCMS group Montreal, Canada, April 2011.
15. Attended Conference on Canadian LCMS group, LA, US March 2013.
16. Attended Meeting on Pre-Application Advice at MHRA,UK, London, 07th May 2015

- **Conference**

- National**

1. Attended workshop on Clinical Trial and Biostatistics conducted by Indian Society of Clinical Pharmacology and Therapeutics, September 1998.
2. Attended seminar-cum-workshop on Good Clinical Practice conducted by Express Pharma Pulse Seminar June 2001.
3. Attended seminar on Schedule Y- The New Look conducted by Indian drug Manufacturers Association, August 2005.
4. Attended seminar on BA/ BE-the Lifeline of Pharmaceuticals conducted by Indian Drug Manufacturers Association, March 2006.
5. Attended workshop on Good Laboratory Practice, Pharma Edge Centre (I) Ltd. March 2007.
6. Attended workshop on Auditing B.A.B.E conducted by Pinnacle Health Care, April 2007.
7. Attended workshop on Pharmacovigilance conducted by Pinnacle Health Care, December 2007.
8. Attended seminar on Fundamentals of Good Clinical Practice, April 2008.
9. Attended workshop on Good Laboratory Practice conducted by Pharma Edge Centre (I) Ltd., April 2009.
10. Attended seminar on Advanced Good Clinical Practice, April 2009.
11. Attended Conference on IPA-EDQM- IPC Technical Conference, January 2010.

12. Attended conference on Applied Pharmaceutical Analysis- India, February 2010.
13. Attended conference on fixed dose combination by IDMA on 26 April 2014.
14. Attended Conference on 5th Biosimilar conference at Kohinóor Hotel Mumbai on 10 September 2014.
15. Invited as a speaker for Evolving trends in Clinical Research on 20th February 2016 at Shri C.B. Patel Research centre for Chemistry and Biological science, Mumbai
16. Attended Meeting on "Fixed Dose combination Product –Infectious Diseases"- Delhi on 06th March 2017.

- **Organising Committee Member in Conference**

1. Committee Member in Controlled Release Society – Indian Chapter, Conference held on Feb. 2004, Mumbai.
2. Committee Member in Controlled Release Society – Indian Chapter, Conference held on Feb. 2005, Mumbai.

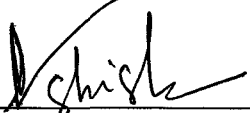
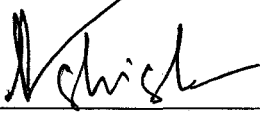
- **Presentation**

International

1. Mungantiwar A., Bioequivalence study of four-drug anti-TB product through urine excretion study, at Eastern Region International Union of Tubercle and Lung Disease, Manila, 2001.
2. Invited as a speaker for Tuberculosis conference in Moscow, October 2005.
3. Invited as a speaker for MDR-Tuberculosis conference in Moscow, June 2006.
4. Invited as a speaker for "TB-HIV Double Trouble" in Moscow, June 2007.
5. Invited as Speaker on "Quality of Anti TB Med" Moscow, October 2010.

- **Guide for Ph. D Students.**

Signature Of Employee

Initial	Full Signature	Date
		07/03/17

STATEMENT OF INVESTIGATORS

Study Title: Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

The study was conducted in accordance with the protocol and comply with all requirements regarding the obligations of investigators and Guideline on the investigation of Bioequivalence, 2010; Directive 2001/20/EC, national and ICH 'Guideline for Good Clinical Practice', Schedule Y of Drug and Cosmetic Act of India and in accordance with Indian GCP, European guidelines (EMA) and Declaration of Helsinki (2013).

We the undersigned have read this report and confirm that to the best of our knowledge it accurately describes the conduct and results of the study.

Mr. Satyendra Varma, CRA, Report Author

Date _____

Dr. Rajendra Sonde, Principal Investigator

Date _____

Dr. Mandar Mote, Head Bioanalytical

Date _____

Mr. Pankaj Bhangale, Biostatistician

Date _____

Dr. Ashish Mungantiwar, Study Director

Date _____

**Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road,
Shanti Nagar, Andheri (East),
Mumbai – 400 093,
India**

APPENDIX 16.1.6

LISTING OF SUBJECTS RECEIVING TEST DRUG/ INVESTIGATIONAL PRODUCT FROM SPECIFIC BATCHES WHERE MORE THAN ONE BATCHES WERE USED

(Not Applicable)

APPENDIX 16.1.7

RANDOMIZATION SCHEME AND CODES

RANDOMIZATION SCHEDULE

Study No./Protocol No: BEQ-2321-LEVT-2017

Study Title:

Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design:

An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

Total No. of Subjects: 30

Formulation Code:

i) Test Formulation (T) : Levothyroxine Sodium Tablets 200 mcg
(Macleods Pharmaceuticals Limited, India)

ii) Reference Formulation (R) : Euthyrox® (levothyroxine sodium) Tablets 200 mcg
(Merck B.V., Schiphol-Rijk, Netherlands)

Prepared by Biostatistician:

Mr. Pankaj B.

(Signature/Date)

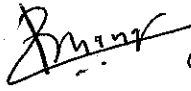
The SAS System
RANDOMIZATION SCHEDULE FOR BEQ-2321-LEVT-2017 STUDY
SUBJECT SAMPLE SIZE 30
Seed No.: 23212017

16:00 Monday, April 2, 2018 1

SUBJECT ID	BLOCK	SEQ	PERIOD 1	PERIOD 2
01	4	RT	R	T
02	4	RT	R	T
03	4	TR	T	R
04	4	TR	T	R
05	4	TR	T	R
06	4	RT	R	T
07	1	TR	T	R
08	1	RT	R	T
09	1	TR	T	R
10	1	RT	R	T
11	1	TR	T	R
12	1	RT	R	T
13	2	TR	T	R
14	2	TR	T	R
15	2	TR	T	R
16	2	RT	R	T
17	2	RT	R	T
18	2	RT	R	T
19	5	RT	R	T
20	5	RT	R	T
21	5	TR	T	R
22	5	RT	R	T
23	5	TR	T	R
24	5	TR	T	R
25	3	RT	R	T
26	3	TR	T	R
27	3	RT	R	T
28	3	TR	T	R
29	3	TR	T	R
30	3	RT	R	T

SAS Version Used: Version 9.4

Prepared By Biostatistician: Mr. Pankaj B.

(Signature/Date)  02/04/18

QUALITY ASSURANCE STATEMENT

Study No.: BEQ-2321-LEVT-2017

Study Title: Three Tablets as Single dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets 200 mcg (Macleods Pharmaceuticals Limited, India) with Three Tablets as Single dose of Euthyrox® (levothyroxine sodium) Tablets 200 mcg (Merck B.V., Schiphol-Rijk, Netherlands) in healthy adult, human subjects.

Study Design: An open label, balanced, analyst blind, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 30 healthy, adult, human subjects under fasting condition.

The conduct of this study has been subjected to periodic audits and the Quality Assurance (QA) has audited this report. The dates of audits are given below:

Clinical Phase:

Date of Audit	Audit Activity	Phase of Audit	Date of Report to Management
03 rd April 2018– 04 th April 2018	Period-1 Dispensing, Dosing, Blood Sample Collection, separation and storage, vitals And Subject questionnaire, Meal and ICFs.	In Process	09 th May 2018
08 th May 2018 – 09 th May 2018	Period-2 Dispensing, Dosing, Blood Sample Collection, separation and storage, vitals And Subject questionnaire and Meal.	In Process	08 th June 2018
02 nd July 2018– 05 th July 2018	Study Master File, Report & Appendices, Case record forms, Raw Data, Logbooks.	Retrospective	13 th July 2018

Pharmacokinetic and Statistics:

Date of Audit	Audit Activity	Phase of Audit	Date of Report to Management
10 th July 2018	Pharmacokinetic and statistics raw data and its part of clinical report.	Retrospective	13 th July 2018

Final Report:

Date of Audit	Audit Activity	Phase of Audit	Date of Report to Management
10 th July 2018	Clinical Report and its Appendices.	Retrospective	13 th July 2018

Quality Assurance reviews the documents to confirm to adherence to the protocol and the standard operating procedure (SOP). Refer appendix 16.1.10.

This report accurately describes the methods and procedures used in the study. There was no significant deviation from the applicable international, national and ICH 'Guideline for Good Clinical Practice (GCP)', 'Principles of Good Laboratory Practice (GLP)' and in accordance with European guidelines (EMA) which affected the quality or integrity of the study.

~~1000~~ 1000

Mr. Khurshid Shaikh
Clinical – Quality Assurance

13167/2018

Date _____

11/11/2020

Dr. Sagar Pawar
Head – Quality Assurance

13/08/2018

Date _____

**Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road,
Shanti Nagar, Andheri (East),
Mumbai – 400 093,
India**

Macleods Pharmaceuticals Limited
Bioequivalence Department
 R and D II, Plot No 95, Opposite Suncity Hotel (MDC), Andheri (East) Mumbai



Actual Time Point of Blood Collection (Hrs.)

Study No: BEQ-2321-LEVT-2017, PERIOD: I

Product: Levothyroxine

Sub. No.	Time Point (hrs)																							
	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
01	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.52	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
02	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
03	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
04	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
05	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.02	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
06	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
07	-0.50	-0.25	-0.03	0.50	1.02	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
08	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.53	5.00	5.50	6.00	8.00	10.00	12.02	18.00	24.00	30.00	36.00	48.00	72.00
09	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
10	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
11	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
12	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
13	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.02	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
14	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
15	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
16	-0.50	-0.23	-0.03	0.50	1.00	1.50	2.02	2.50	3.00	3.50	4.03	4.52	5.00	5.50	6.00	8.02	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
17	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.03	4.50	5.00	5.52	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
18	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.02	2.50	3.02	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
19	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
20	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.02	3.50	4.00	4.50	5.02	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
21	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.02	5.50	6.00	8.00	10.02	12.00	18.00	24.00	30.00	36.00	48.00	72.00
22	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.52	5.03	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
23	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.02	2.50	3.00	3.52	4.02	4.57	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
24	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.52	4.02	4.52	5.02	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
25	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.02	4.52	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
26	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.53	5.03	5.50	6.00	8.00	10.00	12.00	18.00	24.02	30.00	36.02	48.00	72.00
27	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.53	5.02	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
28	-0.50	-0.25	-0.03	0.50	1.02	1.50	2.00	2.50	3.00	3.50	4.00	4.60	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
29	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.53	5.00	5.50	6.02	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00
30	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.53	5.02	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.02	48.00	72.00

Prepared By:

Date: 18/06/18

Checked By:

Date: 18/06/18

Verified By:

Date: 18/06/18

18/06/18



Macleods Pharmaceuticals Limited
Bioequivalence Department
 R and D II, Plot No 95, Opposite Suncity Hotel. (MIDC), Andheri (East) Mumbai

Actual Time Point of Blood Collection (Hrs.)

Study No: BEQ-2321-LEVT-2017, PERIOD: II

Product: Levothyroxine

Sub. No.	Time Point (hrs)																							
	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
01	-0.48	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.52	5.00	5.52	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
02	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
03	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
04	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
05	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
06	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.52	5.00	5.50	6.03	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
07	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.02	36.00	48.00	72.00
08	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
09	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.02	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
10	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.03	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
11	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
12	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
13	-0.50	-0.23	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.02	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
14	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
15	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
16	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
17	-0.50	-0.25	-0.01	0.50	1.00	1.50	2.00	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
18	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
19	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.02	72.00
20	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
21	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
22	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.03	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
23	-0.50	-0.25	-0.01	0.50	1.00	1.53	2.00	2.53	3.02	3.50	4.00	4.55	5.00	5.57	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
24	-0.50	-0.25	-0.01	0.50	1.00	1.53	2.00	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
25	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.02	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
26	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.00	2.52	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.03	36.02	48.02	72.00
27	-0.50	-0.25	-0.03	0.50	1.02	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.02	10.00	12.00	18.00	24.00	30.02	36.00	48.02	72.00
28	-0.50	-0.25	-0.03	0.50	1.00	1.50	2.02	2.50	3.00	3.50	4.00	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.02	24.00	30.00	36.00	48.00	72.00
29	-0.50	-0.25	-0.03	0.50	1.00	1.52	2.00	2.50	3.07	3.52	4.02	4.60	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
30	-0.50	-0.25	-0.01	0.50	1.05	1.50	2.07	2.50	3.00	3.50	4.02	4.50	5.00	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00

Prepared By:

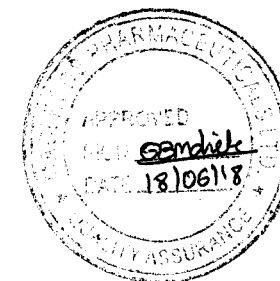
Date: 18/06/18

Checked By:

Date: 18/06/18

Verified By:

Date: 18/06/18



Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition

Obs	subject	seq	form	period	Cmax	Tmax	AUC72
1	1	RT	R	1	72.64	2.00	2722.3341
2	1	RT	T	2	61.78	3.00	2348.0069
3	2	RT	R	1	38.71	5.50	1909.0000
4	2	RT	T	2	45.47	3.00	1311.9150
5	3	TR	T	1	47.64	1.50	1938.2175
6	3	TR	R	2	59.24	3.00	2252.9100
7	4	TR	T	1	37.24	3.50	1482.0825
8	4	TR	R	2	66.07	4.00	2454.6696
9	5	TR	T	1	68.76	4.50	2676.1801
10	5	TR	R	2	76.76	4.50	3085.3950
11	6	RT	R	1	57.95	2.50	2460.2052
12	6	RT	T	2	48.89	4.52	2041.4834
13	7	TR	T	1	60.49	2.50	2461.8940
14	7	TR	R	2	72.63	2.00	2706.6762
15	8	RT	R	1	64.25	2.50	2866.9023
16	8	RT	T	2	60.84	2.00	2598.5725
17	9	TR	T	1	62.35	2.00	2273.9212
18	9	TR	R	2	83.76	4.00	3717.2454
19	10	RT	R	1	80.81	4.50	3323.3650
20	10	RT	T	2	63.76	4.50	2270.3728
21	11	TR	T	1	53.38	4.00	2157.0338
22	11	TR	R	2	57.53	3.50	1948.1900
23	12	RT	R	1	68.66	2.50	2350.5325
24	12	RT	T	2	70.01	2.50	2403.7250
25	13	TR	T	1	82.37	4.50	2962.8033
26	13	TR	R	2	115.49	4.00	4067.2396
27	14	TR	T	1	56.05	4.50	2109.5209
28	14	TR	R	2	66.63	4.50	2586.3425
29	15	TR	T	1	62.55	4.00	2702.9075
30	15	TR	R	2	67.46	5.50	3232.8475
31	16	RT	R	1	69.91	4.52	2632.0583
32	16	RT	T	2	55.22	1.50	1933.5750
33	17	RT	R	1	72.67	1.50	3006.2731
34	17	RT	T	2	69.12	4.00	2734.8985

SAS Version Used: Version 9.4

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition

Obs	subject	seq	form	period	Cmax	Tmax	AUC72
35	18	RT	R	1	57.05	1.50	1768.7318
36	18	RT	T	2	44.59	3.50	1876.5175
37	19	RT	R	1	66.95	3.00	2605.9075
38	19	RT	T	2	53.86	4.50	2286.5288
39	20	RT	R	1	80.90	3.50	3060.2705
40	20	RT	T	2	69.34	2.50	2813.0645
41	21	TR	T	1	56.31	4.50	1944.7120
42	21	TR	R	2	64.91	5.00	2781.9275
43	22	RT	R	1	59.71	4.52	2403.0682
44	22	RT	T	2	64.42	2.50	1824.1391
45	23	TR	T	1	57.40	4.57	2311.8996
46	23	TR	R	2	66.50	2.00	1865.8722
47	24	TR	T	1	54.79	3.52	2531.0661
48	24	TR	R	2	62.81	3.50	2520.8802
49	25	RT	R	1	61.19	4.52	2213.8496
50	25	RT	T	2	50.94	4.50	2226.8556
51	26	TR	T	1	56.51	2.50	1751.5858
52	26	TR	R	2	67.78	2.52	2359.6414
53	27	RT	R	1	96.90	1.52	3762.5491
54	27	RT	T	2	80.62	1.50	2745.7423
55	28	TR	T	1	44.87	2.50	1634.9526
56	28	TR	R	2	49.88	4.50	1718.7516
57	29	TR	T	1	80.90	4.53	3050.2654
58	29	TR	R	2	85.46	5.00	3022.6380
59	30	RT	R	1	78.19	2.50	2749.0101
60	30	RT	T	2	71.70	3.00	2869.3482

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
Ratio Analysis

Obs	subject	seq	Ratio Cmax (T/R)(%)	Ratio AUC72 (T/R)(%)
1	1	RT	85.05	86.25
2	2	RT	117.46	68.72
3	3	TR	80.42	86.03
4	4	TR	56.36	60.38
5	5	TR	89.58	86.74
6	6	RT	84.37	82.98
7	7	TR	83.29	90.96
8	8	RT	94.69	90.64
9	9	TR	74.44	61.17
10	10	RT	78.90	68.32
11	11	TR	92.79	110.72
12	12	RT	101.97	102.26
13	13	TR	71.32	72.85
14	14	TR	84.12	81.56
15	15	TR	92.72	83.61
16	16	RT	78.99	73.46
17	17	RT	95.11	90.97
18	18	RT	78.16	106.09
19	19	RT	80.45	87.74
20	20	RT	85.71	91.92
21	21	TR	86.75	69.91
22	22	RT	107.89	75.91
23	23	TR	86.32	123.90
24	24	TR	87.23	100.40
25	25	RT	83.25	100.59
26	26	TR	83.37	74.23
27	27	RT	83.20	72.98
28	28	TR	89.96	95.12
29	29	TR	94.66	100.91
30	30	RT	91.70	104.38

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
Ratio Analysis

18:55 Tuesday, June 26, 2018 4

Bioavailability of Cmax (%)	Bioavailability of AUC72 (%)
85.77	85.18

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
SUMMARY STATISTICS - FORMULATION

The MEANS Procedure

form	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
R	30	Cmax	concentration	30	69.646667	67.205000	14.276549	20.498539	38.710000	115.490000
		AUC72		30	2671.842788	2618.982900	582.826467	21.813651	1718.751600	4067.239600
		Tmax	time	30	3.470000	3.500000	1.238394	35.688599	1.500000	5.500000
T	30	Cmax	concentration	30	59.739000	58.945000	11.184815	18.722802	37.240000	82.370000
		AUC72		30	2275.792908	2280.225000	445.738194	19.586061	1311.915000	3050.265350
		Tmax	time	30	3.338000	3.500000	1.074136	32.179031	1.500000	4.570000

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
SUMMARY STATISTICS - SEQUENCE

The MEANS Procedure

seq	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	30	Cmax	concentration	30	64.56833	64.33500	12.52402	19.39654	38.71000	96.90000
		AUC72		30	2470.627	2431.965	506.6239	20.50589	1311.915	3762.549
		Tmax	time	30	3.120000	3.000000	1.181758	37.87686	1.500000	5.500000
TR	30	Cmax	concentration	30	64.81733	62.68000	14.92682	23.02906	37.24000	115.4900
		AUC72		30	2477.009	2458.282	602.3392	24.31720	1482.083	4067.240
		Tmax	time	30	3.688000	4.000000	1.064413	28.86153	1.500000	5.500000

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
SUMMARY STATISTICS - PERIOD

The MEANS Procedure

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
1	30	Cmax	concentration	30	63.60333	61.77000	13.44905	21.14519	37.24000	96.90000
		AUC72		30	2460.770	2461.050	524.7885	21.32619	1482.083	3762.549
		Tmax	time	30	3.323333	3.500000	1.197144	36.02239	1.500000	5.500000
2	30	Cmax	concentration	30	65.78233	65.49000	14.01287	21.30188	44.59000	115.4900
		AUC72		30	2486.866	2429.197	586.2988	23.57581	1311.915	4067.240
		Tmax	time	30	3.484667	3.500000	1.117938	32.08162	1.500000	5.500000

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
SUMMARY STATISTICS - SEQUENCE/FORMULATION

The MEANS Procedure

form=R

seq	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	15	Cmax	concentration	15	68.43267	68.66000	13.42503	19.61787	38.71000	96.90000
		AUC72		15	2655.604	2632.058	517.7517	19.49657	1768.732	3762.549
		Tmax	time	15	3.105333	2.500000	1.314892	42.34302	1.500000	5.500000
TR	15	Cmax	concentration	15	70.86067	66.63000	15.45344	21.80820	49.88000	115.4900
		AUC72		15	2688.082	2586.343	659.5490	24.53605	1718.752	4067.240
		Tmax	time	15	3.834667	4.000000	1.078371	28.12163	2.000000	5.500000

form=T

seq	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	15	Cmax	concentration	15	60.70400	61.78000	10.61485	17.48625	44.59000	80.62000
		AUC72		15	2285.650	2286.529	436.2123	19.08483	1311.915	2869.348
		Tmax	time	15	3.134667	3.000000	1.078636	34.40991	1.500000	4.520000
TR	15	Cmax	concentration	15	58.77400	56.51000	12.01937	20.45015	37.24000	82.37000
		AUC72		15	2265.936	2273.921	470.1780	20.74983	1482.083	3050.265
		Tmax	time	15	3.541333	4.000000	1.066723	30.12207	1.500000	4.570000

Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
SUMMARY STATISTICS - PERIOD/FORMULATION

The MEANS Procedure

form=R

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
1	15	Cmax	concentration	15	68.43267	68.66000	13.42503	19.61787	38.71000	96.90000
		AUC72		15	2655.604	2632.058	517.7517	19.49657	1768.732	3762.549
		Tmax	time	15	3.105333	2.500000	1.314892	42.34302	1.500000	5.500000
2	15	Cmax	concentration	15	70.86067	66.63000	15.45344	21.80820	49.88000	115.4900
		AUC72		15	2688.082	2586.343	659.5490	24.53605	1718.752	4067.240
		Tmax	time	15	3.834667	4.000000	1.078371	28.12163	2.000000	5.500000

form=T

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
1	15	Cmax	concentration	15	58.77400	56.51000	12.01937	20.45015	37.24000	82.37000
		AUC72		15	2265.936	2273.921	470.1780	20.74983	1482.083	3050.265
		Tmax	time	15	3.541333	4.000000	1.066723	30.12207	1.500000	4.570000
2	15	Cmax	concentration	15	60.70400	61.78000	10.61485	17.48625	44.59000	80.62000
		AUC72		15	2285.650	2286.529	436.2123	19.08483	1311.915	2869.348
		Tmax	time	15	3.134667	3.000000	1.078636	34.40991	1.500000	4.520000

The SAS System
Protocol No: BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed Cmax

18:55 Tuesday, June 26, 2018 10

The GLM Procedure

Class Level Information		
Class	Levels	Values
form	2	R T
period	2	1 2
seq	2	RT TR
subject	30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Number of Observations Read	60
Number of Observations Used	60

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed Cmax

18:55 Tuesday, June 26, 2018 11

The GLM Procedure

Dependent Variable: LCmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	31	2.32581357	0.07502624	9.16	<.0001
Error	28	0.22943614	0.00819415		
Corrected Total	59	2.55524971			

R-Square	Coeff Var	Root MSE	LCmax Mean
0.910210	2.182094	0.090522	4.148379

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00001501	0.00001501	0.00	0.9662
subject(seq)	28	1.96354882	0.07012674	8.56	<.0001
period	1	0.01958400	0.01958400	2.39	0.1333
form	1	0.34266573	0.34266573	41.82	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00001501	0.00001501	0.00	0.9662
subject(seq)	28	1.96354882	0.07012674	8.56	<.0001
period	1	0.01958400	0.01958400	2.39	0.1333
form	1	0.34266573	0.34266573	41.82	<.0001

Tests of Hypotheses Using the Type III MS for subject(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00001501	0.00001501	0.00	0.9884

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed Cmax

18:55 Tuesday, June 26, 2018 12

The GLM Procedure
Least Squares Means

form	LCmax LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2
			Pr > t	Pr > t
R	4.22395121	0.01652690	<.0001	<.0001
T	4.07280763	0.01652690	<.0001	

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed Cmax

18:55 Tuesday, June 26, 2018 13

The GLM Procedure

Dependent Variable: LCmax

Parameter	Estimate	Standard Error	t Value	Pr > t
R vs T	-0.15114358	0.02337256	-6.47	<.0001

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed AUC72

18:55 Tuesday, June 26, 2018 14

The GLM Procedure

Class Level Information		
Class	Levels	Values
form	2	R T
period	2	1 2
seq	2	RT TR
subject	30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Number of Observations Read	60
Number of Observations Used	60

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed AUC72

18:55 Tuesday, June 26, 2018 15

The GLM Procedure

Dependent Variable: LAUC72

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	31	2.55191343	0.08231979	5.05	<.0001
Error	28	0.45664436	0.01630873		
Corrected Total	59	3.00855779			

R-Square	Coeff Var	Root MSE	LAUC72 Mean
0.848218	1.639593	0.127706	7.788861

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00023602	0.00023602	0.01	0.9051
subject(seq)	28	2.17861696	0.07780775	4.77	<.0001
period	1	0.00061816	0.00061816	0.04	0.8470
form	1	0.37244229	0.37244229	22.84	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00023602	0.00023602	0.01	0.9051
subject(seq)	28	2.17861696	0.07780775	4.77	<.0001
period	1	0.00061816	0.00061816	0.04	0.8470
form	1	0.37244229	0.37244229	22.84	<.0001

Tests of Hypotheses Using the Type III MS for subject(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00023602	0.00023602	0.00	0.9565

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed AUC72

18:55 Tuesday, June 26, 2018 16

The GLM Procedure
Least Squares Means

form	LAUC72 LSMEAN	Standard Error	H0:LSMEAN=0	H0:LSMean1=LSMean2
			Pr > t	Pr > t
R	7.86764820	0.02331575	<.0001	<.0001
T	7.71007445	0.02331575	<.0001	

SAS Version Used: Version 9.4

The SAS System
Protocol No:BEQ-2321-LEVT-2017
Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
ANOVA for log transformed AUC72

18:55 Tuesday, June 26, 2018 17

The GLM Procedure

Dependent Variable: LAUC72

Parameter	Estimate	Standard Error	t Value	Pr > t
R vs T	-0.15757375	0.03297345	-4.78	<.0001

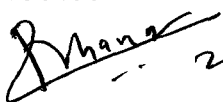
Protocol No:BEQ-2321-LEVT-2017

Statistical Data Processing of Baseline-Corrected Levothyroxine Under Fasting Condition
90% C.I Equivalent to Schuirmann's Two One Sided Test

NAME	Gmref	GMtest	n1	n2	DF	mse	diff	Ratio	Intra_CV	Power	Lower	Upper	Bioequivalence
LCmax	68.303	58.722	15	15	28	0.008194	-9.581	85.97	9.07	100.00	82.62	89.46	Yes
LAUC72	2611.417	2230.708	15	15	28	0.016309	-380.708	85.42	12.82	100.00	80.76	90.35	Yes

SAS Version Used: Version 9.4

Prepared By Biostatistician:

(Signature/Date)  26/06/18

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

STANDARD OPERATING PROCEDURE**ESTIMATION OF PHARMACOKINETIC PARAMETERS**

Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-002/06	BEQ/ST/SOP-002/07	1 of 7

SITE OF DISTRIBUTION: Pharmacokinetic and Statistics, Quality Assurance and Head – Bioequivalence

Issue Date	Effective Date	Review Date
01/08/2016	02/08/2016	31/07/2019

REVISION CARD

SR. NO.	REVISION NO.	ISSUED DATE	REASON (S) FOR REVISION	REVISION DATE
1.	00	15/09/2005	New SOP	27/08/2007
2.	01	27/08/2007	1. Modification in title of SOP 2. Incorporation of format number 3. Separation of annexures	08/03/2008
3.	02	08/03/2008	1. Modification in Procedure of Treatment of Missing Values	18/06/2009
4.	03	18/06/2009	1. Incorporation of SAS Program for estimation of Pk parameters using second bestfit regression procedure 2. Modification in procedure of BLQ's occurred in initial as well as terminal portion	08/10/2009
5.	04	08/10/2009	1. Incorporation of SAS program for format conversion 2. Remove section 4.2.8.3	11/06/2010
6.	05	11/06/2010	1. Inclusion of the actual time point of blood collection	28/06/2011
7.	06	28/06/2011	1. Modification in SAS programs: Incorporate Pk parameters Ke_first, Ke_last and npoints. 2. Upgrade SAS® version form 9.1.3 to 9.2	01/08/2016
8.	07	01/08/2016	1. Modification in procedure & SAS Programs 2. Remove section 4.2.8.1 & 6.2 3. Remove annexure no 05 4. Renumbering for annexure numbers	N/AP

	Prepared By	Checked By	Approved By	Authorised By
Design. - Dept.	Biostatistician - ST	Biostatistician - ST	Head - QA	Head - Bioequivalence
Sign and Date	01/08/16	01/08/16	01/08/2016	01/08/16
Name	Mr. Sadashiv K.	Mr. Pankaj B.	Dr. Sagar P.	Dr. Ashish M.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-002/06	BEQ/ST/SOP-002/07	2 of 7

1. OBJECTIVE:

To lay down the procedure for estimation of pharmacokinetic parameters.

2. SCOPE:

This procedure is applicable to biostatistician and serves as a guideline for estimation of pharmacokinetic parameters.

3. RESPONSIBILITY:

Biostatistician and Quality Assurance staff.

4. PROCEDURE:**4.1 Definitions of pharmacokinetic parameters:**

4.1.1 C_{max} (Unit/mL): Maximum measured concentration.

C_{max} = Maximum of ($C_1, C_2, \dots, C_k$)

Where, C_1 : Concentration at first sampling time point.

C_2 : Concentration at second sampling time point.

C_k : Concentration at last sampling time point.

4.1.2 T_{max} (hrs): Sampling time at which C_{max} occurred.

4.1.3 AUC_{0-t} (Unit.hrs/mL): The area under the concentration versus time curve from time zero to the last measurable concentration at time t' , as calculated by the linear up-linear down trapezoidal method.

$$AUC_{0-tk} = \sum_{i=2}^k (C_{i-1} + C_i) \times (t_i - t_{i-1}) \times 0.5$$

Where, C_i : Concentration at i^{th} sampling time point.

tk : Time at which last quantifiable concentration occurred.

4.1.4 K_e (hrs^{-1}): Terminal disposition rate constant calculated as the slope of terminal portion of the natural log concentration-time curve multiplied by (-1). Minimum three non-zero concentration points in elimination phase required calculating K_e constant.

4.1.5 $AUC_{0-\infty}$ (Unit.hrs/mL): The area under the concentration versus time curve, from time zero to time infinity. $AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant (K_e).

$$AUC_{0-\infty} = AUC_{0-t} + CT/K_e$$

Where, CT is last quantifiable concentration in elimination phase.

4.1.6 T_{half} (hrs): Drug half-life = $\ln(2)/K_e$.

4.1.7 Res_area: Residual area = $(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}$.

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STANDARD OPERATING PROCEDURE		
ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-002/06	BEQ/ST/SOP-002/07	3 of 7

- 4.1.8 npoints: No. of time points of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
- 4.1.9 K_{e_first} (hrs): First time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
- 4.1.10 K_{e_last} (hrs): Last time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
- 4.2 **Calculation of pharmacokinetic parameters**
- 4.2.1 Obtain the subject sample concentration data from the bioanalytical department with the form 'Data Transfer Sheet' of SOP No. BEQ/GN/SOP-023, 'Data Handling and Analysis'.
- 4.2.2 Arrange the concentration data of the subjects according to the randomization i.e. each subject arrange with sequence, formulation, period and concentration results by time in excel worksheet. If study is conducted in multiple groups then group variable is added for calculation of the pharmacokinetic parameters.
- 4.2.3 For estimation of PK parameters, concentrations that are below level of quantification (BLQ) set to zero if they preceded quantifiable samples in the initial & terminal portion of the profile.
- 4.2.4 Treatment of missing values.
- 4.2.4.1 In case of missing value/Not Reported, calculation of pharmacokinetic parameters without considering the missing / Not Reported point.
- 4.2.4.2 Missing / Not Reported samples may also be due to the following reasons:
- Spillage of blood samples during centrifugation in clinical section report the sample as 'Missing'.
 - Subject not reported to the facility for ambulatory sample collection in clinical section report the sample as 'Missing'.
 - Spillage of samples during separation in clinical section report the sample as 'Missing'
 - Spillage of matrix or samples during analysis in analytical section then report the sample as 'Not Reported'.
 - Sample lost during analysis and insufficient sample is available for reanalysis then report the sample as 'Not Reported'.
 - The sample as 'Not Reported (NR)' treated as missing value.
- 4.2.5 Time Points Deviation
- 4.2.5.1 Pivotal bioequivalence study, consider the actual time point of blood collection in calculation of pharmacokinetic parameters.
- 4.2.5.2 Pilot bioequivalence study, consider time point deviations (more than 2 minutes) & similarly time point deviations (more than 1 hour) for ambulatory visits in calculation of pharmacokinetic parameters.

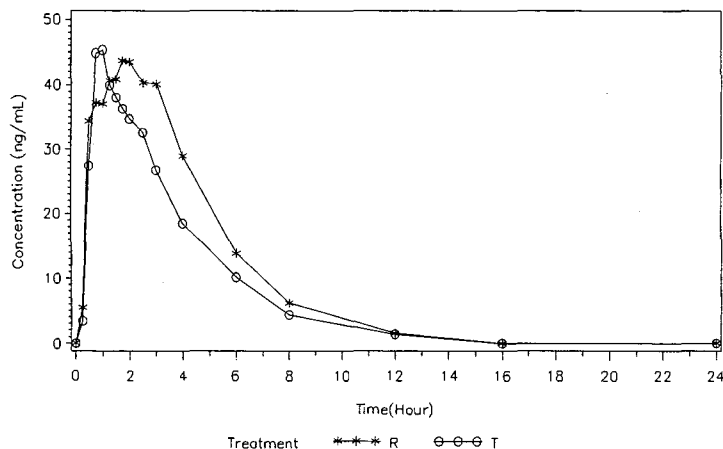
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STANDARD OPERATING PROCEDURE		
ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-002/06	BEQ/ST/SOP-002/07	4 of 7

- 4.2.6. Example of format of the data to generate vertical concentration data for calculation of the pharmacokinetic parameters shown in Annexure No. ANX/ST/SOP-002-01, 'Format of the Data Stored in Excel Worksheet to Generate Vertical Format Data'.
- 4.2.7. Transfer this data into SAS program 'Vertical Format Data' mention in the Annexure No. ANX/ST/SOP-002-02, 'SAS Program for Vertical Format Data'. And execute the program.
- 4.2.8. Export the subject concentration data from SAS to Excel and same data is created in pdf format after execution of SAS program as shown in Annexure No. ANX/ST/SOP-002-03, 'Vertical Format Concentration Data to Calculate the Pharmacokinetic Parameters'.
- 4.2.9. Take the printout of pdf format and get it approved from QA.
- 4.2.10. After receiving QA approval, to calculate the pharmacokinetic parameters. Execute the SAS program mention in the Annexure No. ANX/ST/SOP-002-04, 'SAS Program for Estimate Pharmacokinetic Parameters Using Bestfit Regression'.
- 4.2.11. If required for any of the subject(s), the drug half life computed by the 'SAS Program to Estimate Pharmacokinetic Parameters Using Bestfit Regression' is large and unrealistic, then follow the below procedure:
 - 4.2.11.1. Execute the SAS program mention in the Annexure No. ANX/ST/SOP-002-04, 'SAS Program for Estimate Pharmacokinetic Parameters Using Bestfit Regression' by omitting the data for the subject(s) with unrealistic drug half -life.
 - 4.2.11.2. Execute the SAS program mention in the Annexure No. ANX/ST/SOP-002-05, 'SAS Program for Estimate Pharmacokinetic Parameters Using Second Bestfit Regression' with the data of subject(s) with unrealistic drug half-life.
- 4.3. Graphical representation**
 - 4.3.1 Obtain the plot of concentration versus time profile for each individual subject. Each plot must include profile for all formulations given to that subject.
 - 4.3.2 Obtained the semi log plot of concentration versus time profile for each individual subject.
 - 4.3.3 Obtain a profile of the arithmetic mean over all subjects for each formulation and sampling time.
 - 4.3.4 Obtain the profile of the semi log plot of arithmetic mean over all subjects for each formulation.
 - 4.3.5 In case of missing value/Not Reported obtain the concentration time profile without considering the missing / Not Reported point. Refer SAS programs mention in SOP No. BEQ/ST/SOP-003 & SOP No. BEQ/ST/SOP-016

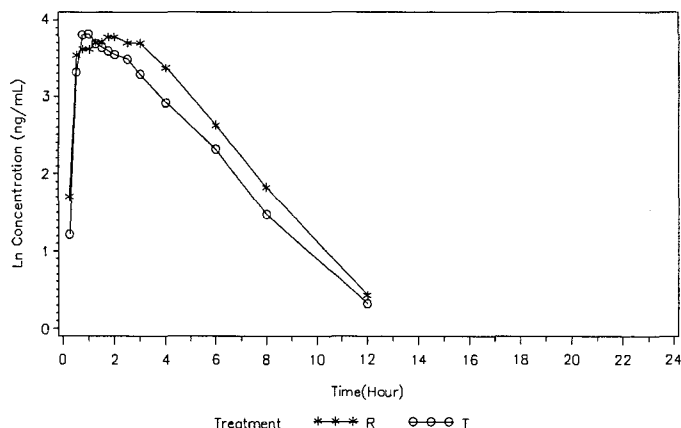
Example graph are shown below:

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STANDARD OPERATING PROCEDURE ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes BEQ/ST/SOP-002/06	SOP No.: BEQ/ST/SOP-002/07	Page No.: 5 of 7

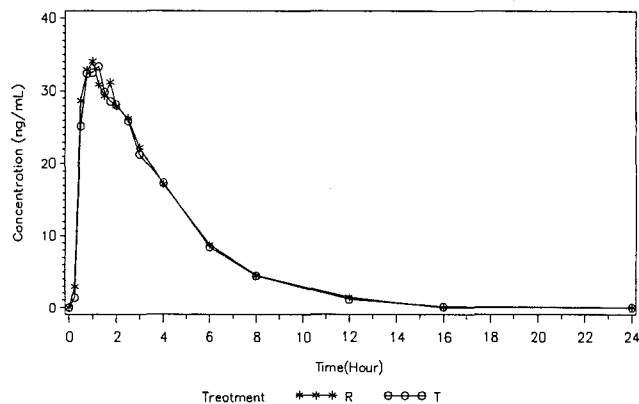
Comparative Linear Plot of Plasma Concentration (ng/mL) Vs Time (Hour)
Subject No.=3



Comparative Semi Log Plot of Plasma Concentration (ng/mL) Vs Time (Hour)
Subject No.=3

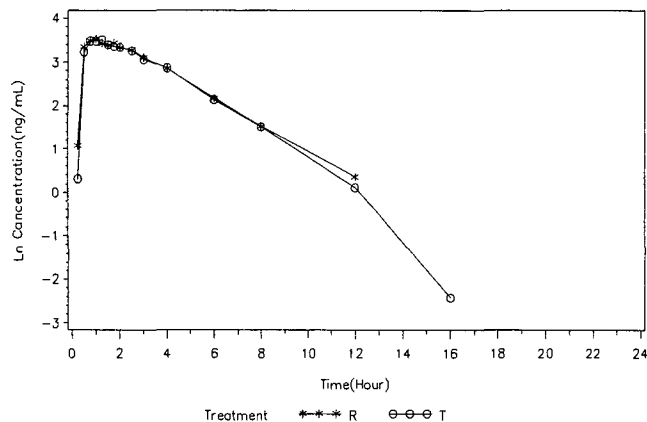


Comparative Linear Plot of Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=12)
subject=MEAN



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STANDARD OPERATING PROCEDURE ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes BEQ/ST/SOP-002/06	SOP No.: BEQ/ST/SOP-002/07	Page No.: 6 of 7

Comparative Semi Log Plot of Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=12)
subject=MEAN



5. ABBREVIATION (S):

- 5.1 AUC_{0-t} : Area Under Curve for time 0 to t
- 5.2 $AUC_{0-\infty}$: Area Under Curve for time 0 to infinity (∞)
- 5.3 BLQ : Bellow Limit of Quantification
- 5.4 BEQ : Bioequivalence
- 5.5 C_{max} : Maximum observed concentration
- 5.6 form : Formulation
- 5.7 hrs : Hours
- 5.8 K_e : Elimination Rate
- 5.9 mL : Milliliter
- 5.10 No. : Number
- 5.11 N/AP : Not Applicable
- 5.12 SAS : Statistical Analysis System
- 5.13 SOP : Standard Operating Procedure
- 5.14 ST : Statistics
- 5.15 Seq : Sequence
- 5.16 t_{half} : Terminal-half life
- 5.17 t_{max} : Sampling time at which C_{max} occurred
- 5.18 Res_area : Residual Area
- 5.19 QA : Quality Assurance.

6. REFERENCE (S):

- 6.1 BEQ/GN/SOP-023, 'Data Handling and Analysis'

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE ESTIMATION OF PHARMACOKINETIC PARAMETERS		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-002/06	BEQ/ST/SOP-002/07	7 of 7

7. ANNEXURE (S):

- 7.1 Annexure No. ANX/ST/SOP-002-01, 'Format of the Data Stored in Excel Worksheet to Generate Vertical Format Data'
- 7.2 Annexure No. ANX/ST/SOP-002-02, 'SAS Program for Vertical Format Data'
- 7.3 Annexure No. ANX/ST/SOP-002-03, 'Vertical Format Concentration Data to Calculate the Pharmacokinetic Parameters'
- 7.4 Annexure No. ANX/ST/SOP-002-04, 'SAS Program for Estimate Pharmacokinetic Parameters Using Bestfit Regression'
- 7.5 Annexure No. ANX/ST/SOP-002-05, 'SAS Program for Estimate Pharmacokinetic Parameters Using Second Bestfit Regression'

8 FORM (S): N/AP

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/ST/SOP-002/07

FORMAT OF THE DATA STORED IN EXCEL WORKSHEET TO GENERATE VERTICAL FORMAT DATA

Subject	Seq	Form	Period	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16
1	TR	T	1	0.00	0.00	0.12	0.29	0.39	0.51	0.72	1.21	1.18	1.42	2.89	1.60	1.06	0.82	0.42	0.13	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
2	TR	T	1	0.00	0.00	0.25	0.93	0.72	0.70	2.04	3.91	3.54	3.44	3.41	2.57	1.52	1.10	0.80	0.33	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
3	TR	T	1	0.00	0.09	0.44	0.66	0.81	0.69	0.86	1.11	1.77	3.33	3.01	1.44	0.68	0.52	0.41	0.14	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
4	TR	T	1	0.00	0.00	0.26	0.60	0.58	0.62	0.49	0.77	1.11	1.32	1.79	0.74	0.45	0.32	0.20	0.00	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
5	RT	R	1	0.00	0.16	0.54	0.71	0.67	0.67	0.71	1.50	2.23	1.88	1.61	1.59	0.64	0.42	0.35	0.13	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
6	RT	R	1	0.00	0.07	0.44	0.68	0.80	0.90	0.95	1.04	1.04	1.20	1.17	1.11	0.93	0.53	0.38	0.08	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
7	TR	T	1	0.00	0.00	0.57	1.16	1.35	2.60	5.02	4.31	2.60	2.21	1.78	1.07	0.64	0.41	0.28	0.15	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
8	RT	R	1	0.00	0.13	0.39	0.58	0.67	0.81	2.60	3.44	3.34	1.85	1.84	1.26	0.85	0.53	0.40	0.17	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
1	TR	R	2	0.00	0.09	0.33	0.44	0.32	0.42	0.66	0.50	0.56	0.80	1.22	1.86	1.03	0.59	0.42	0.26	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
2	TR	R	2	0.00	0.09	0.81	1.29	1.14	1.82	2.62	3.33	2.76	4.20	3.64	1.70	1.14	1.17	0.83	0.34	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
3	TR	R	2	0.00	0.33	0.76	1.64	3.36	3.25	3.58	2.28	1.82	1.36	1.11	0.72	0.39	0.40	0.25	0.12	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
4	TR	R	2	0.00	0.00	0.21	0.30	0.29	0.42	0.59	1.01	1.01	0.88	0.72	0.41	0.32	0.28	0.16	0.05	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
5	RT	T	2	0.00	0.20	0.66	0.73	0.87	1.37	1.44	1.69	1.63	1.43	1.11	0.62	0.36	0.29	0.23	0.06	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
6	RT	T	2	0.00	0.00	0.14	0.44	0.52	0.35	0.65	1.23	1.56	1.73	1.57	1.05	0.77	0.46	0.38	0.25	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
7	TR	R	2	0.00	0.09	0.79	1.18	1.44	1.58	2.39	2.98	1.81	1.35	1.36	1.48	1.32	0.48	0.32	0.19	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00
8	RT	T	2	0.00	0.09	0.48	0.84	0.56	1.04	1.57	2.98	3.32	2.47	1.96	1.11	0.70	0.50	0.45	0.17	0.00	0.25	0.50	0.75	1.00	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00	10.00	12.00	24.00

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-002/07

SAS PROGRAM FOR VERTICAL FORMAT DATA

```
Ods pdf File="D:\Vertical Format Data of -----.pdf";
Options ps=90 ls=100 PAGENO=1;
Title2 '      Protocol No: -----';
Title3 '      Vertical Format Concentration Data To Calculate The
Pharmacokinetic Parameters Of (Analyte Name)';
FOOTNOTE1 "      SAS Version Used: Version &sysver  ";
FOOTNOTE7 j=1 'ANX-ST-SOP-002-03      ';
FOOTNOTE8      '      ';
FOOTNOTE9      '      ';
Data original ;
input subject seq$  form$ period c1-c16 t1-t16;
format C1-C16 20.2 T1-T16 8.2;
datalines;
1      TR      T      1      0.00      0.00      0.12      0.29      0.39
      0.51      0.72      1.21      1.18      1.42      2.89      1.60      1.06
      0.82      0.42      0.13      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
2      TR      T      1      0.00      0.00      0.25      0.93      0.72
      0.70      2.04      3.91      3.54      3.44      3.41      2.57      1.52
      1.10      0.80      0.33      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
3      TR      T      1      0.00      0.09      0.44      0.66      0.81
      0.69      0.86      1.11      1.77      3.33      3.01      1.44      0.68
      0.52      0.41      0.14      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
4      TR      T      1      0.00      0.00      0.26      0.60      0.58
      0.62      0.49      0.77      1.11      1.32      1.79      0.74      0.45
      0.32      0.20      0.00      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
5      RT      R      1      0.00      0.16      0.54      0.71      0.67
      0.67      0.71      1.50      2.23      1.88      1.61      1.59      0.64
      0.42      0.35      0.13      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
6      RT      R      1      0.00      0.07      0.44      0.68      0.80
      0.90      0.95      1.04      1.04      1.20      1.17      1.11      0.93
      0.53      0.38      0.08      0.00      0.25      0.50      0.75      1.00
      1.50      2.00      2.50      3.00      3.50      4.00      6.00      8.00
      10.00      12.00      24.00
7      TR      T      1      0.00      0.00      0.57      1.16      1.35
      2.60      5.02      4.31      2.60      2.21      1.78      1.07      0.64
```

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-002/07

	0.41	0.28	0.15	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
8	RT	R	1	0.00	0.13	0.39	0.58	0.67
	0.81	2.60	3.44	3.34	1.85	1.84	1.26	0.85
	0.53	0.40	0.17	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
1	TR	R	2	0.00	0.09	0.33	0.44	0.32
	0.42	0.66	0.50	0.56	0.80	1.22	1.86	1.03
	0.59	0.42	0.26	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
2	TR	R	2	0.00	0.09	0.81	1.29	1.14
	1.82	2.62	3.33	2.76	4.20	3.64	1.70	1.14
	1.17	0.83	0.34	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
3	TR	R	2	0.00	0.33	0.76	1.64	3.36
	3.25	3.58	2.28	1.82	1.36	1.11	0.72	0.39
	0.40	0.25	0.12	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
4	TR	R	2	0.00	0.00	0.21	0.30	0.29
	0.42	0.59	1.01	1.01	0.88	0.72	0.41	0.32
	0.28	0.16	0.05	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
5	RT	T	2	0.00	0.20	0.66	0.73	0.87
	1.37	1.44	1.69	1.63	1.43	1.11	0.62	0.36
	0.29	0.23	0.06	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
6	RT	T	2	0.00	0.00	0.14	0.44	0.52
	0.35	0.65	1.23	1.56	1.73	1.57	1.05	0.77
	0.46	0.38	0.25	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
7	TR	R	2	0.00	0.09	0.79	1.18	1.44
	1.58	2.39	2.98	1.81	1.35	1.36	1.48	1.32
	0.48	0.32	0.19	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					
8	RT	T	2	0.00	0.09	0.48	0.84	0.56
	1.04	1.57	2.98	3.32	2.47	1.96	1.11	0.70
	0.50	0.45	0.17	0.00	0.25	0.50	0.75	1.00
	1.50	2.00	2.50	3.00	3.50	4.00	6.00	8.00
	10.00	12.00	24.00					

;

run;

proc sort data=original;

by subject form;

run;

ANX/ST/SOP-002-02

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-002/07

```
data converted;
  set original;
  array c{16} c1-c16 ;array t{16} t1-t16;
  do i=1 to 16;
    concentration=c{i};
    time=t(i);
    output;
  end;
  drop c1-c16 t1-t16 i;
run;
proc sort data=converted;
  by subject period;
run;
data inputdata;
set converted;
format concentration 20.2 Time 8.2;
if concentration=. then delete;
keep Subject seq form Period concentration Time;
run;
Proc datasets library=work nolist;
save inputdata;
Run;
proc print data=inputdata;
var Subject seq form Period concentration Time;
run;

ods pdf close;
```

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-002/07**VERTICAL FORMAT CONCENTRATION DATA TO CALCULATE THE PHARMACOKINETIC
PARAMETERS****Find attached vertical format concentration data in pdf format**

The SAS System
Protocol No: -----

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
1	1	TR	T	1	0.00	0.00
2	1	TR	T	1	0.00	0.25
3	1	TR	T	1	0.12	0.50
4	1	TR	T	1	0.29	0.75
5	1	TR	T	1	0.39	1.00
6	1	TR	T	1	0.51	1.50
7	1	TR	T	1	0.72	2.00
8	1	TR	T	1	1.21	2.50
9	1	TR	T	1	1.18	3.00
10	1	TR	T	1	1.42	3.50
11	1	TR	T	1	2.89	4.00
12	1	TR	T	1	1.60	6.00
13	1	TR	T	1	1.06	8.00
14	1	TR	T	1	0.82	10.00
15	1	TR	T	1	0.42	12.00
16	1	TR	T	1	0.13	24.00
17	1	TR	R	2	0.00	0.00
18	1	TR	R	2	0.09	0.25
19	1	TR	R	2	0.33	0.50
20	1	TR	R	2	0.44	0.75
21	1	TR	R	2	0.32	1.00
22	1	TR	R	2	0.42	1.50
23	1	TR	R	2	0.66	2.00
24	1	TR	R	2	0.50	2.50
25	1	TR	R	2	0.56	3.00
26	1	TR	R	2	0.80	3.50
27	1	TR	R	2	1.22	4.00
28	1	TR	R	2	1.86	6.00
29	1	TR	R	2	1.03	8.00
30	1	TR	R	2	0.59	10.00
31	1	TR	R	2	0.42	12.00
32	1	TR	R	2	0.26	24.00
33	2	TR	T	1	0.00	0.00

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

17:51 Friday, July 29, 2016 2

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
34	2	TR	T	1	0.00	0.25
35	2	TR	T	1	0.25	0.50
36	2	TR	T	1	0.93	0.75
37	2	TR	T	1	0.72	1.00
38	2	TR	T	1	0.70	1.50
39	2	TR	T	1	2.04	2.00
40	2	TR	T	1	3.91	2.50
41	2	TR	T	1	3.54	3.00
42	2	TR	T	1	3.44	3.50
43	2	TR	T	1	3.41	4.00
44	2	TR	T	1	2.57	6.00
45	2	TR	T	1	1.52	8.00
46	2	TR	T	1	1.10	10.00
47	2	TR	T	1	0.80	12.00
48	2	TR	T	1	0.33	24.00
49	2	TR	R	2	0.00	0.00
50	2	TR	R	2	0.09	0.25
51	2	TR	R	2	0.81	0.50
52	2	TR	R	2	1.29	0.75
53	2	TR	R	2	1.14	1.00
54	2	TR	R	2	1.82	1.50
55	2	TR	R	2	2.62	2.00
56	2	TR	R	2	3.33	2.50
57	2	TR	R	2	2.76	3.00
58	2	TR	R	2	4.20	3.50
59	2	TR	R	2	3.64	4.00
60	2	TR	R	2	1.70	6.00
61	2	TR	R	2	1.14	8.00
62	2	TR	R	2	1.17	10.00
63	2	TR	R	2	0.83	12.00
64	2	TR	R	2	0.34	24.00
65	3	TR	T	1	0.00	0.00
66	3	TR	T	1	0.09	0.25

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

17:51 Friday, July 29, 2016 3

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
67	3	TR	T	1	0.44	0.50
68	3	TR	T	1	0.66	0.75
69	3	TR	T	1	0.81	1.00
70	3	TR	T	1	0.69	1.50
71	3	TR	T	1	0.86	2.00
72	3	TR	T	1	1.11	2.50
73	3	TR	T	1	1.77	3.00
74	3	TR	T	1	3.33	3.50
75	3	TR	T	1	3.01	4.00
76	3	TR	T	1	1.44	6.00
77	3	TR	T	1	0.68	8.00
78	3	TR	T	1	0.52	10.00
79	3	TR	T	1	0.41	12.00
80	3	TR	T	1	0.14	24.00
81	3	TR	R	2	0.00	0.00
82	3	TR	R	2	0.33	0.25
83	3	TR	R	2	0.76	0.50
84	3	TR	R	2	1.64	0.75
85	3	TR	R	2	3.36	1.00
86	3	TR	R	2	3.25	1.50
87	3	TR	R	2	3.58	2.00
88	3	TR	R	2	2.28	2.50
89	3	TR	R	2	1.82	3.00
90	3	TR	R	2	1.36	3.50
91	3	TR	R	2	1.11	4.00
92	3	TR	R	2	0.72	6.00
93	3	TR	R	2	0.39	8.00
94	3	TR	R	2	0.40	10.00
95	3	TR	R	2	0.25	12.00
96	3	TR	R	2	0.12	24.00
97	4	TR	T	1	0.00	0.00
98	4	TR	T	1	0.00	0.25
99	4	TR	T	1	0.26	0.50

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
100	4	TR	T	1	0.60	0.75
101	4	TR	T	1	0.58	1.00
102	4	TR	T	1	0.62	1.50
103	4	TR	T	1	0.49	2.00
104	4	TR	T	1	0.77	2.50
105	4	TR	T	1	1.11	3.00
106	4	TR	T	1	1.32	3.50
107	4	TR	T	1	1.79	4.00
108	4	TR	T	1	0.74	6.00
109	4	TR	T	1	0.45	8.00
110	4	TR	T	1	0.32	10.00
111	4	TR	T	1	0.20	12.00
112	4	TR	T	1	0.00	24.00
113	4	TR	R	2	0.00	0.00
114	4	TR	R	2	0.00	0.25
115	4	TR	R	2	0.21	0.50
116	4	TR	R	2	0.30	0.75
117	4	TR	R	2	0.29	1.00
118	4	TR	R	2	0.42	1.50
119	4	TR	R	2	0.59	2.00
120	4	TR	R	2	1.01	2.50
121	4	TR	R	2	1.01	3.00
122	4	TR	R	2	0.88	3.50
123	4	TR	R	2	0.72	4.00
124	4	TR	R	2	0.41	6.00
125	4	TR	R	2	0.32	8.00
126	4	TR	R	2	0.28	10.00
127	4	TR	R	2	0.16	12.00
128	4	TR	R	2	0.05	24.00
129	5	RT	R	1	0.00	0.00
130	5	RT	R	1	0.16	0.25
131	5	RT	R	1	0.54	0.50
132	5	RT	R	1	0.71	0.75

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

17:51 Friday, July 29, 2016 5

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
133	5	RT	R	1	0.67	1.00
134	5	RT	R	1	0.67	1.50
135	5	RT	R	1	0.71	2.00
136	5	RT	R	1	1.50	2.50
137	5	RT	R	1	2.23	3.00
138	5	RT	R	1	1.88	3.50
139	5	RT	R	1	1.61	4.00
140	5	RT	R	1	1.59	6.00
141	5	RT	R	1	0.64	8.00
142	5	RT	R	1	0.42	10.00
143	5	RT	R	1	0.35	12.00
144	5	RT	R	1	0.13	24.00
145	5	RT	T	2	0.00	0.00
146	5	RT	T	2	0.20	0.25
147	5	RT	T	2	0.66	0.50
148	5	RT	T	2	0.73	0.75
149	5	RT	T	2	0.87	1.00
150	5	RT	T	2	1.37	1.50
151	5	RT	T	2	1.44	2.00
152	5	RT	T	2	1.69	2.50
153	5	RT	T	2	1.63	3.00
154	5	RT	T	2	1.43	3.50
155	5	RT	T	2	1.11	4.00
156	5	RT	T	2	0.62	6.00
157	5	RT	T	2	0.36	8.00
158	5	RT	T	2	0.29	10.00
159	5	RT	T	2	0.23	12.00
160	5	RT	T	2	0.06	24.00
161	6	RT	R	1	0.00	0.00
162	6	RT	R	1	0.07	0.25
163	6	RT	R	1	0.44	0.50
164	6	RT	R	1	0.68	0.75
165	6	RT	R	1	0.80	1.00

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
166	6	RT	R	1	0.90	1.50
167	6	RT	R	1	0.95	2.00
168	6	RT	R	1	1.04	2.50
169	6	RT	R	1	1.04	3.00
170	6	RT	R	1	1.20	3.50
171	6	RT	R	1	1.17	4.00
172	6	RT	R	1	1.11	6.00
173	6	RT	R	1	0.93	8.00
174	6	RT	R	1	0.53	10.00
175	6	RT	R	1	0.38	12.00
176	6	RT	R	1	0.08	24.00
177	6	RT	T	2	0.00	0.00
178	6	RT	T	2	0.00	0.25
179	6	RT	T	2	0.14	0.50
180	6	RT	T	2	0.44	0.75
181	6	RT	T	2	0.52	1.00
182	6	RT	T	2	0.35	1.50
183	6	RT	T	2	0.65	2.00
184	6	RT	T	2	1.23	2.50
185	6	RT	T	2	1.56	3.00
186	6	RT	T	2	1.73	3.50
187	6	RT	T	2	1.57	4.00
188	6	RT	T	2	1.05	6.00
189	6	RT	T	2	0.77	8.00
190	6	RT	T	2	0.46	10.00
191	6	RT	T	2	0.38	12.00
192	6	RT	T	2	0.25	24.00
193	7	TR	T	1	0.00	0.00
194	7	TR	T	1	0.00	0.25
195	7	TR	T	1	0.57	0.50
196	7	TR	T	1	1.16	0.75
197	7	TR	T	1	1.35	1.00
198	7	TR	T	1	2.60	1.50

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
199	7	TR	T	1	5.02	2.00
200	7	TR	T	1	4.31	2.50
201	7	TR	T	1	2.60	3.00
202	7	TR	T	1	2.21	3.50
203	7	TR	T	1	1.78	4.00
204	7	TR	T	1	1.07	6.00
205	7	TR	T	1	0.64	8.00
206	7	TR	T	1	0.41	10.00
207	7	TR	T	1	0.28	12.00
208	7	TR	T	1	0.15	24.00
209	7	TR	R	2	0.00	0.00
210	7	TR	R	2	0.09	0.25
211	7	TR	R	2	0.79	0.50
212	7	TR	R	2	1.18	0.75
213	7	TR	R	2	1.44	1.00
214	7	TR	R	2	1.58	1.50
215	7	TR	R	2	2.39	2.00
216	7	TR	R	2	2.98	2.50
217	7	TR	R	2	1.81	3.00
218	7	TR	R	2	1.35	3.50
219	7	TR	R	2	1.36	4.00
220	7	TR	R	2	1.48	6.00
221	7	TR	R	2	1.32	8.00
222	7	TR	R	2	0.48	10.00
223	7	TR	R	2	0.32	12.00
224	7	TR	R	2	0.19	24.00
225	8	RT	R	1	0.00	0.00
226	8	RT	R	1	0.13	0.25
227	8	RT	R	1	0.39	0.50
228	8	RT	R	1	0.58	0.75
229	8	RT	R	1	0.67	1.00
230	8	RT	R	1	0.81	1.50
231	8	RT	R	1	2.60	2.00

SAS Version Used: Version 9.4

The SAS System
Protocol No: -----

17:51 Friday, July 29, 2016 8

Vertical Format Concentration Data To Calculate The Pharmacokinetic Parameters Of (Analyte Name)

Obs	subject	seq	form	period	concentration	time
232	8	RT	R	1	3.44	2.50
233	8	RT	R	1	3.34	3.00
234	8	RT	R	1	1.85	3.50
235	8	RT	R	1	1.84	4.00
236	8	RT	R	1	1.26	6.00
237	8	RT	R	1	0.85	8.00
238	8	RT	R	1	0.53	10.00
239	8	RT	R	1	0.40	12.00
240	8	RT	R	1	0.17	24.00
241	8	RT	T	2	0.00	0.00
242	8	RT	T	2	0.09	0.25
243	8	RT	T	2	0.48	0.50
244	8	RT	T	2	0.84	0.75
245	8	RT	T	2	0.56	1.00
246	8	RT	T	2	1.04	1.50
247	8	RT	T	2	1.57	2.00
248	8	RT	T	2	2.98	2.50
249	8	RT	T	2	3.32	3.00
250	8	RT	T	2	2.47	3.50
251	8	RT	T	2	1.96	4.00
252	8	RT	T	2	1.11	6.00
253	8	RT	T	2	0.70	8.00
254	8	RT	T	2	0.50	10.00
255	8	RT	T	2	0.45	12.00
256	8	RT	T	2	0.17	24.00

SAS Version Used: Version 9.4

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-002/07

SAS PROGRAM FOR ESTIMATE PHARMACOKINETIC PARAMETERS

USING BESTFIT REGRESSION

/* Estimation of pharmacokinetic parameters Using Bestfit Regression */

Ods rtf File="D:\Pharmacokinetic Parameters of -----.doc";

Ods pdf File="D:\Pharmacokinetic Parameters of -----.pdf";

Options ps=90 ls=100 PAGENO=1;

Title2 ' Protocol No: -----';

Title3 ' All Pharmacokinetic parameters of ----- Under -----
Condition';

FOOTNOTE1 " SAS Version Used: Version &sysver ";

FOOTNOTE2 ' ';

FOOTNOTE3 ' ';

FOOTNOTE4 j=1 'Prepared By Biostatistician: ';

FOOTNOTE5 ' ';

FOOTNOTE6 ' ';

FOOTNOTE7 j=1 ' (Signature/Date) ';

proc sort data = inputdata out = temp nodupkey ; by subject period;run;

data temp;

set temp;

order = _n_;

run;-

proc sort data = temp;by subject period;run;

proc sort data = inputdata;by subject period time;run;

data temp2;

merge inputdata temp;

by subject period;

run;

proc sql;

create table max as

select max(order) as max

from temp2;

quit;

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Reference SOP No. : BEQ/ST/SOP-002/07

```
data max;
set max;
call symput('max',max);
run;

%macro auc (dsn);
data auctree;
set &dsn;
if concentration = 0 and time > Ke_last then delete;
x = time;
y = concentration;
xpre = lag(x);
ypre = lag(y);
xdif = x - xpre;
auc = xdif * (( y + ypre ) / 2);
run;
proc summary data = auctree noprint;
var auc;
output out = aucest sum = AUCt;
run;
proc sort data = auctree out = part1 nodupkey ; by subject ;run;
data AUCs&i (keep = subject period AUCt);
merge part1 aucest;
run;
%mend auc;

%MACRO ke (DSN);
data &dsn;
set &dsn;
where concentration > 0 and time >= tmax;
lny = log (concentration);
run;
proc sort data = &dsn out=&dsn; by descending time; run;
%global npoints;
%let opensdn = %sysfunc(open (&dsn) );
%let npoints = %sysfunc(attrn(&opensdn,NOBS));
%let rc = %sysfunc(close(&opensdn) );
%put _user_;
```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
%if (%eval (&npoints > 2)) %then %do;
%do j = 3 %to &npoints;
data point&j;
set &dsn( obs = &j );
orderreg = &j;
run;
data point&j ;
set point&j;
rename time = x;
rename lny = y;
x2 = time ** 2;
y2 = lny ** 2;
xy = time * lny;
run;
proc sql;
create table operats as
select
sum(x) as sumX,
sum(Y) as sumY,
sum(x2) as sumX2,
sum(Y2) as sumY2,
sum(xy) as sumXY
from point&j;
quit;
data _null_;
set operats;
call symput('sumX',sumX);
call symput('sumY',sumY);
call symput('sumX2',sumX2);
call symput('sumY2',sumY2);
call symput('sumXY',sumXY);
run;
data point&j;
set point&j;
m = ((&sumX * &sumY) - (orderreg * &sumXY)) / ((&sumX**2)-(orderreg *
&sumX2));
```


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Reference SOP No. : BEQ/ST/SOP-002/07

```

r = (&sumXY - ((&sumX * &sumY) / orderreg)) / (sqrt((&sumX2 - ((&sumX
*&sumX)/orderreg))*(&sumY2 - ((&sumY *&sumY)/orderreg))));
r2 = r * r;
adjr2 = 1 - ((1 - r2) * (orderreg - 1)) / (orderreg - 2);
run;
proc sort data = point&j nodupkey; by subject;run;
%end;
data allestimates;
set %do k = 3 %to &npoints;
point&k
%end;;
run;
proc sort data = allestimates out = estimatecomp ;by descending adjr2
descending
orderreg;run;
data estimatecomp;
set estimatecomp;
regnum = _n_;
where m < 0;
run;
proc sql;
create table maxi as
select max(regnum) as maxi
from estimatecomp;
quit;
data _null_;
set maxi;
call symput('maxi',maxi);
run;
%if &maxi = . %then %goto skip;
%if &maxi = 1 %then %do;
data best_estimate;
set estimatecomp (obs = 1);
run;
%end;
%else %do;

```

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Reference SOP No. : BEQ/ST/SOP-002/07

```

data estimate2 ;
set estimatecomp (firstobs = 2);
run;
data estimate2;
set estimate2 (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate2' , adjr2);
call symput ('oderreg2' , orderreg);
run;
data estimate1;
set estimatecomp (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate1' , adjr2);
call symput ('oderreg1' , orderreg);
run;
data _null_;
dif1 = &estimate1;
dif2 = &estimate2;
dif = (dif1 - dif2);
call symput('dif',dif);
run;
%let difer = %SYSFUNC(PUTN(&dif,15.10));
%if &difer < 0.0001 and &oderreg2 > &oderreg1 %then %do;
data best_estimate;
set estimatecomp;
where regnum = 2;
%end;
%else %do;
data best_estimate;
set estimatecomp;
where regnum = 1;
run;
%end;
%end;
data ke&i (keep=m r2 adjr2 subject period orderreg);
set best_estimate;

```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
m=m*-1;
run;
proc datasets library = work nodetails nolist;
delete %do iii=1 %to &npoints; point&iii %end;;
run;
quit;
%end;
%else %do;
%put Warning, Less than 3 points, ke is not estimable;
%skip;;
proc sort data=profileno&i out=iddata nodupkey;by subject;run;
data ke&i (keep=m r2 adjr2 subject period orderreg);
set iddata;
m=.;
r2=.;
adjr2=.;
orderreg=.;
run;
%end;
%MEND ke;
%macro indcalc;
%do i = 1 %to &max;
data ProfileNo&i;
set temp2 (where = (order = &i));
run;
/*****
i) Cmax , Tmax
*****/
proc sort data=profileno&i out=profilenoinvCmax&i;
by descending concentration;run;
data Cmax&i;
set profilenoinvCmax&i (obs = 1);
rename concentration = Cmax time = Tmax;
run;
/*****
ii) Clast
```

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Reference SOP No. : BEQ/ST/SOP-002/07

```

*****/
proc sort data=profileno&i (where =(concentration > 0)) out = profilenoinv&i;
by descending time;run;
data Clast&i (keep = subject period clast order Ke_last);
set profilenoinv&i (obs = 1);
rename concentration=Clast time=Ke_last ;
run;
proc sort data = profileNo&i; by subject period time;
proc sort data = Cmax&i; by subject period;
proc sort data = Clast&i; by subject period;
data profileNo&i;
merge profileNo&i Cmax&i Clast&i;
by subject period;
run;
%auc (profileno&i);
%ke (profileno&i);
/*****
ii) Cfirst
*****/
proc sort data=profileno&i out = profileno_ke_f&i;
by descending time;
run;
Data _null_;
set ke&i;
call symput('orderreg',orderreg);
run;
data Cfirst&i (keep = subject period Cfirst order Ke_first);
merge profileno_ke_f&i (firstobs=&orderreg);
rename concentration=Cfirst time=Ke_first ;
run;
data Cfirst&i;
set Cfirst&i (obs=1);
run;
proc sort data = Cfirst&i; by subject period;run;
data Pkparam&i;
merge cmax&i aucs&i ke&i clast&i cfirst&i;

```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
run;
%end;

/*****
Joint PK Parameters of all Subjects
*****/

data allPkParam (rename = (m = ke orderreg = npoints));
set %do i = 1 %to &max;Pkparam&i %end;;

run;
%mend indcalc;
%indcalc;

data PkNCA (keep = subject seq period form r2 adjr2 npoints ke thalf tmax cmax
AUCt AUCinf Ke_first Ke_last Res_area);
set allPkParam;
AUCinf = AUCt + clast / ke;
thalf = log(2) / ke;
Res_area=(AUCinf-AUCt)/AUCinf;

run;

data one ;
set PkNCA;
if npoints=. then do;
Ke_first=.;
Ke_last=.;
end;
format AUCt AUCinf 16.4 ke thalf Res_area 10.4 Tmax 8.2;
keep subject seq form period Cmax Tmax AUCt Res_area Ke_first Ke_last AUCinf
npoints ke thalf;

run;

proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints;
run;

ods rtf close;
ods pdf close;
```

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Reference SOP No. : BEQ/ST/SOP-002/07	

SAS PROGRAM FOR ESTIMATE PHARMACOKINETIC PARAMETERS
USING SECOND BESTFIT REGRESSION

```

/* Estimation of pharmacokinetic parameters Using Second Bestfit Regression */
Ods rtf File="D:\Pharmacokinetic Parameters of -----.doc";
Ods pdf File="D:\Pharmacokinetic Parameters of -----.pdf";
Options ps=90 ls=100 PAGENO=1;
Title2 '          Protocol No: -----';
Title3 '          All Pharmacokinetic parameters of ----- Under -----
Condition';
FOOTNOTE1 " SAS Version Used: Version &sysver  ";
FOOTNOTE2 '          ';
FOOTNOTE3 '          ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:  ';
FOOTNOTE5 '          ';
FOOTNOTE6 '          ';
FOOTNOTE7 j=1 ' (Signature/Date)          ';

proc sort data = inputdata2 out = temp nodupkey ; by subject period;run;
data temp;
set temp;
order = _n_;
run;
proc sort data = temp;by subject period;run;
proc sort data = inputdata2;by subject period time;run;
data temp2;
merge inputdata2 temp;
by subject period;
run;
proc sql;
create table max as
select max(order) as max
from temp2;
quit;
data max;
set max;

```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
call symput('max',max);
run;
%macro auc (dsn);
data auctree;
set &dsn;
if concentration = 0 and time > Ke_last then delete;
x = time;
y = concentration;
xpre = lag(x);
ypre = lag(y);
xdif = x - xpre;
auc = xdif * (( y + ypre ) / 2);
run;
proc summary data = auctree noprint;
var auc;
output out = aucest sum = AUCT;
run;
proc sort data = auctree out = part1 nodupkey ; by subject ;run;
data AUCs&i (keep = subject period AUCT);
merge part1 aucest;
run;
%mend auc;
%MACRO ke (DSN);
data &dsn;
set &dsn;
where concentration > 0 and time >= tmax;
lny = log (concentration);
run;
proc sort data = &dsn out=&dsn; by descending time; run;
%global npoints;
%let opensn = %sysfunc(open (&dsn) );
%let npoints = %sysfunc(attrn(&opensn,NOBS));
%let rc = %sysfunc(close(&opensn) );
%put _user_;
%if (%eval (&npoints > 2)) %then %do;
%do j = 3 %to &npoints;
```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
data point&j;
set &dsn( obs = &j );
orderreg = &j;
run;
data point&j ;
set point&j;
rename time = x;
rename lny = y;
x2 = time ** 2;
y2 = lny ** 2;
xy = time * lny;
run;
proc sql;
create table operats as
select
sum(x) as sumX,
sum(Y) as sumY,
sum(x2) as sumX2,
sum(Y2) as sumY2,
sum(xy) as sumXY
from point&j;
quit;
data _null_;
set operats;
call symput('sumX',sumX);
call symput('sumY',sumY);
call symput('sumX2',sumX2);
call symput('sumY2',sumY2);
call symput('sumXY',sumXY);
run;
data point&j;
set point&j;
m = ((&sumX * &sumY) - (orderreg * &sumXY)) / ((&sumX**2)-(orderreg *
&sumX2));
r = (&sumXY - ((&sumX * &sumY) / orderreg)) / (sqrt((&sumX2 - ((&sumX
*&sumX)/orderreg))*(&sumY2 - ((&sumY *&sumY)/orderreg))));
```


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Reference SOP No. : BEQ/ST/SOP-002/07

```
r2 = r * r;
adjr2 = 1 - ((1 - r2) * (orderreg - 1)) / (orderreg - 2);
run;
proc sort data = point&j nodupkey; by subject;run;
%end;
data allestimates;
set %do k = 3 %to &npoints;
point&k
%end;;
run;
proc sort data = allestimates out = estimatecomp ;by descending adjr2
descending
orderreg;run;
data estimatecomp;
set estimatecomp;
regnum = _n_;
where m < 0;
run;
proc sql;
create table maxi as
select max(regnum) as maxi
from estimatecomp;
quit;
data _null_;
set maxi;
call symput('maxi',maxi);
run;
%if &maxi = . %then %goto skip;
%if &maxi = 1 %then %do;
data best_estimate;
set estimatecomp (obs = 1);
run;
%end;
%else %do;
data estimate2 ;
set estimatecomp (firstobs = 3);
```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
run;
data estimate2;
set estimate2 (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate2' , adjr2);
call symput ('oderreg2' , orderreg);
run;
data estimate1 ;
set estimatecomp (firstobs = 2);
run;
data estimate1;
set estimate1 (obs = 1);
adjr2 = adjr2 *1;
call symput ('estimate1' , adjr2);
call symput ('oderreg1' , orderreg);
run;
data _null_;
dif1 = &estimate1;
dif2 = &estimate2;
dif = (dif1 - dif2);
call symput('dif',dif);
run;
%let difer = %SYSFUNC(PUTN(&dif,15.10));
%if &difer < 0.0001 and &oderreg2 > &oderreg1 %then %do;
data best_estimate;
set estimatecomp;
where regnum = 3;
%end;
%else %do;
data best_estimate;
set estimatecomp;
where regnum = 2;
run;
%end;
%end;
data ke&i (keep=m r2 adjr2 subject period orderreg);
```

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Reference SOP No. : BEQ/ST/SOP-002/07

```
set best_estimate;
m=m*-1;
run;
proc datasets library = work nodetails nolist;
delete %do iii=1 %to &npoints; point&iii %end;;
run;
quit;
%end;
%else %do;
%put Warning, Less than 3 points, ke is not estimable;
%skip;;
proc sort data=profileno&i out=iddata nodupkey;by subject;run;
data ke&i (keep=m r2 adjr2 subject period orderreg);
set iddata;
m=.;
r2=.;
adjr2=.;
orderreg=.;
run;
%end;
%MEND ke;
%macro indcalc;
%do i = 1 %to &max;
data ProfileNo&i;
set temp2 (where = (order = &i));
run;
/*****
i) Cmax , Tmax
*****/
proc sort data=profileno&i out=profilenoinvCmax&i;
by descending concentration;run;
data Cmax&i;
set profilenoinvCmax&i (obs = 1);
rename concentration = Cmax time = Tmax;
run;
/*****/
```

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Reference SOP No. : BEQ/ST/SOP-002/07

ii) Clast

*****/

proc sort data=profileno&i (where =(concentration > 0)) out = profilenoinv&i;

by descending time;run;

data Clast&i (keep = subject period clast order Ke_last);

set profilenoinv&i (obs = 1);

rename concentration=Clast time=Ke_last ;

run;

proc sort data = profileNo&i; by subject period time;

proc sort data = Cmax&i; by subject period;

proc sort data = Clast&i; by subject period;

data profileNo&i;

merge profileNo&i Cmax&i Clast&i;

by subject period;

run;

%auc (profileno&i);

%ke (profileno&i);

/*****

ii) Cfirst

*****/

proc sort data=profileno&i out = profileno_ke_f&i;

by descending time;

run;

Data _null_;

set ke&i;

call symput('orderreg',orderreg);

run;

data Cfirst&i (keep = subject period Cfirst order Ke_first);

merge profileno_ke_f&i (firstobs=&orderreg);

rename concentration=Cfirst time=Ke_first ;

run;

data Cfirst&i;

set Cfirst&i (obs=1);

run;

proc sort data = Cfirst&i; by subject period;run;

data Pkparam&i;

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Reference SOP No. : BEQ/ST/SOP-002/07

```

merge cmax&i aucs&i ke&i clast&i cfirst&i;
run;
%end;
/*****
Joint PK Parameters of all Subjects
*****/
data allPkParam (rename = (m = ke orderreg = npoints));
set %do i = 1 %to &max;Pkparam&i %end;;
run;
%mend indcalc;
%indcalc;
data PkNCA (keep = subject seq period form r2 adjr2 npoints ke thalf tmax cmax
AUCt AUCinf Ke_first Ke_last Res_area);
set allPkParam;
AUCinf = AUCt + clast / ke;
thalf = log(2) / ke;
Res_area=(AUCinf-AUCt)/AUCinf;
run;
data one ;
set PkNCA;
if npoints=. then do;
Ke_first=.;
Ke_last=.;
end;
format AUCt AUCinf 16.4 ke thalf Res_area 10.4 Tmax 8.2;
keep subject seq form period Cmax Tmax AUCt Res_area Ke_first Ke_last AUCinf
npoints ke thalf;
run;
proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;
proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints;
run;
ods rtf close;
ods pdf close;

```

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STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE

SITE OF DISTRIBUTION: Pharmacokinetic and Statistics, Quality Assurance and Head – Bioequivalence.

REVISION CARD

	Prepared By	Checked By	Approved By	Authorised By
Design. – Dept.	Biostatistician - ST	Biostatistician - ST	Head - QA	Head - Bioequivalence
Sign and Date	 30/06/16	 30/06/16	 30/06/16	 30/06/16
Name	Mr. Sadashiv K.	Mr. Pankaj B.	Dr. Sagar P.	Dr. Ashish M.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	2 of 16

1. OBJECTIVE:

To lay down the procedure for statistical analysis of pharmacokinetic parameters.

2. SCOPE:

This procedure is applicable to biostatistician and serves as a guideline for statistical analysis for bioequivalence projects as per requirement based on EMEA/WHO guidance.

3. RESPONSIBILITY:

Biostatistician and Quality Assurance Staff.

4. PROCEDURE

4.1 Two Formulation, Two Period, Two Sequence, 2 X 2 Crossover Design

4.1.1 Descriptive Analysis of Pharmacokinetic Parameters

4.1.1.1 In descriptive analysis, summary statistics are obtained using "**PROC MEANS**" procedure in SAS.

4.1.1.2 Summary statistics are to be obtained for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e , t_{half} , Res_area & t_{max} on the original scale. Summary statistics include minimum, maximum, mean, median, S.D. and C.V. for each parameter.

4.1.1.3 Summary statistics is presented according to formulation, sequence, period, group and sequence by formulation, period by formulation for each parameter.

4.1.2 Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters

4.1.2.1 The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using Standard ANOVA Model with main effects of "seq, subject (seq), period and form". "**PROC GLM**" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-01, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design With Standard ANOVA Model' and its SAS output refer Annexure No. ANX/ST/SOP-016-02, 'Sample SAS Output Of 2 X 2 Crossover Design'.

4.1.2.2 If the study is conducted in multiple groups then group effect is to be added in analysis of variance model. The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using an ANOVA model with main effects of "form, group, form*group, period (group), seq, seq*group and subject (seq*group)". "**PROC GLM**" procedure is used to obtain the ANOVA.

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STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	3 of 16

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-03, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design With Group ANOVA Model'.

- 4.1.2.3 The seq effect is to be tested at 5% level of significance with subject (seq) as an error term.
- 4.1.2.4 The seq & group effect is to be tested at 5% level of significance with subject (seq*group) as an error term.
- 4.1.2.5 The form, period and group*form effects are to be tested at 5% level of significance.
- 4.1.2.6 Each analysis of variance includes mean square error, p-value of factors and the associated degrees of freedom.
- 4.1.2.7 Analysis of variance is presented after the descriptive analysis.
- 4.1.3 **90% Confidence Interval For Primary Pharmacokinetic Parameters**
- 4.1.3.1 A 90% confidence interval for the ratio of both the formulations averages (geometric means) is calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- 4.1.4 **Intra Subject Variability Primary Pharmacokinetic Parameters**
- 4.1.4.1 Report the intra subject variability (C.V.%) from the ANOVA result using the log-transformed data. Intra subject C.V. = $100 \times \sqrt{e^{MSE} - 1}$ Where, MSE = Mean Square Error obtained from ANOVA.
- 4.1.5 **Ratio Analysis For Primary Pharmacokinetic Parameters**
- 4.1.5.1 Report the geometric means of the test and reference formulation. Calculate ratio of geometric mean of test to geometric mean of reference.
- 4.1.5.2 Calculate ratio of AUC_{0-t} to AUC_{0-∞} for each subject for both test and reference product.
- 4.1.5.3 Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters (C_{max} & AUC_{0-t}).
- 4.1.5.4 Calculate ratio of mean of AUC_{0-t} to mean of AUC_{0-∞} for both test and reference.
- 4.1.5.5 Calculate % bioavailability of C_{max} & AUC_{0-t}.
- 4.1.6 **Power Test For Primary Pharmacokinetic Parameters**
- 4.1.6.1 Power of the test to detect the ratio of two formulations averages (GM) being equal to 125% (or 80%) at the 5% level of significance.
- 4.1.7 **Graphical Analysis**
- 4.1.7.1 Comparative linear & semi log plots of plasma concentration vs time (Hours) for each subject.
- 4.1.7.2 Comparative mean linear & mean semi log plots of plasma concentration vs time (Hours).

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	4 of 16

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-04, 'SAS Program For Graphs (The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design)'.

4.1.8 **Bioequivalence Criteria For Primary Pharmacokinetic Parameters**

4.1.8.1 If the 90% confidence interval for log-transformed C_{max} & AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.

4.1.8.2 90% confidence interval for C_{max} & AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T.

4.2 **Three Formulation, Three Period, Three Sequence, 3 X 3 Crossover Design**

4.2.1 **Descriptive Analysis of Pharmacokinetic Parameters**

4.2.1.1 In descriptive analysis, summary statistics are obtained using "PROC MEANS" procedure in SAS.

4.2.1.2 Summary statistics are to be obtained for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e , t_{half} , Res_area & t_{max} on the original scale. Summary statistics include minimum, maximum, mean, median, S.D. & C.V. for each parameter.

4.2.1.3 Summary statistics is presented according to formulation, sequence, period, group and sequence by formulation, period by formulation for each parameter.

4.2.2 **Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters**

4.2.2.1 The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using Standard ANOVA Model with main effects of "seq, subject (seq), period and form". "PROC GLM" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-05; 'SAS Program For The Statistical Analysis Of The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design With Standard ANOVA Model'

4.2.2.2 If the study is conducted in multiple groups then group effect is to be added in analysis of variance model. The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using an ANOVA model main effects of "form, group, form*group, period (group), seq, seq*group and subject (seq*group)". "PROC GLM" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-06, 'SAS Program For The Statistical Analysis Of The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design With Group ANOVA Model'

4.2.2.3 The seq effect is to be tested at 5% level of significance with subject (seq) as an error term.

4.2.2.4 The seq & group effect is to be tested at 5% level of significance with subject (seq*group) as an error term.

4.2.2.5 The form, period and group*form effects are to be tested at 5% level of significance.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
MACLEODS		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	5 of 16

- 4.2.2.6 Each analysis of variance includes mean square error, p-value of factors and the associated degrees of freedom.
- 4.2.2.7 Analysis of variance is presented after the descriptive analysis.
- 4.2.3 **90% Confidence Interval for Primary Pharmacokinetic Parameters**
- 4.2.3.1 A 90% confidence interval for the ratio of both the formulations averages (geometric means) is calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- 4.2.4 **Intra Subject Variability For Primary Pharmacokinetic Parameters**
- 4.2.4.1 Report the intra subject variability (C.V.%) from the ANOVA result using the log-transformed data. Intra Subject C.V. = $100 \times \sqrt{e^{MSE} - 1}$ Where, MSE = Mean Square Error obtained from ANOVA.
- 4.2.5 **Power Test For Primary Pharmacokinetic Parameters**
- 4.2.5.1 Power of the test to detect the ratio of two formulations averages (GM) being equal to 125% (or 80%) at the 5% level of significance.
- 4.2.6 **Graphical Analysis**
- 4.2.6.1 Comparative linear & semi log plots of plasma concentration vs time (Hours) for each subject.
- 4.2.6.2 Comparative mean linear & mean semi log plots of plasma concentration vs time (Hours).
Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-07, 'SAS Program For Graphs (The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design)'.
- 4.2.7 **Bioequivalence Criteria For Primary Pharmacokinetic Parameters**
- 4.2.7.1 If the 90% confidence interval for log-transformed C_{max} & AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.
- 4.2.7.2 90% confidence interval for C_{max} & AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T.
- 4.3 **Two Formulation, Single Period Parallel Design**
- 4.3.1 **Descriptive Analysis of Pharmacokinetic Parameters**
- 4.3.1.1 In descriptive analysis, summary statistics are obtained using "PROC MEANS" procedure in SAS.
- 4.3.1.2 Summary statistics are to be obtained for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e , t_{half} , Res_area & t_{max} on the original scale. Summary statistics include minimum, maximum, mean, median, S.D. & C.V. for each parameter.
- 4.3.1.3 Summary statistics is presented according to formulation, group for each parameter.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	6 of 16

4.3.2 Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters

4.3.2.1 The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analyzed using Standard ANOVA Model with main effect of "form" "PROC GLM" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-08; 'SAS Program For The Statistical Analysis Of The Two Formulation, Single Period, Parallel Design With Standard ANOVA Model'.

4.3.2.2 If the study is conducted in multiple groups then group effect is to be added in analysis of variance model. The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using an ANOVA model with main effects of "form, group and form*group". "PROC GLM" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-09; 'SAS Program For The Statistical Analysis Of The Two Formulation, Single Period, Parallel Design With Group ANOVA Model'.

4.3.2.3 The form, group and group*form effect is to be tested at 5% level of significance.

4.3.2.4 Each analysis of variance includes mean square error, p-value of factors and the associated degrees of freedom.

4.3.2.5 Analysis of variance is presented after the descriptive analysis.

4.3.3 90% Confidence Interval for Primary Pharmacokinetic Parameters

4.3.3.1 A 90% confidence interval for the ratio of both the formulations averages (geometric means) is calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.

4.3.4 Inter Subject Coefficient of Variation based on ANOVA For Primary Pharmacokinetic Parameters

4.3.4.1 Report the Coefficient of Variation (C.V.%) from the ANOVA result using the log-transformed data. Inter Subject C.V. = $100 \times \sqrt{e^{MSE} - 1}$ Where, MSE = Mean Square Error obtained from ANOVA.

4.3.5 Ratio Analysis For Primary Pharmacokinetic Parameters

4.3.5.1 Report the geometric means of the test and reference formulation. Calculate ratio of geometric mean of test to geometric mean of reference.

4.3.5.2 Calculate ratio of AUC_{0-t} to $AUC_{0-\infty}$ for each subject

4.3.5.3 Calculate ratio of mean of AUC_{0-t} to mean of $AUC_{0-\infty}$ for both test and reference.

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

STANDARD OPERATING PROCEDURE**STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE**

Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	7 of 16

4.3.5.4 Calculate % bioavailability of C_{max} & AUC_{0-t} .**4.3.6 Power Test For Primary Pharmacokinetic Parameters**

4.3.6.1 Power of the test to detect the ratio of two formulations averages (GM) being equal to 125% (or 80%) at the 5% level of significance.

4.3.7 Graphical Analysis

4.3.7.1 Comparative linear & semi log plots of plasma concentration vs time (Hours) for each subject.

4.3.7.2 Comparative mean linear & mean semi log plots of plasma concentration vs time (Hours).

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-10, 'SAS Program For Graphs (The Two Formulation, Single Period, Parallel Design)'.**4.3.8 Bioequivalence Criteria For Primary Pharmacokinetic Parameters**4.3.8.1 If the 90% confidence interval for log-transformed C_{max} & AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.4.3.8.2 90% confidence interval for C_{max} & AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T.**4.4 Two Formulation, Two Sequence, Four Period, Partial Replicated 4-Way & 3-Way Crossover Design (Unscaled Average Bioequivalence Approach)****4.4.1 Descriptive Analysis of Pharmacokinetic Parameters**

4.4.1.1 In descriptive analysis, summary statistics are obtained using "PROC MEANS" procedure in SAS.

4.4.1.2 Summary statistics are to be obtained for C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e , t_{half} , Res_area & t_{max} on the original scale. Summary statistics include minimum, maximum, mean, median, S.D. & C.V. for each parameter.

4.4.1.3 Summary statistics is presented according to formulation, sequence, period, group and sequence by formulation, period by formulation for each parameter.

4.4.2 Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters4.4.2.1 The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using Standard ANOVA Model with main effects of "seq, subject (seq), period and form". "PROC GLM" procedure is used to obtain the ANOVA.**Note:** Refer SAS program, Annexure No. ANX/ST/SOP-016-11, 'SAS Program For The Statistical Analysis of Unscaled Average Bioequivalence (Two Formulation, Two Sequence, Four Period, Partial Replicated 4-Way & 3-Way Crossover Design With Standard ANOVA Model)'.4.4.2.2 If the study is conducted in multiple groups then group effect is to be added in analysis of variance model. The log transformed pharmacokinetic parameters (C_{max} and AUC_{0-t}) are analysed using an ANOVA model with main effects of "form, group, form*group, period (group),

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	8 of 16

seq, seq*group and subject (seq*group)". "PROC GLM" procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-12, 'SAS Program For The Statistical Analysis of Unscaled Average Bioequivalence (Two Formulation, Two Sequence, Four Period, Partial Replicated 4-Way & 3-Way Crossover Design With Group ANOVA Model)'.

- 4.4.2.3 The seq effect is to be tested at 5% level of significance with subject (seq) as an error term.
- 4.4.2.4 The seq & group effect is to be tested at 5% level of significance with subject (seq*group) as an error term.
- 4.4.2.5 The form, period and group*form effects are to be tested at 5% level of significance.
- 4.4.2.6 Each analysis of variance includes mean square error, p-value of factors and the associated degrees of freedom.
- 4.4.2.7 Analysis of variance is presented after the descriptive analysis.
- 4.4.3 **90% Confidence Interval for Primary Pharmacokinetic Parameters**
- 4.4.3.1 A 90% confidence interval for the ratio of both the formulations averages (geometric means) is calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- 4.4.4 **Intra Subject Variability Primary Pharmacokinetic Parameters**
- 4.4.4.1 Report the intra subject variability (C.V.%) from the ANOVA result using the log-transformed data. Intra subject C.V. = $100 \times \sqrt{e^{\frac{MSE}{n}} - 1}$ Where, MSE = Mean Square Error obtained from ANOVA.
- 4.4.5 **Ratio Analysis For Primary Pharmacokinetic Parameters**
- 4.4.5.1 Report the geometric means of the test and reference formulation. Calculate ratio of geometric mean of test to geometric mean of reference.
- 4.4.5.2 Calculate ratio of AUC_{0-t} to AUC_{0-∞} for each subject for test and reference products.
- 4.4.5.3 Ratios of mean of AUC_{0-t} to mean of AUC_{0-∞} for both test and reference.
- 4.4.5.4 Calculate % bioavailability of C_{max} & AUC_{0-t}.
- 4.4.6 **Power Test For Primary Pharmacokinetic Parameters**
- 4.4.6.1 Power of the test to detect the ratio of two formulations averages (GM) being equal to 125% (or 80%) at the 5% level of significance.
- 4.4.7 **Graphical Analysis**
- 4.4.7.1 Comparative linear & semi log plots of plasma concentration vs time (Hours) for each subject.
- 4.4.7.2 Comparative mean linear & mean semi log plots of plasma concentration vs time (Hours).

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	9 of 16

Note: i) Refer SAS program, Annexure No. ANX/ST/SOP-016-13, 'SAS Program For Graphs (Two Formulation, Two Sequence, Four Period, Partial Replicated 4-Way Crossover Design)'.

ii) Refer SAS program, Annexure No. ANX/ST/SOP-016-14, 'SAS Program For Graphs (Two Formulation, Three Sequence, Three Period, Partial Replicated 3-Way Crossover Design)'.

4.4.8 **Bioequivalence Criteria For Primary Pharmacokinetic Parameters**

4.4.8.1 If the 90% confidence interval for log-transformed C_{max} & AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.

4.4.8.2 90% confidence interval for C_{max} & AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T.

4.5 **Two Formulation, Two Sequence, Two Period, Multiple Dose 2 X 2 Crossover Steady State Design**

4.5.1 **Descriptive Analysis of Pharmacokinetic Parameters**

4.5.1.1 In descriptive analysis, summary statistics are obtained using “PROC MEANS” procedure in SAS.

4.5.1.2 Summary statistics are to be obtained for $C_{max, ss}$, $C_{tau, ss}$, $C_{min, ss}$, AUC_{0-tau} , $t_{max, ss}$, $C_{avg, ss}$, Fluctuation, Swing, K_e & t_{half} on the original scale. Summary statistics minimum, maximum, mean, median, S.D. & C.V. for each parameter.

4.5.1.3 Summary statistics is presented according to formulation, sequence, period, group and sequence by formulation, period by formulation for each parameter.

4.5.2 **Analysis of Variance (ANOVA) For Primary Pharmacokinetic Parameters**

4.5.2.1 The log transformed pharmacokinetic parameters ($C_{max, ss}$, $C_{tau, ss}$ and AUC_{0-tau}) are analysed using Standard ANOVA Model with main effects of “seq, subject (seq), period and form”. “PROC GLM” procedure is used to obtained the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-15, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Standard ANOVA Model'.

4.5.2.2 If the study is conducted in multiple groups then group effect is to be added in analysis of variance model. The log transformed pharmacokinetic parameters ($C_{max, ss}$, $C_{tau, ss}$ and AUC_{0-tau}) are analysed using an ANOVA model with main effects of “form, group, form*group, period (group), seq, seq*group and subject (seq*group)”. “PROC GLM” procedure is used to obtain the ANOVA.

Note: Refer SAS program, Annexure No. ANX/ST/SOP-016-16, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Group ANOVA Model'.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	10 of 16

- 4.5.2.3 The seq effect is to be tested at 5% level of significance with subject (seq) as an error term.
- 4.5.2.4 The seq & group effect is to be tested at 5% level of significance with subject (seq*group) as an error term.
- 4.5.2.5 The form, period and form*group effects are to be tested at 5% level of significance.
- 4.5.2.6 Each analysis of variance includes mean square error, p-value of factors and the associated degrees of freedom.
- 4.5.2.7 Analysis of variance is presented after the descriptive analysis.
- 4.5.3 **90% Confidence Interval for Primary Pharmacokinetic Parameters**
- 4.5.3.1 A 90% confidence interval for the ratio of both the formulations averages (geometric means) is calculated by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- 4.5.4 **Intra Subject Variability Primary Pharmacokinetic Parameters**
- 4.5.4.1 Report the intra subject variability (C.V.%) from the ANOVA result using the log-transformed data. Intra subject C.V. = $100 \times \sqrt{e^{MSE} - 1}$ Where, MSE = Mean Square Error obtained from ANOVA.
- 4.5.5 **Ratio Analysis For Primary Pharmacokinetic Parameters**
- 4.5.5.1 Report the geometric means of the test and reference formulation. Calculate ratio of geometric mean of test to geometric mean of reference.
- 4.5.5.2 Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters ($C_{max, ss}$, $C_{tau, ss}$ & AUC_{0-tau}).
- 4.5.5.3 Calculate % bioavailability of $C_{max, ss}$, $C_{tau, ss}$ & AUC_{0-tau} .
- 4.5.6 **Power Test For Primary Pharmacokinetic Parameters**
- 4.5.6.1 Power of the test to detect the ratio of two formulations averages (GM) being equal to 125% (or 80%) at the 5% level of significance.
- 4.5.7 **Graphical Analysis**
- 4.5.7.1 Comparative linear & semi log plots of plasma concentration vs time (Hours) for each subject.
- 4.5.7.2 Comparative mean linear & mean semi log plots of plasma concentration vs time (Hours).
- Note:** Refer SAS program, Annexure No. ANX/ST/SOP-016-17, 'SAS Program For Graphs (The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design)'.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	11 of 16

4.5.8 Statistical analysis of pre-dose concentration data

- 4.5.8.1 Last three pre-dose concentration data are used for statistical analysis. In descriptive analysis, summary statistics are obtained using “**PROC MEANS**” procedure in SAS.
- 4.5.8.2 Summary statistics are to be obtained for Cpd on the original scale. Summary statistics including minimum, maximum, mean, median, S.D. & C.V. for Cpd.
- 4.5.8.3 Summary statistics is presented according to formulation, time and group.
- 4.5.8.4 Intra subject statistics including mean, S.D. & C.V. for Cpd is presented.
- 4.5.8.5 **Note:** i) Refer SAS program, Annexure No. ANX/ST/SOP-016-18, ‘SAS Program For The Statistical Analysis Of Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design’.
- ii) Refer SAS program, Annexure No. ANX/ST/SOP-016-19, ‘SAS Program For The Statistical Analysis Of Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Group’.

4.5.9 Graphical Analysis

- 4.5.9.1 Comparative linear & semi log plots of plasma concentration vs time for each subject.
- 4.5.9.2 Comparative mean linear & mean semi log plots of plasma concentration vs time.
- Note:** Refer SAS program, Annexure No. ANX/ST/SOP-016-20, ‘SAS Program For Graphs (Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design)’.

4.5.10 Bioequivalence Criteria For Primary Pharmacokinetic Parameters

- 4.5.10.1 If the 90% confidence interval for log-transformed $C_{max, ss}$, $C_{tau, ss}$ and AUC_{0-tau} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.
- 4.5.10.2 90% confidence interval for $C_{max, ss}$, $C_{tau, ss}$ and AUC_{0-tau} is form the basis for concluding the bioequivalence in product R and T.

4.6 Scaled Average Bioequivalence Approach For Partial Replicated 3-Way Crossover Design -Two Formulation, Three Period, Three Sequence & Partial Replicated 4-Way Crossover Design -Two Formulation, Four Period, Two Sequence

4.6.1 Widening Limits For Primary Pharmacokinetic Parameter C_{max}

- 4.6.1.1 If $S_{WR} \geq 0.294$, i.e. intra-subject C.V. for reference formulation for $C_{max} \geq 30\%$ then scaled average bioequivalence procedure is used to determine bioequivalence (BE) for the relevant pharmacokinetic parameter C_{max} .
- 4.6.1.2 The extent of the widening is defined based upon the within-subject variability of reference product. Widening limits is calculated as $[U, L] = 100 * e^{\pm K * S_{RR}}$

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	12 of 16

Where, U is upper limit of the acceptance range, L is lower limits of the acceptance range, K is the regulatory constant set to 0.760 and S_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product.

- 4.6.2 **Scaled-Average Bioequivalence Criteria For Primary Pharmacokinetic Parameter C_{max}**
- 4.6.2.1 If $S_{WR} \geq 0.294$, i.e. intra-subject C.V. for reference formulation for $C_{max} \geq 30\%$ then acceptance criteria for C_{max} can be widened to maximum of 69.84 – 143.19%.
- 4.6.2.2 The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC_{0-t} where the acceptance range should remain at 80.00 – 125.00% regardless of variability.
- 4.6.2.3 The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology:

Widening limits $[U, L] = 100 * e^{\pm K * S_{WR}}$		
Within-Subject C.V.(%) *	L=Lower Limit (%)	U=Upper Limit (%)
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥ 50	69.84	143.19

* C.V. (%) = $100 * \sqrt{e^{S_{WR}^2} - 1}$

- 4.6.2.4 If the 90% confidence interval for log-transformed C_{max} is entirely included in the widening limits $[U, L] = 100 * e^{\pm K * S_{WR}}$, the geometric mean ratio (GMR) test to reference for C_{max} & 90% confidence interval for log-transformed AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.
- 4.6.2.5 The geometric mean ratio (GMR) test to reference for C_{max} , 90 % confidence interval for C_{max} & AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T.
- Note:** i) Calculation of within subject variability of reference product & Widening limits, Refer SAS program, Annexure No. ANX/ST/SOP-016-21, 'SAS Program For the Statistical Analysis Of The Scaled-Average Bioequivalence Approach For Partial Replicated Crossover Design'.
- ii) Under scaled-average bioequivalence approach, Calculation of geometric mean ratio (GMR) test to reference for C_{max} , 90 % confidence interval for C_{max} & AUC_{0-t} & bioequivalence criteria, Refer SAS program, Annexure No. ANX/ST/SOP-016-22 & ANX/ST/SOP-016-23.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE		
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE		
Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	13 of 16

- 4.6.3 **Partial Replicated 3-Way & 4-Way Crossover Design: Unscaled-Average Bioequivalence Criteria For Primary Pharmacokinetic Parameters**
- 4.6.3.1 If $S_{WR} < 0.294$, i.e. intra-subject C.V. for reference formulation for $C_{max} < 30\%$ then use following acceptance criteria for C_{max} .
- 4.6.3.2 If the 90% confidence intervals for log-transformed C_{max} and AUC_{0-t} are entirely included in the range of 80.00 – 125.00%, then the products are claimed to be bioequivalent.
- 4.6.3.3 The 90 % confidence interval for C_{max} and AUC_{0-t} is form the basis for concluding the bioequivalence in product R and T. Statistical analysis, Refer section 4.4 for statistical analysis. Note: Refer SAS program for unscaled-average bioequivalence criteria for 4-way & 3-way replicated design, Refer SAS program, Annexure No. ANX/ST/SOP-016-11 & ANX/ST/SOP-016-12.
- 4.7 Primary and secondary pharmacokinetic parameters, statistical analysis and bioequivalence criteria for primary parameters should be according to regulatory guidelines or product specific guidance's or sponsor requirement.

5. ABBREVIATION (S):

- 5.1 R : Reference
- 5.2 T : Test
- 5.3 form : Formulation
- 5.4 C_{pd} : Pre-dose concentration determined immediately before a dose at steady state
- 5.5 C_{max} : Maximum observed concentration
- 5.6 $C_{max, ss}$: Maximum observed concentration at steady state
- 5.7 $C_{tau, ss}$: Concentration at the end of dosing interval (tau) at steady state
- 5.8 $C_{min, ss}$: Minimum observed concentration at steady state
- 5.9 t_{max} : Sampling time at which C_{max} occurred
- 5.10 $t_{max, ss}$: Sampling time at which C_{max} occurred at steady state
- 5.11 $C_{avg, ss}$: Average concentration during a dosing interval at steady state.
- 5.12 AUC_{0-tau} : Area under the concentration versus time curve calculated throughout the dosing Interval (tau)
- 5.13 AUC_{0-t} : Area Under Curve for time 0 to t
- 5.14 K_e : Elimination Rate
- 5.15 $AUC_{0-\infty}$: Area Under Curve for time 0 to infinity (∞)
- 5.16 t_{half} : Terminal-half life
- 5.17 Res_area : Residual Area

ANX/GN/SOP-001-01

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

STANDARD OPERATING PROCEDURE**STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE**

Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	14 of 16

5.18	ANOVA	: Analysis of Variance
5.19	GLM	: General Linear Model
5.20	C.V.	: Coefficient of Variance
5.21	S.D.	: Standard Deviation
5.22	GM	: Geometric Mean
5.23	MSE	: Mean Square Error
5.24	N/AP	: Not Applicable
5.25	No.	: Number
5.26	hrs.	: Hour
5.27	mL	: Milliliter
5.28	BEQ	: Bioequivalence
5.29	ST	: Statistics
5.30	SOP	: Standard Operating Procedure
5.31	SAS®	: Statistical Analysis System
5.32	Seq	: Sequence

6 REFERENCE (S):

- 6.1 EmeA, Guideline On The Investigation Of Bioequivalence, London, 20 January 2010
- 6.2 EMA, Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party, 2 May 2014, EMA/618604/2008 Rev. 9, Committee for Human Medicinal Products (CHMP)
- 6.3 EmeA, Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), 20 November 2014, EMA/CHMP/EWP/280/96, Committee for Medicinal Products for Human Use (CHMP)

7 ANNEXURE (S):

- 7.1 Annexure No. ANX/ST/SOP-016-01, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design With Standard ANOVA Model'
- 7.2 Annexure No. ANX/ST/SOP-016-02, 'Sample SAS Output Of 2 X 2 Crossover Design'
- 7.3 Annexure No. ANX/ST/SOP-016-03, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design With Group ANOVA Model'
- 7.4 Annexure No. ANX/ST/SOP-016-04, 'SAS Program For Graphs (The Two Formulation, Two Sequence, Two Period, 2 X 2 Crossover Design)'

ANX/GN/SOP-001-01

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.			
STANDARD OPERATING PROCEDURE			
STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE			
Supersedes	SOP No.:	Page No.:	
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	15 of 16	

- 7.5 Annexure No. ANX/ST/SOP-016-05, 'SAS Program For The Statistical Analysis Of The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design With Standard ANOVA Model'
- 7.6 Annexure No. ANX/ST/SOP-016-06, 'SAS Program For The Statistical Analysis Of The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design With Group ANOVA Model'
- 7.7 Annexure No. ANX/ST/SOP-016-07, 'SAS Program For Graphs (The Three Formulation, Three Sequence, Three Period, 3 X 3 Cross Over Design)'
- 7.8 Annexure No. ANX/ST/SOP-016-08, 'SAS Program For The Statistical Analysis Of The Two Formulation, Single Period, Parallel Design With Standard ANOVA Model'
- 7.9 Annexure No. ANX/ST/SOP-016-09, 'SAS Program For The Statistical Analysis Of The Two Formulation, Single Period, Parallel Design With Group ANOVA Model'
- 7.10 Annexure No. ANX/ST/SOP-016-10, 'SAS Program For Graphs (The Two Formulation, Single Period, Parallel Design)'
- 7.11 Annexure No. ANX/ST/SOP-016-11, 'SAS Program For The Statistical Analysis of Unscaled Average Bioequivalence (Two Formulation, Two Sequence, Four Period, Partial Replicated 4 Way & 3-Way Crossover Design With Standard ANOVA Model)'
- 7.12 Annexure No. ANX/ST/SOP-016-12, 'SAS Program For The Statistical Analysis of Unscaled Average Bioequivalence (Two Formulation, Two Sequence, Four Period, Partial Replicated 4 Way & 3-Way Crossover Design With Group ANOVA Model)'
- 7.13 Annexure No. ANX/ST/SOP-016-13, 'SAS Program For Graphs (Two Formulation, Two Sequence, Four Period, Partial Replicated 4-Way Crossover Design)'
- 7.14 Annexure No. ANX/ST/SOP-016-14, 'SAS Program For Graphs (Two Formulation, Three Sequence, Three Period, Partial Replicated 3-Way Crossover Design)'
- 7.15 Annexure No. ANX/ST/SOP-016-15, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Standard ANOVA Model'
- 7.16 Annexure No. ANX/ST/SOP-016-16, 'SAS Program For The Statistical Analysis Of The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Group ANOVA Model'
- 7.17 Annexure No. ANX/ST/SOP-016-17, 'SAS Program For Graphs (The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design)'

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STANDARD OPERATING PROCEDURE**STATISTICAL ANALYSIS FOR BIOEQUIVALENCE PROJECTS AS PER REQUIREMENT BASED ON EMEA/WHO GUIDANCE**

Supersedes	SOP No.:	Page No.:
BEQ/ST/SOP-016/00	BEQ/ST/SOP-016/01	16 of 16

- 7.18 Annexure No. ANX/ST/SOP-016-18, 'SAS Program For The Statistical Analysis Of Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design'
- 7.19 Annexure No. ANX/ST/SOP-016-19, 'SAS Program For The Statistical Analysis Of Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design With Group'
- 7.20 Annexure No. ANX/ST/SOP-016-20, 'SAS Program For Graphs (Pre-dose Concentration for The Two Formulation, Two Sequence, Two Period, Multiple Dose, 2 X 2 Crossover Steady State Design)'
- 7.21 Annexure No. ANX/ST/SOP-016-21, 'SAS Program For The Statistical Analysis Of The Scaled-Average Bioequivalence Approach For Partial Replicated Crossover Design'
- 7.22 Annexure No. ANX/ST/SOP-016-22, 'SAS Program For The Statistical Analysis Of The Unscaled-Average Bioequivalence Approach For Partial Replicated 4 Way and 3 Way Crossover Design With Standard ANOVA Model (Under scaled-average bioequivalence approach)'.
- 7.23 Annexure No. ANX/ST/SOP-016-23, 'SAS Program For The Statistical Analysis Of The Unscaled-Average Bioequivalence Approach For Partial Replicated Crossover Design With Group ANOVA Model (Under scaled-average bioequivalence approach)'

8 FORM (S): N/AP

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, TWO SEQUENCE,
TWO PERIOD, 2 X 2 Crossover Design With Standard ANOVA Model**

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1   " SAS Version Used: Version &sysver    ";
FOOTNOTE2   '                                     ';
FOOTNOTE3   '                                     ';
FOOTNOTE4   j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5   '                                     ';
FOOTNOTE6   '                                     ';
FOOTNOTE7   j=1 ' (Signature/Date)                  ';
proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;
proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints;
run;
proc sort data=one;
by form subject;
run;
Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
run;
Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
run;
proc univariate data=T_Data nextrobs=0 noprint;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

var cmax_T AUCt_T AUCinf_T;
output out=M_T
      mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
run;

proc univariate data=R_Data nextrobs=0 noprint;
var cmax_R AUCt_R AUCinf_R;
output out=M_R
      mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;

Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
      R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
      (%)"
      B_cmax="Bioavailability of Cmax (%)"
      B_AUCt="Bioavailability of AUCt (%)"
      ;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;

Data Ratio;
merge T_Data R_Data;
Ratio_Cmax=100*(cmax_T/cmax_R);
Ratio_AUCt=100*(AUCt_T/AUCt_R);
tbyinf__T=100*(AUCt_T/AUCinf_T);
tbyinf__R=100*(AUCt_R/AUCinf_R);
format Ratio_Cmax Ratio_AUCt tbyinf__T tbyinf__R 15.2;
Label Ratio_Cmax="Ratio Cmax (T/R) (%)"
      Ratio_AUCt="Ratio AUCt (T/R) (%)"
      tbyinf__T="Test Formulation: Ratio AUCt/AUCinf (%)"
      tbyinf__R="Reference Formulation: Ratio AUCt/AUCinf (%)"
run;

```

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MACLEODS

Reference SOP No. : BEQ/ST/SOP-016/01

```
proc print data=Ratio label;
TITLE4    "Ratio Analysis";
Var Subject seq Ratio_Cmax Ratio_AUCt tbyinf__T tbyinf__R;
run;

proc print data=M_T_R label noobs;
TITLE4    "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;

PROC SORT data=one;
        BY form;

Run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
        CLASS form;
        TITLE4    "SUMMARY STATISTICS - FORMULATION ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS seq;
        TITLE4    "SUMMARY STATISTICS - SEQUENCE ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS period;
        TITLE4    "SUMMARY STATISTICS - PERIOD ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS seq;
        BY form;
        TITLE4    "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS period;
        BY form;
        TITLE4    "SUMMARY STATISTICS - PERIOD/FORMULATION";
```


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**Reference SOP No. : BEQ/ST/SOP-016/01**

```
VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;

set one;

LCmax=log(Cmax);

LAUCt=log(AUCt);

run;

proc glm data=two;
Title4 "ANOVA for log transformed Cmax ";
class form period seq subject;
model LCmax=seq subject(seq) period form/ssl ss3;
test h=seq e=subject(seq);
lsmeans form/stderr pdiff;
estimate 'R vs T' form -1 1;
run;
quit;

proc glm data=two;
Title4 "ANOVA for log transformed AUCt ";
class form period seq subject;
model LAUCt=seq subject(seq) period form/ssl ss3;
test h=seq e=subject(seq);
lsmeans form/stderr pdiff;
estimate 'R vs T' form -1 1;
run;
quit;

proc glm data=two outstat=tanova noprint;
class form period seq subject;
model LCmax LAUCt=seq subject(seq) period form/ssl ss3;
test h=seq e=subject(seq);
lsmeans form/stderr pdiff out=lsmean1;
run;
quit;

proc sort data=two;
by seq subject form;
run;

proc means n noprint data=two; by seq;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
var LCmax LAUCt;
output out=no      n=n;
run;
data no; set no; n=n/2;
run;
proc sort data=no; by seq;
run;
data two; merge two no; by seq;
run;
proc sort data=two; by seq subject form;
run;
data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
keep mse sse df id;run;
proc sort data=error; by id;run;
data nol; set no; if seq='RT';
n1=n; id=1;
keep n1 id;
run;
proc sort data=nol; by id;run;
data no2; set no; if seq='TR';
n2=n; id=1;
keep n2 id;
run;
proc sort data=no2; by id;run;
data lsmean11; set lsmean1; if form='R';
my1=lsmean; id=1; keep ID my1 _name_;run;
proc sort data=lsmean11; by id;run;
data lsmean12; set lsmean1; if form='T';
my2=lsmean;
id=1;
keep id my2 _name_;run;
proc sort data=lsmean12; by id;run;
data twoside; merge lsmean11 lsmean12 nol no2 error;
by id;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
data twoside;
set twoside;
by id;
retain n;
if first.id then n=1;
else n=n+1;
run;
data twoside;
set twoside;
by id;
format Gmref GMtest 12.3 Ratio Intra_CV Power Lower Upper 8.2;
length Bioequivalence $20;
spool=mse*(0.5)*((1/n1)+(1/n2));
se=sqrt(spool);
diff=exp(my2)- exp(my1);
Ratio=100*exp(my2-my1);
Intra_cv=100*sqrt(exp(mse)-1);
ct=tinv(0.05,df,0);
absct=abs(ct);
Lower=Round(100*exp((my2-my1)-(absct*se)),0.01);
Upper=Round(100*exp((my2-my1)+(absct*se)),0.01);
pt=tinv(0.025,df,0);
apt=abs(pt);
pw=(log(1.25)/se-apt);
Power=100*probt(pw,df);
Gmref=exp(my1); Gmtest=exp(my2);
if (Lower>=80.00) and (Upper<=125.00) then Bioequivalence="Yes"; else
Bioequivalence="No";
run;
proc print data=twoside noobs;
Title4 " 90% C.I Equivalent to Schuirmanns's Two One Sided Test ";
var _name_ GMref Gmtest n1 n2 df mse diff Ratio Intra_CV Power Lower Upper
Bioequivalence;
run;
ods pdf close; ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAMPLE SAS OUTPUT OF 2 X 2 CROSSOVER DESIGN

The SAS System

12:00 Thursday, June 9, 2016 1

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

Obs	subject	seq	form	period	Cmax	Tmax	AUCt	AUCinf	ke	thalf
1	1	RT	R	1	3638.52	0.50	11094.0143	12174.7952	0.2062	3.3612
2	1	RT	T	2	2677.80	0.83	13401.1920	14205.4887	0.1627	4.2616
3	2	RT	R	1	1782.88	0.50	5752.6451	6377.6222	0.2604	2.6614
4	2	RT	T	2	2559.21	0.33	6433.6153	6968.9523	0.3398	2.0397
5	3	RT	R	1	1916.67	2.67	13094.8156	14089.6472	0.1291	5.3675
6	3	RT	T	2	2961.07	0.67	14915.5204	16000.1025	0.1545	4.4863
7	4	TR	T	1	1742.64	0.50	6148.7343	6516.7678	0.3037	2.2824
8	4	TR	R	2	1955.29	0.67	5345.4546	5854.6821	0.3331	2.0807
9	5	TR	T	1	2500.41	0.50	10089.1049	11101.1615	0.2044	3.3914
10	5	TR	R	2	2788.71	0.67	9647.5112	10524.8787	0.2115	3.2775
11	6	TR	T	1	2845.75	0.33	14303.9221	15125.8473	0.1773	3.9094
12	6	TR	R	2	2782.84	0.67	13149.3354	13894.6553	0.1741	3.9804
13	7	TR	T	1	2019.70	0.83	12237.1395	13162.4618	0.1640	4.2269
14	7	TR	R	2	2647.60	0.50	11878.9867	12381.2444	0.2020	3.4316
15	8	TR	T	1	2709.35	0.50	12299.5187	12810.8713	0.2079	3.3337
16	8	TR	R	2	3290.05	0.33	11043.4994	11845.6847	0.2276	3.0451
17	9	RT	R	1	2035.85	0.50	10316.6867	11340.0716	0.2095	3.3078
18	9	RT	T	2	2847.23	0.67	13484.5241	14154.4232	0.1830	3.7877
19	10	RT	R	1	1797.44	2.33	8919.6284	9776.1677	0.2196	3.1560
20	10	RT	T	2	3690.00	0.33	11082.4668	11826.2139	0.2335	2.9686
21	11	RT	R	1	3776.28	0.33	3796.8446	4018.0329	0.4698	1.4753
22	11	RT	T	2	2341.72	0.33	5035.7950	5391.0029	0.3855	1.7978
23	12	TR	T	1	2382.38	0.33	5178.6974	5783.2980	0.2581	2.6857
24	12	TR	R	2	2553.48	0.33	5368.5954	5787.3749	0.2585	2.6815

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

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**Reference SOP No. : BEQ/ST/SOP-016/01**

The SAS System

12:00 Thursday, June 9, 2016 2

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

Obs	subject	seq	form	period	Res_area	Ke_first	Ke_last	npoints
1	1	RT	R	1	0.0888	0.83	12	16
2	1	RT	T	2	0.0566	10.00	16	3
3	2	RT	R	1	0.0980	0.50	10	17
4	2	RT	T	2	0.0768	0.83	8	14
5	3	RT	R	1	0.0706	12.00	20	3
6	3	RT	T	2	0.0678	8.00	16	4
7	4	TR	T	1	0.0565	5.00	10	4
8	4	TR	R	2	0.0870	1.00	8	13
9	5	TR	T	1	0.0912	0.83	12	16
10	5	TR	R	2	0.0834	1.25	12	14
11	6	TR	T	1	0.0543	8.00	16	4
12	6	TR	R	2	0.0536	10.00	16	3
13	7	TR	T	1	0.0703	10.00	16	3
14	7	TR	R	2	0.0406	1.75	16	13
15	8	TR	T	1	0.0399	1.00	16	16
16	8	TR	R	2	0.0677	8.00	12	3
17	9	RT	R	1	0.0902	2.33	12	10
18	9	RT	T	2	0.0473	10.00	16	3
19	10	RT	R	1	0.0876	3.00	12	8
20	10	RT	T	2	0.0629	0.83	12	16
21	11	RT	R	1	0.0550	0.67	6	14
22	11	RT	T	2	0.0659	0.33	8	17
23	12	TR	T	1	0.1045	4.00	8	4
24	12	TR	R	2	0.0724	1.75	10	11

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 2 of 21

Macleods Pharmaceuticals Limited

Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 3

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

Ratio Analysis

Obs	subject	seq	Ratio Cmax (T/R) (%)	Ratio AUCt (T/R) (%)	Test	Reference
					Formulation: Ratio AUCt/AUCinf (%)	Formulation: Ratio AUCt/AUCinf (%)
1	1	RT	73.60	120.80	94.34	91.12
2	2	RT	143.54	111.84	92.32	90.20
3	3	RT	154.49	113.90	93.22	92.94
4	4	TR	89.12	115.03	94.35	91.30
5	5	TR	89.66	104.58	90.88	91.66
6	6	TR	102.26	108.78	94.57	94.64
7	7	TR	76.28	103.02	92.97	95.94
8	8	TR	82.35	111.37	96.01	93.23
9	9	RT	139.85	130.71	95.27	90.98
10	10	RT	205.29	124.25	93.71	91.24
11	11	RT	62.01	132.63	93.41	94.50
12	12	TR	93.30	96.46	89.55	92.76

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 4

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

Ratio Analysis

Ratio of mean AUcT to mean AUcinf for Test formulation (%)	Ratio of mean AUcT to mean AUcinf for Reference formulation (%)	Bioavailability of Cmax (%)	Bioavailability of AUcT (%)
93.66	92.67	101.01	113.89

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 5

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - FORMULATION

The MEANS Procedure

form	N	Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation
R	12	Cmax	concentration		12	2580.467500	2600.540000	708.382585	27.451715
		AUCt			12	9117.334763	9982.098963	3261.190174	35.769117
		AUCinf			12	9838.738089	10932.475181	3455.495125	35.121324
		Tmax	time		12	0.833333	0.500000	0.791883	95.025968
		thalf			12	3.152177	3.216766	0.962435	30.532397
		ke			12	0.241805	0.215556	0.087249	36.082343
		Res_area			12	0.074576	0.077861	0.017685	23.714455
T	12	Cmax	concentration		12	2606.438333	2618.505000	491.284346	18.848877
		AUCt			12	10384.185863	11659.803143	3711.613300	35.742940
		AUCinf			12	11087.215935	12318.542585	3882.710018	35.019702
		Tmax	time		12	0.512500	0.500000	0.194988	38.046506
		thalf			12	3.264267	3.362550	0.912640	27.958498
		ke			12	0.231199	0.206152	0.075796	32.783686
		Res_area			12	0.066172	0.064389	0.018117	27.379271

form	N	Obs	Variable	Label	Minimum	Maximum
R	12	Cmax	concentration		1782.880000	3776.280000
		AUCt			3796.844550	13149.335350
		AUCinf			4018.032923	14089.647182
		Tmax	time		0.330000	2.670000
		thalf			1.475328	5.367516
		ke			0.129137	0.469826
		Res_area			0.040566	0.097995
T	12	Cmax	concentration		1742.640000	3690.000000
		AUCt			5035.795000	14915.520385
		AUCinf			5391.002912	16000.102528
		Tmax	time		0.330000	0.830000
		thalf			1.797819	4.486334
		ke			0.154502	0.385549
		Res_area			0.039916	0.104543

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 6

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - SEQUENCE

The MEANS Procedure

seq	N	Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	12	Cmax	concentration		12	2668.723	2618.505	735.8667	27.57374	1782.880	3776.280
		AUCt			12	9777.312	10699.58	3746.184	38.31507	3796.845	14915.52
		AUCinf			12	10526.88	11583.14	3972.484	37.73659	4018.033	16000.10
		Tmax	time		12	0.832500	0.500000	0.798489	95.91455	0.330000	2.670000
		thalf			12	3.222585	3.231900	1.147684	35.61376	1.475328	5.367516
		ke			12	0.246152	0.214589	0.102377	41.59090	0.129137	0.469826
		Res_area			12	0.072301	0.069197	0.016036	22.17900	0.047328	0.097995
TR	12	Cmax	concentration		12	2518.183	2600.540	435.5149	17.29481	1742.640	3290.050
		AUCt			12	9724.208	10566.30	3354.312	34.49445	5178.697	14303.92
		AUCinf			12	10399.08	11473.42	3475.132	33.41769	5783.298	15125.85
		Tmax	time		12	0.513333	0.500000	0.167622	32.65354	0.330000	0.830000
		thalf			12	3.193859	3.305630	0.669640	20.96650	2.080698	4.226865
		ke			12	0.226853	0.209702	0.052294	23.05172	0.163986	0.333132
		Res_area			12	0.068447	0.069010	0.020354	29.73693	0.039916	0.104543

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No. : BEQ/ST/SOP-016/01**

The SAS System

12:00 Thursday, June 9, 2016 7

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - PERIOD

The MEANS Procedure

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum
1	12	Cmax	concentration	12	2428.989	2209.115	701.2752	28.87107	1742.640
		AUCt		12	9435.979	10202.90	3459.446	36.66229	3796.845
		AUCinf		12	10189.73	11220.62	3656.587	35.88503	4018.033
		Tmax	time	12	0.818333	0.500000	0.799850	97.74139	0.330000
		thalf		12	3.263224	3.320764	0.985022	30.18556	1.475328
		ke		12	0.234182	0.208734	0.087384	37.31471	0.129137
		Res_area		12	0.075585	0.079111	0.020627	27.29037	0.039916
2	12	Cmax	concentration	12	2757.917	2730.320	439.0133	15.91829	1955.290
		AUCt		12	10065.54	11062.98	3619.791	35.96220	5035.795
		AUCinf		12	10736.23	11835.95	3785.835	35.26225	5391.003
		Tmax	time	12	0.527500	0.585000	0.188010	35.64169	0.330000
		thalf		12	3.153219	3.161305	0.888356	28.17299	1.797819
		ke		12	0.238823	0.219557	0.075967	31.80890	0.154502
		Res_area		12	0.065163	0.066804	0.013957	21.41814	0.040566

period	N Obs	Variable	Label	Maximum
1	12	Cmax	concentration	3776.280
		AUCt		14303.92
		AUCinf		15125.85
		Tmax	time	2.670000
		thalf		5.367516
		ke		0.469826
		Res_area		0.104543
2	12	Cmax	concentration	3690.000
		AUCt		14915.52
		AUCinf		16000.10
		Tmax	time	0.830000
		thalf		4.486334
		ke		0.385549
		Res_area		0.086978

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited

Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 8

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - SEQUENCE/FORMULATION

form=R

The MEANS Procedure

seq	N	Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	6	Cmax	concentration		6	2491.273	1976.260	947.4410	38.03039	1782.880	3776.280
		AUCt			6	8829.106	9618.158	3473.772	39.34455	3796.845	13094.82
		AUCinf			6	9629.389	10558.12	3778.420	39.23841	4018.033	14089.65
		Tmax	time		6	1.138333	0.500000	1.062251	93.31632	0.330000	2.670000
		thalf			6	3.221543	3.231900	1.264866	39.26273	1.475328	5.367516
		ke			6	0.249134	0.214589	0.116199	46.64114	0.129137	0.469826
		Res_area			6	0.081714	0.088194	0.015855	19.40289	0.055049	0.097995
TR	6	Cmax	concentration		6	2669.662	2715.220	432.7067	16.20830	1955.290	3290.050
		AUCt			6	9405.564	10345.51	3336.364	35.47224	5345.455	13149.34
		AUCinf			6	10048.09	11185.28	3447.803	34.31303	5787.375	13894.66
		Tmax	time		6	0.528333	0.585000	0.167143	31.63583	0.330000	0.670000
		thalf			6	3.082812	3.161305	0.652983	21.18141	2.080698	3.980402
		ke			6	0.234477	0.219557	0.055823	23.80745	0.174140	0.333132
		Res_area			6	0.067438	0.070040	0.017732	26.29404	0.040566	0.086978

SAS Version Used: Version 9.4

Analysis Performed By: _____
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Macleods Pharmaceuticals Limited



Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

form=T

seq	N	Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum	Maximum
RT	6	Cmax	concentration		6	2846.172	2762.515	466.9939	16.40779	2341.720	3690.000
		AUCt			6	10725.52	12241.83	4080.398	38.04383	5035.795	14915.52
		AUCinf	time		6	11424.36	12990.32	4302.067	37.65695	5391.003	16000.10
		Tmax			6	0.526667	0.500000	0.223219	42.38333	0.330000	0.830000
		thalf			6	3.223627	3.378166	1.139256	35.34081	1.797819	4.486334
		ke			6	0.243169	0.208246	0.097645	40.15534	0.154502	0.385549
		Res_area			6	0.062888	0.064389	0.010084	16.03499	0.047328	0.076817
TR	6	Cmax	concentration		6	2366.705	2441.395	418.3018	17.67444	1742.640	2845.750
		AUCt			6	10042.85	11163.12	3657.607	36.42000	5178.697	14303.92
		AUCinf	time		6	10750.07	11956.02	3792.806	35.28170	5783.298	15125.85
		Tmax			6	0.498333	0.500000	0.182583	36.63879	0.330000	0.830000
		thalf			6	3.304906	3.362550	0.728380	22.03936	2.282378	4.226865
		ke			6	0.219230	0.206152	0.052540	23.96580	0.163986	0.303695
		Res_area			6	0.069456	0.063387	0.024384	35.10633	0.039916	0.104543

SAS Version Used: Version 9.4

Analysis Performed By: _____
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Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 9

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - PERIOD/FORMULATION

----- form=R -----

The MEANS Procedure

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum
1	6	Cmax	concentration	6	2491.273	1976.260	947.4410	38.03039	1782.880
		AUCt		6	8829.106	9618.158	3473.772	39.34455	3796.845
		AUCinf		6	9629.389	10558.12	3778.420	39.23841	4018.033
		Tmax	time	6	1.138333	0.500000	1.062251	93.31632	0.330000
		thalf		6	3.221543	3.231900	1.264866	39.26273	1.475328
		ke		6	0.249134	0.214589	0.116199	46.64114	0.129137
		Res_area		6	0.081714	0.088194	0.015855	19.40289	0.055049
2	6	Cmax	concentration	6	2669.662	2715.220	432.7067	16.20830	1955.290
		AUCt		6	9405.564	10345.51	3336.364	35.47224	5345.455
		AUCinf		6	10048.09	11185.28	3447.803	34.31303	5787.375
		Tmax	time	6	0.528333	0.585000	0.167143	31.63583	0.330000
		thalf		6	3.082812	3.161305	0.652983	21.18141	2.080698
		ke		6	0.234477	0.219557	0.055823	23.80745	0.174140
		Res_area		6	0.067438	0.070040	0.017732	26.29404	0.040566

period	N Obs	Variable	Label	Maximum
1	6	Cmax	concentration	3776.280
		AUCt		13094.82
		AUCinf		14089.65
		Tmax	time	2.670000
		thalf		5.367516
		ke		0.469826
		Res_area		0.097995
2	6	Cmax	concentration	3290.050
		AUCt		13149.34
		AUCinf		13894.66
		Tmax	time	0.670000
		thalf		3.980402
		ke		0.333132
		Res_area		0.086978

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No. : BEQ/ST/SOP-016/01**

form=T

period	N Obs	Variable	Label	N	Mean	Median	Std Dev	Coeff of Variation	Minimum
1	6	Cmax	concentration	6	2366.705	2441.395	418.3018	17.67444	1742.640
		AUCt		6	10042.85	11163.12	3657.607	36.42000	5178.697
		AUCinf		6	10750.07	11956.02	3792.806	35.28170	5783.298
		Tmax	time	6	0.498333	0.500000	0.182583	36.63879	0.330000
		thalf		6	3.304906	3.362550	0.728380	22.03936	2.282378
		ke		6	0.219230	0.206152	0.052540	23.96580	0.163986
		Res_area		6	0.069456	0.063387	0.024384	35.10633	0.039916
2	6	Cmax	concentration	6	2846.172	2762.515	466.9939	16.40779	2341.720
		AUCt		6	10725.52	12241.83	4080.398	38.04383	5035.795
		AUCinf		6	11424.36	12990.32	4302.067	37.65695	5391.003
		Tmax	time	6	0.526667	0.500000	0.223219	42.38333	0.330000
		thalf		6	3.223627	3.378166	1.139256	35.34081	1.797819
		ke		6	0.243169	0.208246	0.097645	40.15534	0.154502
		Res_area		6	0.062888	0.064389	0.010084	16.03499	0.047328

period	N Obs	Variable	Label	Maximum
1	6	Cmax	concentration	2845.750
		AUCt		14303.92
		AUCinf		15125.85
		Tmax	time	0.830000
		thalf		4.226865
		ke		0.303695

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 11 of 21

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 10

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

SUMMARY STATISTICS - PERIOD/FORMULATION

----- form=T -----

The MEANS Procedure

period	N Obs	Variable	Label	Maximum
1	6	Res_area		0.104543
2	6	Cmax	concentration	3690.000
		AUCt		14915.52
		AUCinf		16000.10
		Tmax	time	0.830000
		thalf		4.486334
		ke		0.385549
		Res_area		0.076817

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

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Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 11
Protocol No: -----
Statistical Data Processing of ----- Under ----- Condition
ANOVA for log transformed Cmax

The GLM Procedure

Class Level Information

Class	Levels	Values
form	2	R T
period	2	1 2
seq	2	RT TR
subject	12	1 2 3 4 5 6 7 8 9 10 11 12

Number of Observations Read 24
Number of Observations Used 24

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 13 of 21

Macleods Pharmaceuticals Limited



Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 12

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition
ANOVA for log transformed Cmax

The GLM Procedure

Dependent Variable: LCmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	0.64792232	0.04984018	0.88	0.5941
Error	10	0.56677413	0.05667741		
Corrected Total	23	1.21469645			

R-Square	Coeff Var	Root MSE	LCmax Mean
0.533403	3.038342	0.238070	7.835529

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00853049	0.00853049	0.15	0.7062
subject(seq)	10	0.49941139	0.04994114	0.88	0.5773
period	1	0.13542841	0.13542841	2.39	0.1532
form	1	0.00455204	0.00455204	0.08	0.7827

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00853049	0.00853049	0.15	0.7062
subject(seq)	10	0.49941139	0.04994114	0.88	0.5773
period	1	0.13542841	0.13542841	2.39	0.1532
form	1	0.00455204	0.00455204	0.08	0.7827

Tests of Hypotheses Using the Type III MS for subject(seq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00853049	0.00853049	0.17	0.6881

SAS Version Used: Version 9.4

Analysis Performed By: _____
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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 13

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

ANOVA for log transformed Cmax

The GLM Procedure

Least Squares Means

				H0:LSMean1=
form	LCmax	LSMEAN	Standard Error	LSMean2
			H0:LSMEAN=0 Pr > t	Pr > t
R	7.82175659		0.06872494	<.0001
T	7.84930061		0.06872494	<.0001
				0.7827

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 15 of 21

Macleods Pharmaceuticals Limited

Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 14

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition
ANOVA for log transformed Cmax

The GLM Procedure

Dependent Variable: LCmax

Parameter	Estimate	Standard Error	t Value	Pr > t
R vs T	0.02754402	0.09719175	0.28	0.7827

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 16 of 21

Macleods Pharmaceuticals Limited

Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 15
Protocol No: -----
Statistical Data Processing of ----- Under ----- Condition
ANOVA for log transformed AUCt

The GLM Procedure

Class Level Information

Class	Levels	Values
form	2	R T
period	2	1 2
seq	2	RT TR
subject	12	1 2 3 4 5 6 7 8 9 10 11 12

Number of Observations Read 24
Number of Observations Used 24

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited

Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System 12:00 Thursday, June 9, 2016 16

Protocol NO: -----

Statistical Data Processing of ----- Under ----- Condition
ANOVA for log transformed AUCt

The GLM Procedure

Dependent Variable: LAUCt

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	3.87164827	0.29781910	135.22	<.0001
Error	10	0.02202503	0.00220250		
Corrected Total	23	3.89367330			

R-Square	Coeff Var	Root MSE	LAUCt Mean
0.994343	0.515071	0.046931	9.111528

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.00101520	0.00101520	0.46	0.5126
subject(seq)	10	3.73954588	0.37395459	169.79	<.0001
period	1	0.02856348	0.02856348	12.97	0.0048
form	1	0.10252371	0.10252371	46.55	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00101520	0.00101520	0.46	0.5126
subject(seq)	10	3.73954588	0.37395459	169.79	<.0001
period	1	0.02856348	0.02856348	12.97	0.0048
form	1	0.10252371	0.10252371	46.55	<.0001

Tests of Hypotheses Using the Type III MS for subject(seq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00101520	0.00101520	0.00	0.9595

SAS Version Used: Version 9.4

Analysis Performed By: _____
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Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No. : BEQ/ST/SOP-016/01**

The SAS System

12:00 Thursday, June 9, 2016 17

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

ANOVA for log transformed AUCt

The GLM Procedure

Least Squares Means

form	LAUCt LSMEAN	Standard Error	H0:LSMEAN=0	
			Pr > t	Pr > t
R	9.04616913	0.01354776	<.0001	<.0001
T	9.17688747	0.01354776	<.0001	

SAS Version Used: Version 9.4

Analysis Performed By: _____
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Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 18

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

ANOVA for log transformed AUCt

The GLM Procedure

Dependent Variable: LAUCt

Parameter	Estimate	Standard Error	t Value	Pr > t
R vs T	0.13071834	0.01915943	6.82	<.0001

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-016/01

The SAS System

12:00 Thursday, June 9, 2016 19

Protocol No: -----

Statistical Data Processing of ----- Under ----- Condition

90% C.I Equivalent to Schuirmann's Two One Sided Test

NAME	Gmref	GMtest	n1	n2	DF	mse	diff
LCmax	2494.283	2563.940	6	6	10	0.056677	69.66
LAUCt	8485.967	9671.005	6	6	10	0.002203	1185.04

Ratio	Intra_CV	Power	Lower	Upper	Bioequivalence
102.79	24.15	52.63	86.19	122.59	Yes
113.96	4.70	100.00	110.08	117.99	Yes

SAS Version Used: Version 9.4

Analysis Performed By: _____
(Signature / Date)

ANX/ST/SOP-016-02

Page 21 of 21

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, TWO SEQUENCE,
TWO PERIOD, 2 X 2 Crossover Design With Group ANOVA Model**

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1   " SAS Version Used: Version &sysver      ";
FOOTNOTE2   '                                     ';
FOOTNOTE3   '                                     ';
FOOTNOTE4   j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5   '                                     ';
FOOTNOTE6   '                                     ';
FOOTNOTE7   j=1 ' (Signature/Date)                  ';
proc print data=one;
var subject seq form period group Cmax Tmax AUCt AUCinf ke thalf;
run;
proc print data=one;
var subject seq form period group Res_area Ke_first Ke_last npoints;
run;
proc sort data=one;
by form subject;
run;
Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
run;
Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
run;
proc univariate data=T_Data nextrobs=0 noprint;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

var cmax_T AUCt_T AUCinf_T;
output out=M_T
      mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;

run;

proc univariate data=R_Data nextrobs=0 noprint;
var cmax_R AUCt_R AUCinf_R;
output out=M_R
      mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;

run;

Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
      R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
      (%)"
      B_cmax="Bioavailability of Cmax (%)"
      B_AUCt="Bioavailability of AUCt (%)"
      ;

keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;

run;

Data Ratio;
merge T_Data R_Data;
Ratio_Cmax=100*(cmax_T/cmax_R);
Ratio_AUCt=100*(AUCt_T/AUCt_R);
tbyinf__T=100*(AUCt_T/AUCinf_T);
tbyinf__R=100*(AUCt_R/AUCinf_R);
format Ratio_Cmax Ratio_AUCt tbyinf__T tbyinf__R 15.2;
Label Ratio_Cmax="Ratio Cmax (T/R) (%)"
      Ratio_AUCt="Ratio AUCt (T/R) (%)"
      tbyinf__T="Test Formulation: Ratio AUCt/AUCinf (%)"
      tbyinf__R="Reference Formulation: Ratio AUCt/AUCinf (%)";

run;

```

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MACLEODS**Reference SOP No. : BEQ/ST/SOP-016/01**

```

proc print data=Ratio label;
TITLE4    "Ratio Analysis";
Var Subject seq Ratio_Cmax Ratio_AUCt tbyinf__T tbyinf__R;
run;

proc print data=M_T_R label noobs;
TITLE4    "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;

PROC SORT data=one;
        BY form;

Run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
        CLASS form;
        TITLE4    "SUMMARY STATISTICS - FORMULATION ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS seq;
        TITLE4    "SUMMARY STATISTICS - SEQUENCE ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS period;
        TITLE4    "SUMMARY STATISTICS - PERIOD ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS group;
        TITLE4    "SUMMARY STATISTICS - GROUP ";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
        CLASS seq;
        BY form;
        TITLE4    "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
        VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS period;

BY form;

TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;

set one;

LCmax=log(Cmax);

LAUCt=log(AUCt);

run;

/***** LCmax *****/

Proc Glm Data= two outstat=tanova;

Title4 "ANOVA for log transformed Cmax ";

class seq subject group form period;

model LCmax=form group form*group period(group) seq seq*group

subject(seq*group)/ss1 ss3 clparm alpha=0.1;

test h=seq e=subject(seq*group);

test h=group e=subject(seq*group);

lsmeans form/stderr pdiff out=lsmean;

estimate 'R vs T' Form -1 1;

ods output Estimates=ep;

Run;Quit;

Data error; set tanova;

if _SOURCE_ = 'ERROR';

mse=SS/DF; sse=SS; id=1;

keep mse sse df id;

Run;

Proc Sort Data=error;

by id;

Run;

Data test ;

set ep;

length Bioequivalence \$20;

Ratio=100*exp(estimate);

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Reference SOP No. : BEQ/ST/SOP-016/01

```

lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort Data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
myl=lsmean; id=1; keep ID myl ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(myl);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCt *****/
Proc Glim Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

class seq subject group form period;
model LAUCt=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
test h=seq e=subject(seq*group);
test h=group e=subject(seq*group);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
myl=lsmean; id=1; keep ID myl ;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_AUCT;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
Data CIALl;
set CI_Cmax CI_AUCT;
format Gmref Gmtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;
Run;
Proc Print Data=CIALL noobs;
Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";
var PK_Parameters Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;
Run;

Ods pdf close;
Ods rtf close;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR GRAPHS (THE TWO FORMULATION, TWO SEQUENCE, TWO PERIOD, 2 X 2
CROSSOVER DESIGN)**

```

/*****
/*   Study Number: ----- */
/*****

ods rtf file="D:\All Graphs.doc";

data data ;
    set data;
    keep subject trt c1-c26 t1-t26;
    label trt="Treatment";
run;

proc sort data=data;
    by subject trt;
run;

data a;
    set data;
    array c{26} c1-c26 ;array t{26} t1-t26;
    do st=1 to 26;
        cons=round(c{st},.0001);
        if (cons > 0)then lcon=log(c{st});
        else lcon=.;
        time=t(st);
        output;
    end;
    drop period seq;
    drop c1-c26 t1-t26 st;
run;

proc sort data=a;
    by subject;
run;

/*                               Linear Plot                               */
    goptions reset=all ;
    goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Concentration (ng/mL)') ;

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```

axis2 minor=(n=1) order=0.00      1.50      3.00      4.50      6.00
7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
19.50      21.00      22.50      24.00

;

proc gplot data=a;
    label subject='Subject No.';
    label time ='Time(Hour) ' ;
    title 'Comparative Linear Plot of ((Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ' ;
    by subject;
    plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
run;

/*                      Semi Log Plot                      */
goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      1.50      3.00      4.50      6.00
7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
19.50      21.00      22.50      24.00

;

proc gplot data=a;
    label subject='Subject No.';
    label time ='Time(Hour) ' ;
    title 'Comparative Semi Log Plot of ((Analyte name) Plasma
Concentration (ng/mL) Vs Time (Hour) ' ;
    by subject;
    plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
run;

/*                      Mean Graph                      */
proc sort data=data;
    by trt;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```
run;
proc means data=data mean noprint ;
  var c1-c26 ;
  by trt;
  output out= b;
run;
data c;
  set b;
  subject= _stat_ ;
run;
data d; set c;
  drop _type_ _stat_ _freq_;
  if subject NE "MEAN" then delete;
run;
data e;
  set d;
  array c{26} c1-c26 ;
  do st=1 to 26;
    cons=round(c{st},.00001);
    if (cons > 0)then lcon=log(c{st});
    else lcon=.;
    output;
  end;
  drop period seq;
  drop c1-c26 st;
run;
data f ;
  input time;
  cards;
```

;

run;

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Reference SOP No. : BEQ/ST/SOP-016/01

```
data g;
merge e f;
run;

/*                               Linear Plot                               */
goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00          1.50      3.00      4.50      6.00
7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
19.50     21.00     22.50     24.00

;

proc gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Linear Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) (N= ) ' ;
by subject;
plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

/*                               Semi Log Plot                               */
goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration(ng/mL)') ;
axis2 minor=(n=1) order=0.00          1.50      3.00      4.50      6.00
7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
19.50     21.00     22.50     24.00

;

proc gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) (N= ) ' ;
by subject;
plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

ods rtf close;

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE THREE FORMULATION, THREE SEQUENCE, THREE PERIOD, 3 X 3 CROSS OVER DESIGN WITH STANDARD ANOVA MODEL

```
Ods pdf file='D:\Statistical Analysis of ----- .pdf';
Ods rtf file='D:\Statistical Analysis of ----- .doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: ----- ';
Title3      ' Statistical Data Processing of ----- Under ----- Condition  ';
FOOTNOTE1 " SAS Version Used: Version &sysver  ";
FOOTNOTE2 '                                     ';
FOOTNOTE3 '                                     ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:  ';
FOOTNOTE5 '                                     ';
FOOTNOTE6 '                                     ';
FOOTNOTE7 j=1 ' (Signature/Date)              ';

proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints ;
run;

proc sort data=one;
by form subject;
run;

PROC SORT data=one;
      BY form;

Run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
      CLASS form;
      TITLE4      "SUMMARY STATISTICS - FORMULATION ";
      VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS seq;
      TITLE4      "SUMMARY STATISTICS - SEQUENCE ";
      VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    TITLE4 "SUMMARY STATISTICS - PERIOD ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS seq;
    BY form;
    TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    BY form;
    TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
RUN;

data two;
set one;
LCmax=log(Cmax);
LAUCt=log(AUCt);
run;

/***** LCmax *****/
Proc Glim Data= two outstat=tanova;
    Title4 "ANOVA for log transformed Cmax ";
    class form period seq subject;
    model LCmax=seq subject(seq) period form/ssl ss3 clparm alpha=0.1;
    test H=seq E=subject(seq);
    lsmeans form/stderr pdiff out=lsmean;
    estimate 'R vs T1' Form -1 1 0 ;
    estimate 'R vs T2' Form -1 0 1;
    ods output Estimates=ep;
Run;Quit;

Data error; set tanova;
    if _SOURCE_ = 'ERROR';
    mse=SS/DF; sse=SS; id=1;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

keep mse sse df id;

Run;

Proc Sort Data=error;
by id;
Run;

Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
id=1;
Run;

Proc Sort Data=test;
by id;
Run;

Data final;
merge test error;
by id;
Run;

Data lsmean_T1; set lsmean; if form='T1';
my1=lsmean; id=1; keep ID my1 ;
Run;

Data lsmean_T2; set lsmean; if form='T2';
my2=lsmean; id=1; keep ID my2 ;
Run;

Data lsmean_R; set lsmean; if form='R';
my3=lsmean;id=1;keep id my3;
Run;

Data CI_Cmax;
merge final lsmean_T1 lsmean_T2 lsmean_R;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

Power=100*probt (pw, DF);
Intra_cv=100*sqrt (exp (mse) -1);
id=1;
GmTest1=exp (my1);
GmTest2=exp (my2);
GmRef=exp (my3);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT PARAMETER GmTest1 GmTest2 GmRef MSE RATIO INTRA_CV POWER LOWER
UPPER Bioequivalence;
Run;
/***** LAUCT *****/
Proc Glm Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";
class form period seq subject;
model LAUCt=seq subject(seq) period form/ssl ss3 clparm alpha=0.1;
test H=seq E=Subject(seq);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T1' Form -1 1 0 ;
estimate 'R vs T2' Form -1 0 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp (estimate);
lower=Round (100*exp (LowerCL) , 0.01);
upper=Round (100*exp (UpperCL) , 0.01);

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```

if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_T1; set lsmean; if form='T1';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T2; set lsmean; if form='T2';
my2=lsmean; id=1; keep ID my2 ;
Run;
Data lsmean_R; set lsmean; if form='R';
my3=lsmean;id=1;keep id my3;
Run;
Data CI_AUCT;
merge final lsmean_T1 lsmean_T2 lsmean_R;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
GmTest1=exp(my1);
GmTest2=exp(my2);
GmRef=exp(my3);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT PARAMETER GmTest1 GmTest2 GmRef MSE RATIO INTRA_CV POWER LOWER
UPPER Bioequivalence ;
Run;
Data CIALl;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
set CI_Cmax CI_AUCT;
format GmTest1 GmTest2 GmRef 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV
8.2;
Run;
Data gm;
set CIALl;
  if GmTest1 =. and GmTest2 =. and GmRef=. then delete;
run;
Proc Print Data=gm noobs;
Title4 "Geometric Means";
var PK_Parameters GmTest1 GmTest2 GmRef;
Run;
Proc Print Data=CIALL noobs;
Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";
var PK_Parameters PARAMETER MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;
Run;

ods pdf close;
ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE THREE FORMULATION, THREE SEQUENCE, THREE PERIOD, 3 X 3 CROSS OVER DESIGN WITH GROUP ANOVA MODEL

```
Ods pdf file='D:\Statistical Analysis of ----- .pdf';
Ods rtf file='D:\Statistical Analysis of ----- .doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: ----- ';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1  " SAS Version Used: Version &sysver ";
FOOTNOTE2  '                                     ';
FOOTNOTE3  '                                     ';
FOOTNOTE4  j=1 'Prepared By Biostatistician:   ';
FOOTNOTE5  '                                     ';
FOOTNOTE6  '                                     ';
FOOTNOTE7  j=1 ' (Signature/Date)              ';

proc print data=one;
var subject seq form period group Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period group Res_area Ke_first Ke_last npoints ;
run;

proc sort data=one;
by form subject;
run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
    TITLE4  "SUMMARY STATISTICS - FORMULATION ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS seq;
    TITLE4  "SUMMARY STATISTICS - SEQUENCE ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    TITLE4  "SUMMARY STATISTICS - PERIOD ";
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS group;
    TITLE4 "SUMMARY STATISTICS - GROUP ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS seq;
    BY form;
    TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    BY form;
    TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;
set one;
LCmax=log(Cmax);
LAUCt=log(AUCt);
run;

/***** LCmax *****/
Proc Glm Data= two outstat=tanova;
    Title4 "ANOVA for log transformed Cmax ";
    class seq subject group form period;
    model LCmax=form group form*group period(group) seq seq*group
    subject(seq*group)/ss1 ss3 clparm alpha=0.1;
    test h=seq e=subject(seq*group);
    test h=group e=subject(seq*group);
    lsmeans form/stderr pdiff out=lsmean;
    estimate 'R vs T1' Form -1 1 0 ;
    estimate 'R vs T2' Form -1 0 1;
    ods output Estimates=ep;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Run;Quit;

Data error; set tanova;
    if _SOURCE_ = 'ERROR';
    mse=SS/DF; sse=SS; id=1;
    keep mse sse df id;
Run;

Proc Sort Data=error;
    by id;
Run;

Data test ;
set ep;
    length Bioequivalence $20;
    Ratio=100*exp(estimate);
    lower=Round(100*exp(LowerCL),0.01);
    upper=Round(100*exp(UpperCL),0.01);
    if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
    id=1;
Run;

Proc Sort Data=test;
    by id;
Run;

Data final;
merge test error;
    by id;
Run;

Data lsmean_T1; set lsmean; if form='T1';
    my1=lsmean; id=1; keep ID my1 ;
Run;

Data lsmean_T2; set lsmean; if form='T2';
    my2=lsmean; id=1; keep ID my2 ;
Run;

Data lsmean_R; set lsmean; if form='R';
    my3=lsmean;id=1;keep id my3;
Run;

Data CI_Cmax;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
merge final lsmean_T1 lsmean_T2 lsmean_R;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
GmTest1=exp(my1);
GmTest2=exp(my2);
GmRef=exp(my3);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT PARAMETER GmTest1 GmTest2 GmRef MSE RATIO INTRA_CV POWER LOWER
UPPER Bioequivalence;
Run;
/***** LAUCT *****/
Proc Glm Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";
class seq subject group form period;
model LAUCt=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
test h=seq e=subject(seq*group);
test h=group e=subject(seq*group);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T1' Form -1 1 0 ;
estimate 'R vs T2' Form -1 0 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_T1; set lsmean; if form='T1';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T2; set lsmean; if form='T2';
my2=lsmean; id=1; keep ID my2 ;
Run;
Data lsmean_R; set lsmean; if form='R';
my3=lsmean;id=1;keep id my3;
Run;
Data CI_AUCT;
merge final lsmean_T1 lsmean_T2 lsmean_R;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
GmTest1=exp(my1);
GmTest2=exp(my2);
GmRef=exp(my3);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Rename DEPENDENT=PK_Parameters;

Keep DEPENDENT PARAMETER GmTest1 GmTest2 GmRef MSE RATIO INTRA_CV POWER LOWER
UPPER Bioequivalence;

Run;

Data CIALl;

set CI_Cmax CI_AUCT;

format GmTest1 GmTest2 GmRef 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV
8.2;

Run;

Data gm;

set CIALl;

if GmTest1 =. and GmTest2 =. and GmRef= . then delete;

run;

Proc Print Data=gm noobs;

Title4 "Geometric Means";

var PK_Parameters GmTest1 GmTest2 GmRef;

Run;

Proc Print Data=CIALl noobs;

Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";

var PK_Parameters PARAMETER MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;

Run;

ods pdf close;

ods rtf close;
```


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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR GRAPHS (THE THREE FORMULATION, THREE SEQUENCE, THREE PERIOD,
3 X 3 CROSS OVER DESIGN)**

```

/*****/
/*   Study Number: ----- */
/*****/

```

Ods rtf file="D:\Graph.doc";

Data data;

set data;

if trt='R' then do;

select(period);

when(1) code="P1R";

when(2) code="P2R";

when(3) code="P3R";

otherwise;

end;end;

if trt='T1' then do;

select(Period);

when(1) code="P1T1";

when(2) code="P2T1";

when(3) code="P3T1";

otherwise;

end;end;

if trt='T2' then do;

select(Period);

when(1) code="P1T2";

when(2) code="P2T2";

when(3) code="P3T2";

otherwise;

end;end;

label trt="Treatment";

label code="Treatment";

Run;

Proc Sort Data=data;

by subject code;

run;

Data a;

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Reference SOP No. : BEQ/ST/SOP-016/01

```

set data;
array c{23} c1-c23 ;array t{23} t1-t23;
do st=1 to 23;
    cons=round(c{st},.0001);
        if (cons > 0)then lcon=log(c{st});
        else lcon=.;
        time=t(st);
    output;
end;
drop c1-c23 t1-t23 st;

Run;

Proc Sort data=a;
by subject;

Run;

*/                                Linear Plot                                /*;

options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00

;

Proc Gplot data=a;
label subject='Subject No.';
label time ='Time(Hour) ' ;
title 'Comparative Linear Plot of (Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ' ;
by subject;
plot const*time=code/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;

Run;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

*/                               Semi Log Plot                               /*;

    goptions reset=all ;
    goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Ln Concentration (ng/ml)') ;
    axis2 minor=(n=1) order=0.00          5.50      11.00      16.50      22.00
    27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
    71.50      77.00

;

proc Gplot data=a;
    label subject='Subject No.';
    label time ='Time(Hour) ' ;
    title 'Comparative Semi Log Plot of (Analyte name) Plasma
Concentration (ng/mL) Vs Time (Hour) ';
    by subject;
    plot lcon*time=code/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
    SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;

Run;

*/                               Mean Graph                               /*;

proc sort data=data;
    by trt;
Run;
Proc Means data=data mean noprint ;
    var c1-c23 ;
    by trt;
    output out= b;
Run;
Data c;
    set b;
    subject= _stat_ ;
Run;
Data d;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

set c;
drop _type_ _stat_ _freq_;
if subject NE "MEAN" then delete;
Run;

Data e;
    set d;
    array c{23} c1-c23;
    do st=1 to 23;
        cons=round(c{st},.00001);
        if (cons > 0) then lcon=log(c{st});
        else lcon=.;
        output;
    end;
    drop c1-c23 st;
Run;

Data f ;
input time;
datalines;

;
Run;

Data g;
merge e f;
Run;

*/                               Mean Linear Plot                               /*;
    goptions reset=all ;
    goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Concentration (ng/mL)') ;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00
```

;

Proc Gplot data=g;

label time ='Time(Hour) ' ;

title 'Comparative Linear Plot of (Analyte name) Mean Plasma

Concentration (ng/mL) Vs Time (Hour)(N=) ';

by subject;

plot const*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;

Run;

/ Mean Semi Log Plot /;

goptions reset=all ;

goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5

ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;

axis1 label=(a=90 'Ln Concentration(ng/mL)') ;

```
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
```

```
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
```

```
71.50      77.00
```

;

Proc Gplot data=g;

label time ='Time(Hour) ' ;

title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma

Concentration (ng/mL) Vs Time (Hour)(N=) ';

by subject;

plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;

Run;

Ods rtf close;

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, SINGLE PERIOD,
PARALLEL DESIGN WITH STANDARD ANOVA MODEL**

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition';
FOOTNOTE1   " SAS Version Used: Version &sysver ";
FOOTNOTE2   '                                     ';
FOOTNOTE3   '                                     ';
FOOTNOTE4   j=1 'Prepared By Biostatistician:   ';
FOOTNOTE5   '                                     ';
FOOTNOTE6   '                                     ';
FOOTNOTE7   j=1 ' (Signature/Date)              ';
proc print data=one;
var subject form period Cmax Tmax AUCt AUCinf ke thalf;
run;
proc print data=one;
var subject form period Res_area Ke_first Ke_last npoints;
run;
Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period ke tmax thalf Res_area Ke_first Ke_last npoints;
run;
Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period ke tmax thalf Res_area Ke_first Ke_last npoints;
run;
proc univariate data=T_Data nextrobs=0 noprint;
var cmax_T AUCt_T AUCinf_T;
output out=M_T
      mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUct_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUct_R mean=M_AUCI_R;
run;
Data M_T_R;
merge M_T M_R;
T_AUct_AUCI=100*(M_AUct_T/M_AUCI_T);
R_AUct_AUCI=100*(M_AUct_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUct=100*(M_AUct_T/M_AUct_R);
format T_AUct_AUCI R_AUct_AUCI B_cmax B_AUct 8.2;
Label T_AUct_AUCI="Ratio of mean AUct to mean AUCinf for Test formulation (%)"
    R_AUct_AUCI="Ratio of mean AUct to mean AUCinf for Reference formulation (%)"
    B_cmax="Bioavailability of Cmax (%)"
    B_AUct="Bioavailability of AUct (%)"
;
keep T_AUct_AUCI R_AUct_AUCI B_cmax B_AUct;
run;
Data Ratio;
set one;
tbyinf=100*(AUct/AUCinf);
format tbyinf 15.2;
Label tbyinf="Ratio AUct/AUCinf (%)"
;
keep subject form tbyinf;
run;
Proc sort data=Ratio;by form subject;run;
proc print data=Ratio label;
TITLE4 "Ratio Analysis";
Var Subject form tbyinf;
run;
proc print data=M_T_R label noobs;
TITLE4 "Ratio Analysis";
var T_AUct_AUCI R_AUct_AUCI B_cmax B_AUct;
```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```
run;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;

    CLASS form;

    TITLE4    "SUMMARY STATISTICS - FORMULATION ";

    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;

set one;

LCmax=log(Cmax);

LAUCt=log(AUCt);

run;

proc glm data=two;

Title4    "ANOVA for log transformed Cmax ";

class form;

model LCmax=form/ss1 ss3;

lsmeans form/stderr pdiff;

estimate 'R vs T' form -1 1;

run;

quit;

proc glm data=two;

Title4    "ANOVA for log transformed AUCt ";

class form;

model LAUCt=form/ss1 ss3;

lsmeans form/stderr pdiff;

estimate 'R vs T' form -1 1;

run;

quit;

proc glm data=two outstat=tanova noprint;

class form;

model LCmax LAUCt=form/ss1 ss3;

lsmeans form/stderr pdiff out=lsmean;

run;

quit;

proc sort data=two;

by form;

run;
```


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**Reference SOP No. : BEQ/ST/SOP-016/01**

```
proc means noprint data=two; by form;
var LCmax LAUCt;
output out=no n=n;
run;
proc sort data=no; by form;
run;
data two; merge two no; by form;
run;
proc sort data=two; by form ;
run;
data error; set tanova;
format mse 8.2;
if _SOURCE_ = 'ERROR';
mse=SS/DF;
sse=SS;
id=1;
keep mse sse df id;
run;
proc sort data=error; by id;run;
data nol;
set no;
if form='R';
n1=n;
id=1;
keep n1 id;
run;
proc sort data=nol;
by id;
run;
data no2;
set no;
if form='T';
n2=n;
id=1;
keep n2 id;
run;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
proc sort data=no2;
by id;
run;
data lsmean11;
set lsmean;
if form='R';
my1=lsmean;
id=1;
keep ID my1 _name_;
run;
proc sort data=lsmean11;
by id;
run;
data lsmean12;
set lsmean;
if form='T';
my2=lsmean;
id=1;
keep id my2 _name_;
run;
proc sort data=lsmean12;
by id;
run;
data twoside; merge lsmean11 lsmean12 no1 no2 error;
by id;
run;
data twoside;
set twoside;
by id;
retain n;
if first.id then n=1;
else n=n+1;
run;
data twosidel;
set twoside;
by id;
```

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G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No. : BEQ/ST/SOP-016/01**

```

format Gmref Gmtest 12.3 Ratio Inter_CV Power Lower Upper 8.2 mse 10.6;
length Bioequivalence $20;
spool=mse*((1/n1)+(1/n2));
se=sqrt(spool);
diff=exp(my2)- exp(my1);
Ratio=100*exp(my2-my1);
Inter_CV=100*sqrt(exp(mse)-1);
ct=tinv(0.05,df,0);
absct=abs(ct);
Lower=Round(100*exp((my2-my1)-(absct*se)),0.01);
Upper=Round(100*exp((my2-my1)+(absct*se)),0.01);
pt=tinv(0.025,df,0);
apt=abs(pt);
pw=(log(1.25)/se-apt);
Power=100*probt(pw,df);
Gmref=exp(my1); Gmtest=exp(my2);
if (Lower>=80.00) and (Upper<=125.00) then Bioequivalence="Yes"; else
Bioequivalence="No";
run;
proc print data=twosidel noobs;
Title4 " 90% C.I Equivalent to Schuirmann's Two One-Sided Test ";
var _name_ GMref GMtest n1 n2 df mse diff Ratio Inter_CV Power Lower Upper
Bioequivalence;
run;
quit;

ods pdf close;
ods rtf close;

```

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, SINGLE PERIOD,
PARALLEL DESIGN WITH GROUP ANOVA MODEL**

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition';
FOOTNOTE1   " SAS Version Used: Version &sysver ";
FOOTNOTE2   '                                     ';
FOOTNOTE3   '                                     ';
FOOTNOTE4   j=1 'Prepared By Biostatistician:   ';
FOOTNOTE5   '                                     ';
FOOTNOTE6   '                                     ';
FOOTNOTE7   j=1 ' (Signature/Date)              ';

proc print data=one;
var subject form period group Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject form period group Res_area Ke_first Ke_last npoints;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period group ke tmax thalf Res_area Ke_first Ke_last npoints;
run;

Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period group ke tmax thalf Res_area Ke_first Ke_last npoints;
run;

proc univariate data=T_Data nextrobs=0 noprint;
var cmax_T AUCt_T AUCinf_T;
output out=M_T
      mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUCt_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;
Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 8.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
    R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation (%)"
    B_cmax="Bioavailability of Cmax (%)"
    B_AUCt="Bioavailability of AUCt (%)"
;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;
Data Ratio;
set one;
tbyinf=100*(AUCt/AUCinf);
format tbyinf 15.2;
Label tbyinf="Ratio AUCt/AUCinf (%)"
;
keep subject form tbyinf;
run;
Proc sort data=Ratio;by form subject;run;
proc print data=Ratio label;
TITLE4 "Ratio Analysis";
Var Subject form tbyinf;
run;
proc print data=M_T_R label noobs;
TITLE4 "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
    TITLE4    "SUMMARY STATISTICS - FORMULATION ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
RUN;
PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS group;
    TITLE4    "SUMMARY STATISTICS - GROUP ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
RUN;
data two;
set one;
LCmax=log(Cmax);
LAUCt=log(AUCt);
run;
/***** LCmax *****/
Proc Glm Data= two outstat=tanova;
    Title4    "ANOVA for log transformed Cmax ";
    class form group;
    model LCmax=form group form*group/ssl  ss3 clparm alpha=0.1;
    lsmeans form/stderr pdiff out=lsmean;
    estimate 'R vs T' Form -1 1;
    ods output Estimates=ep;
Run;Quit;
Data error; set tanova;
    if _SOURCE_ = 'ERROR';
    mse=SS/DF; sse=SS; id=1;
    keep mse sse df id;
Run;
Proc Sort Data=error;
    by id;
Run;
Data test ;
set ep;
    length Bioequivalence $20;
```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort Data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Inter_CV=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT Gmref GMtest MSE RATIO Inter_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCT *****/
Proc Glim Data= two outstat=tanova;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Title4 "ANOVA for log transformed AUct ";
class form group;
model LAUct=form group form*group/ss1 ss3 clparm alpha=0.1;
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
myl=lsmean; id=1; keep ID myl ;
Run;
Data lsmean_T; set lsmean; if form='T';
```


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Reference SOP No. : BEQ/ST/SOP-016/01

```
my2=lsmean;id=1;keep id my2;

Run;

Data CI_AUCT;

merge final lsmean_R lsmean_T;

pt=tinv(0.05,DF,0);

apt=abs(pt);

pw=(log(1.25)/stderr-apt);

Power=100*probt(pw,DF);

Inter_CV=100*sqrt(exp(mse)-1);

id=1;

Gmref=exp(my1);

Gmtest=exp(my2);

Rename DEPENDENT=PK_Parameters;

KEEP DEPENDENT Gmref GMtest MSE RATIO Inter_CV POWER LOWER UPPER

Bioequivalence;

Run;

Data CIALl;

set CI_Cmax CI_AUCT;

format Gmref GMtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER Inter_CV 8.2;

Run;

Proc Print Data=CIALL noobs;

Title4 "90% Confidence Interval Equivalent to Schuirmann's Two One Sided

Test";

var PK_Parameters Gmref GMtest MSE RATIO Inter_CV POWER LOWER UPPER

Bioequivalence;

Run;

Ods pdf close;

Ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR GRAPHS (THE TWO FORMULATION, SINGLE PERIOD, PARALLEL DESIGN)

```

/*****/
/*   Study Number: ----- */
/*****/

ods rtf file="D:\All Graph.doc";
data data ;
set data;
keep subject trt cl-c24 tl-t24;
label trt="Treatment";
run;
proc sort data=data;
by subject trt;
run;
data a;
set data;
array c{24} cl-c24 ;array t{24} tl-t24;
do st=1 to 24;
cons=round(c{st},.0001);
if (cons > 0)then lcon=log(c{st});
else lcon=.;
time=t(st);
output;
end;
drop period;
drop cl-c24 tl-t24 st;
run;
proc sort data=a;
by subject;
run;

/*                               Linear Plot                               */
options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;

```

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```

axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00

;

proc gplot data=a;
    label subject='Subject No.';
    label time ='Time(Hour) ' ;
    title 'Comparative Linear Plot of (Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ' ;
    by subject;
    plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

run;

/*                      Semi Log Plot                      */
options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00

;

proc gplot data=a;
    label subject='Subject No.';
    label time ='Time(Hour) ' ;
    title 'Comparative Semi Log Plot of (Analyte name) Plasma
Concentration (ng/mL) Vs Time (Hour) ' ;
    by subject;
    plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

run;

/*                      Mean Graph                      */
proc sort data=data;
    by trt;

run;

proc means data=data mean noprint ;

```

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/*;

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Reference SOP No. : BEQ/ST/SOP-016/01

```

options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00
;
proc gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Linear Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) (N= )';
by subject;
plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
run;
*/                               Mean Semi Log Plot                               /*;
options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration(ng/mL)') ;
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00
;
proc gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) (N= )';
by subject;
plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
run;
ods rtf close;

```

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Reference SOP No. : BEQ/ST/SOP-016/01	

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF UNSCALED AVERAGE BIOEQUIVALENCE
(TWO FORMULATION, TWO SEQUENCE, FOUR PERIOD, PARTIAL REPLICATED 4-WAY & 3 Way
CROSSOVER DESIGN WITH STANDARD ANOVA MODEL)

```

Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1  " SAS Version Used: Version &sysver      ";
FOOTNOTE2  '                                           ';
FOOTNOTE3  '                                           ';
FOOTNOTE4  j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5  '                                           ';
FOOTNOTE6  '                                           ';
FOOTNOTE7  j=1 ' (Signature/Date)                  ';

proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
run;

Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
run;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T AUCt_T AUCinf_T;
    output out=M_T
        mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
run;

proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUCt_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;

Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
      R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
      (%)"
      B_cmax="Bioavailability of Cmax (%)"
      B_AUCt="Bioavailability of AUCt (%)"
      ;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;

proc print data=M_T_R label noobs;
TITLE4    "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;

PROC SORT data=one;
    BY form;

Run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
    TITLE4    "SUMMARY STATISTICS - FORMULATION ";
    VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS seq;

TITLE4 "SUMMARY STATISTICS - SEQUENCE ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS period;

TITLE4 "SUMMARY STATISTICS - PERIOD ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS seq;

BY form;

TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS period;

BY form;

TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;

set one;

LCmax=log(Cmax);

LAUCt=log(AUCt);

run;

/***** LCmax *****/

Proc Glim Data= two outstat=tanova;

Title4 "ANOVA for log transformed Cmax ";

class seq subject form period;

model LCmax=form period seq subject(seq)/ss1 ss3 clparm alpha=0.1;

test h=seq e=subject(seq);

lsmeans form/stderr pdiff out=lsmean;

estimate 'R vs T' Form -1 1;

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Reference SOP No. : BEQ/ST/SOP-016/01

```
ods output Estimates=ep;

Run;Quit;

Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;
  keep mse sse df id;

Run;

Proc Sort Data=error;
  by id;

Run;

Data test ;

set ep;
  length Bioequivalence $20;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
  id=1;

Run;

Proc Sort Data=test;
  by id;

Run;

Data final;
merge test error;
  by id;

Run;

Data lsmean_R; set lsmean; if form='R';
  my1=lsmean; id=1; keep ID my1 ;

Run;

Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;

Run;

Data CI_Cmax;
merge final lsmean_R lsmean_T;
  pt=tinv(0.05,DF,0);
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCt *****/
Proc Glm Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";
class seq subject form period;
model LAUCt=form period seq subject(seq)/ss1 ss3 clparm alpha=0.1;
test h=seq e=subject(seq);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_AUCT;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
Data CIALI;
set CI_Cmax CI_AUCT;
format Gmref GMtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;
Run;
Proc Print Data=CIALL noobs;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided Test";

var PK_Parameters Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;

Run;

Ods pdf close;

Ods rtf close;

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No. : BEQ/ST/SOP-016/01**

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF UNSCALED AVERAGE BIOEQUIVALENCE
(TWO FORMULATION, TWO SEQUENCE, FOUR PERIOD, PARTIAL REPLICATED 4-WAY & 3 Way
CROSSOVER DESIGN WITH GROUP ANOVA MODEL)

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1 " SAS Version Used: Version &sysver  ";
FOOTNOTE2 '                                     ';
FOOTNOTE3 '                                     ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5 '                                     ';
FOOTNOTE6 '                                     ';
FOOTNOTE7 j=1 ' (Signature/Date)                 ';

proc print data=one;
var subject seq form period group Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period group Res_area Ke_first Ke_last npoints ;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
run;

Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
run;
```

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Bioequivalence Department

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Reference SOP No. : BEQ/ST/SOP-016/01

```
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T AUCt_T AUCinf_T;
    output out=M_T
        mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
run;

proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUCt_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;

Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
B_AUCI=100*(M_AUCI_T/M_AUCI_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt B_AUCI 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
    R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
    (%)"
    B_cmax="Bioavailability of Cmax (%)"
    B_AUCt="Bioavailability of AUCt (%)"
    B_AUCI="Bioavailability of AUCinf (%)"
    ;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt B_AUCI;
run;

proc print data=M_T_R label noobs;
TITLE4 "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt B_AUCI;
run;

PROC SORT data=one;
    BY form;

Run;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

TITLE4 "SUMMARY STATISTICS - FORMULATION ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS seq;

TITLE4 "SUMMARY STATISTICS - SEQUENCE ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS period;

TITLE4 "SUMMARY STATISTICS - PERIOD ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS group;

TITLE4 "SUMMARY STATISTICS - GROUP ";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS seq;

BY form;

TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;

CLASS period;

BY form;

TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;

set one;

LCmax=log(Cmax);

LAUCt=log(AUCt);

LAUCinf=log(AUCinf);

run;

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Reference SOP No. : BEQ/ST/SOP-016/01

```

/***** LCmax *****/
Proc Glm Data= two outstat=tanova;
  Title4 "ANOVA for log transformed Cmax ";
  class seq subject group form period;
  model LCmax=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
  test h=seq e=subject(seq*group);
  test h=group e=subject(seq*group);
  lsmeans form/stderr pdiff out=lsmean;
  estimate 'R vs T' Form -1 1;
  ods output Estimates=ep;
Run;Quit;
Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;
  keep mse sse df id;
Run;
Proc Sort Data=error;
  by id;
Run;
Data test ;
set ep;
  length Bioequivalence $20;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
  id=1;
Run;
Proc Sort Data=test;
  by id;
Run;
Data final;
merge test error;
  by id;

```


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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

Run;
Data lsmean_R; set lsmean; if form='R';
  my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
  my2=lsmean; id=1; keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;
  pt=tinv(0.05,DF,0);
  apt=abs(pt);
  pw=(log(1.25)/stderr-apt);
  Power=100*probt(pw,DF);
  Intra_cv=100*sqrt(exp(mse)-1);
  id=1;
  Gmref=exp(my1);
  Gmtest=exp(my2);
  Rename DEPENDENT=PK_Parameters;
  Keep DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCt *****/
Proc Glm Data= two outstat=tanova;
  Title4 "ANOVA for log transformed AUCt ";
  class seq subject group form period;
  model LAUCt=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
  test h=seq e=subject(seq*group);
  test h=group e=subject(seq*group);
  lsmeans form/stderr pdiff out=lsmean;
  estimate 'R vs T' Form -1 1;
  ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

Keep mse sse df id;

Run;

Proc Sort Data=error;
  by id;
Run;

Data test ;
set ep;
  length Bioequivalence $20;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
  id=1;
Run;

Proc Sort data=test;
  by id;
Run;

Data final;
merge test error;
  by id;
Run;

Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;

Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;

Data CI_AUCT;
merge final lsmean_R lsmean_T;
  pt=tinv(0.05,DF,0);
  apt=abs(pt);
  pw=(log(1.25)/stderr-apt);
  Power=100*probt (pw, DF);
  Intra_cv=100*sqrt (exp (mse) -1);
  id=1;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCinf *****/
Proc Glim Data= two outstat=tanova;
title4 "ANOVA for log transformed AUCinf";
class seq subject group form period;
model LAUCinf=form group form*group period(group) seq seq*group
subject(seq*group)/ss1 ss3 clparm alpha=0.1;
test h=seq e=subject(seq*group);
test h=group e=subject(seq*group);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Proc Sort Data=test;
  by id;
Run;
Data final;
  merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_AUCI;
merge final lsmean_R lsmean_T;
pt=tinv(0.025,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;
Run;
Data CIALI;
set CI_Cmax CI_AUCT CI_AUCI;
format Gmref Gmtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;
Run;
Proc Print Data=CIALL noobs;
Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";
var PK_Parameters Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence; Run; Ods pdf close; Ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR GRAPHS (TWO FORMULATION, TWO SEQUENCE, FOUR PERIOD, PARTIAL
REPLICATED 4-WAY Crossover DESIGN)**

```

/*****
/*   Study Number: ----- */
*****/

ods rtf file="D:\Graph.doc";

data data;
  set data;
  if trt='R' then do;
    select(period);
    when(1) code="P1R";
    when(2) code="P2R";
    when(3) code="P3R";
    when(4) code="P4R";
    otherwise;
  end;end;
  if trt='T' then do;
    select(Period);
    when(1) code="P1T";
    when(2) code="P2T";
    when(3) code="P3T";
    when(4) code="P4T";
    otherwise;
  end;end;
  label trt="Treatment";
  label code="Treatment";

run;

proc sort data=data;
  by subject code;
run;

data a;
  set data;
  array c{22} c1-c22 ;array t{22} t1-t22;
  do st=1 to 22;
    cons=round(c{st},.0001);
    if (cons > 0)then lcon=log(c{st});
  end;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

else lcon=.;
time=t(st);
output;
end;
drop c1-c22 t1-t22 st;
run;
proc sort data=a;
by subject;
run;

*/                               Linear Plot                               /*;

goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      0.90      1.80      2.70      3.60
4.50      5.40      6.30      7.20      8.10      9.00      9.90      10.80
11.70      12.60
;
proc gplot data=a;
label subject='Subject No.';
label time ='Time(Hour) ' ;
title 'Comparative Linear Plot of (Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ' ;
by subject;
plot cons*time=code/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL3 V=square C=green I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL4 V=triangle C=red I=JOIN width=2 height=1.8 bwidth=10 ;
run;

*/                               Semi Log Plot                               /*;

goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration (ng/ml)') ;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

axis2 minor=(n=1)	order=0.00	0.90	1.80	2.70	3.60
4.50	5.40	6.30	7.20	8.10	9.00
9.90	10.80				
11.70	12.60				

;

proc gplot data=a;

label subject='Subject No.';

label time ='Time(Hour) ' ;

title 'Comparative Semi Log Plot of (Analyte name) Plasma

Concentration (ng/mL) Vs Time (Hour) ';

by subject;

plot lcon*time=code/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL3 V=square C=green I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL4 V=triangle C=red I=JOIN width=2 height=1.8 bwidth=10 ;

run;

*/

Mean Graph

/*;

proc sort data=data;

by trt;

run;

proc means data=data mean noprint ;

var c1-c22 ;

by trt;

output out= b;

run;

data c;

set b;

subject= _stat_ ;

run;

data d; set c;

drop _type_ _stat_ _freq_;

if subject NE "MEAN" then delete;

run;

data e;

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Reference SOP No. : BEQ/ST/SOP-016/01

```

set d;
array c{22} c1-c22;
do st=1 to 22;
  cons=round(c{st},.00001);
  if (cons > 0)then lcon=log(c{st});
  else lcon=.;
  output;
end;
drop c1-c22 st;

run;

data f ;
  input time;
  datalines;

;

run;

data g;
  merge e f;
run;

*/                               Mean Linear Plot                               /*;

  goptions reset=all ;
  goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
  axis1 label=(a=90 'Concentration (ng/mL)') ;
  axis2 minor=(n=1) order=0.00          0.90          1.80          2.70          3.60
  4.50          5.40          6.30          7.20          8.10          9.00          9.90          10.80
  11.70          12.60

;

proc gplot data=g;
  label time ='Time(Hour) ' ;

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```

title 'Comparative Linear Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour)';
by subject;
plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10;

run;

*/                               Mean Semi Log Plot                               /*;
goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration(ng/mL)') ;
axis2 minor=(n=1) order=0.00          0.90      1.80      2.70      3.60
4.50      5.40      6.30      7.20      8.10      9.00      9.90      10.80
11.70     12.60

;
proc gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour)';
by subject;
plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

ods rtf close;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR GRAPHS (TWO FORMULATION, THREE SEQUENCE, THREE PERIOD, PARTIAL
REPLICATED 3-WAY CROSSOVER DESIGN)**

```

/*****
/*   Study Number: -----
/*****
Ods rtf file="D:\Graph.doc";

Data data;
set data;

  if trt='R' then do;
    select(period);
    when(1) code="P1R";
    when(2) code="P2R";
    when(3) code="P3R";
    otherwise;
  end;end;

  if trt='T' then do;
    select(Period);
    when(1) code="P1T";
    when(2) code="P2T";
    when(3) code="P3T";
    otherwise;
  end;end;

  label trt="Treatment";
  label code="Treatment";

Run;

Proc Sort Data=data;
  by subject code;
run;

Data a;
  set data;
  array c{23} c1-c23 ;array t{23} t1-t23;
  do st=1 to 23;
    cons=round(c{st},.0001);
    if (cons > 0)then lcon=log(c{st});
    else lcon=.;
    time=t(st);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

output;
end;
drop c1-c23 t1-t23 st;
Run;
Proc Sort data=a;
  by subject;
Run;

/*                                Linear Plot                                */
options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Concentration (ng/mL)') ;
axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00
;
Proc Gplot data=a;
  label subject='Subject No.';
  label time ='Time(Hour) ' ;
  title 'Comparative Linear Plot of (Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ' ;
  by subject;
  plot const*time=code/vaxis=axis1 haxis=axis2 ;
  SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
  SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;
  SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;
Run;

/*                                Semi Log Plot                                */
options reset=all ;
options htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration (ng/ml)') ;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

axis2 minor=(n=1) order=0.00          5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00

```

;

proc Gplot data=a;

label subject='Subject No.';

label time ='Time(Hour) ' ;

title 'Comparative Semi Log Plot of (Analyte name) Plasma

Concentration (ng/mL) Vs Time (Hour) ';

by subject;

plot lcon*time=code/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ; .

SYMBOL3 V=triangle C=green I=JOIN width=2 height=1.8 bwidth=10 ;

Run;

*/

Mean Graph

/*;

proc sort data=data;

by trt;

Run;**Proc Means** data=data mean noprint ;

var cl-c23 ;

by trt;

output out= b;

Run;**Data** c;

set b;

subject= _stat_ ;

Run;**Data** d;

set c;

drop _type_ _stat_ _freq_;

if subject NE "MEAN" then delete;

Run;**Data** e;

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Reference SOP No. : BEQ/ST/SOP-016/01

```

set d;
array c{23} c1-c23;
do st=1 to 23;
  cons=round(c{st},.00001);
  if (cons > 0)then lcon=log(c{st});
  else lcon=.;
  output;
end;
drop c1-c23 st;

Run;

Data f ;
  input time;
  datalines;

;

Run;

Data g;
  merge e f;

Run;

/*                                Mean Linear Plot                                */
  goptions reset=all ;
  goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
  axis1 label=(a=90 'Concentration (ng/mL)') ;
  axis2 minor=(n=1) order=0.00      5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00

;

Proc Gplot data=g;
  label time ='Time(Hour) ' ;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

title 'Comparative Linear Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) ' ;
by subject;
plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

```

Run;

```

*/                               Mean Semi Log Plot                               /*;
goptions reset=all ;
goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
axis1 label=(a=90 'Ln Concentration(ng/mL)') ;
axis2 minor=(n=1) order=0.00          5.50      11.00      16.50      22.00
27.50      33.00      38.50      44.00      49.50      55.00      60.50      66.00
71.50      77.00
;

```

```

Proc Gplot data=g;
label time ='Time(Hour) ' ;
title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour) ' ;
by subject;
plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;
SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10;

```

Run;

Ods rtf close;

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**Reference SOP No. : BEQ/ST/SOP-016/01**

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, TWO SEQUENCE,
TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY STATE DESIGN WITH STANDARD
ANOVA MODEL**

```

Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No:-----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1   " SAS Version Used: Version &sysver  ";
FOOTNOTE2   '                                     ';
FOOTNOTE3   '                                     ';
FOOTNOTE4   j=1 'Prepared By Biostatistician:    ';
FOOTNOTE5   '                                     ';
FOOTNOTE6   '                                     ';
FOOTNOTE7   j=1 ' (Signature/Date)              ';

proc print data=one;
var subject seq form period cmax Ctau auctau;
run;

proc print data=one;
var subject seq form period tmax cmin ke thalf;
run;

proc print data=one;
var subject seq form period Cavg Fluctuation Swing;
run;

proc print data=one;
var subject seq form period Ke_first Ke_last npoints;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T Ctau=Ctau_T AUCtau=AUCtau_T ;
Drop form period tmax cmin Cavg Fluctuation Swing ke thalf Ke_first Ke_last
npoints;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R Ctau=Ctau_R AUCtau=AUCtau_R ;
Drop form period tmax cmin Cavg Fluctuation Swing ke thalf Ke_first Ke_last
npoints;
run;
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T Ctau_T AUCtau_T;
    output out=M_T
           mean=M_cmax_T mean=M_Ctau_T mean=M_AUCtau_T;
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R Ctau_R AUCtau_R;
    output out=M_R
           mean=M_cmax_R mean=M_Ctau_R mean=M_AUCtau_R;
run;
Data M_T_R;
merge M_T M_R;
B_cmax=100*(M_cmax_T/M_cmax_R);
B_Ctau=100*(M_Ctau_T/M_Ctau_R);
B_AUCtau=100*(M_AUCtau_T/M_AUCtau_R);
format B_cmax B_Ctau B_AUCtau 18.2;
Label B_cmax="Bioavailability of Cmax (%)"
      B_Ctau="Bioavailability of Ctau (%)"
      B_AUCtau="Bioavailability of AUCtau (%)"
      ;
keep B_cmax B_Ctau B_AUCtau;
run;
Data Ratio;
merge T_Data R_Data;
Ratio_Cmax=100*(cmax_T/cmax_R);
Ratio_Ctau=100*(Ctau_T/Ctau_R);
Ratio_AUCtau=100*(AUCtau_T/AUCtau_R);
format Ratio_Cmax Ratio_Ctau Ratio_AUCtau 15.2;
```


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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

Label Ratio_Cmax="Ratio Cmax (T/R) (%)"
      Ratio_Ctau= "Ratio Ctau (T/R) (%)"
      Ratio_AUCtau= "Ratio AUCtau (T/R) (%)"
;

run;

proc print data=Ratio label;
TITLE4  "Ratio Analysis";
Var Subject seq Ratio_Cmax Ratio_Ctau Ratio_AUCtau;
run;

proc print data=M_T_R label noobs;
TITLE4  "Ratio Analysis";
var B_cmax B_Ctau B_AUCtau;
run;

PROC SORT data=one;
      BY form;

Run;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
      CLASS form;
      TITLE4  "SUMMARY STATISTICS - FORMULATION ";
      VAR Cmax Ctau Auctau tmax Cavg Cmin Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS seq;
      TITLE4  "SUMMARY STATISTICS - SEQUENCE ";
      VAR Cmax Ctau Auctau tmax Cavg Cmin Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS period;
      TITLE4  "SUMMARY STATISTICS - PERIOD ";
      VAR Cmax Ctau Auctau tmax Cavg Cmin Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS seq;
      BY form;
      TITLE4  "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
      VAR Cmax Ctau Auctau tmax Cavg Cmin Fluctuation Swing ke thalf;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    BY form;
    TITLE4    "SUMMARY STATISTICS - PERIOD/FORMULATION";
    VAR Cmax Ctau Auctau tmax Cavg Cmin Fluctuation Swing ke thalf;
RUN;

data two;
set one;
LCmax=log(Cmax);
LCtau=log(Ctau);
LAuctau =log(Auctau);
run;

proc glm data=two;
Title4    "ANOVA for log transformed Cmax ";
class form period seq subject;
model LCmax=seq subject(seq) period form/ss1 ss3;
test h=seq e=subject(seq);
lsmeans form period/stderr pdiff;
estimate 'R vs T' form -1 1;
run;
quit;

proc glm data=two;
Title4    "ANOVA for log transformed Ctau ";
class form period seq subject;
model LCtau =seq subject(seq) period form/ss1 ss3;
test h=seq e=subject(seq);
lsmeans form period/stderr pdiff;
estimate 'R vs T' form -1 1;
run;
quit;

proc GLM data=two ;
Title4    "ANOVA for log transformed Auctau ";
class form period seq subject;
model LAuctau=seq subject(seq) period form/ss1 ss3;
test h=seq e=subject(seq);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
lsmeans form period/stderr pdiff;
estimate 'R vs T' form -1 1;
run;
quit;
proc glm data=two outstat=tanova noprint;
class form period seq subject;
model LCmax LCtau LAuctau=seq subject(seq) period form/ssl ss3;
test h=seq e=subject(seq);
lsmeans form period/stderr pdiff out=lsmean1;
run;
quit;
proc sort data=two;
by seq subject form;
run;
proc means n noprint data=two; by seq;
var LCmax LCtau LAuctau;
output out=no      n=n;
run;
data no; set no;  n=n/2;
run;
proc sort data=no; by seq;
run;
data two; merge two no; by seq;
run;
proc sort data=two; by seq subject form;
run;
data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
keep mse sse df id;run;
proc sort data=error; by id;run;
data nol; set no; if seq='RT';
n1=n; id=1;
keep n1 id;
run;
proc sort data=nol; by id;run;
```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

data no2; set no; if seq='TR';
n2=n; id=1;
keep n2 id;
run;
proc sort data=no2; by id;run;
data lsmean1; set lsmean1; if form='R';
my1=lsmean; id=1; keep ID my1 _name_;run;
proc sort data=lsmean1; by id;run;
data lsmean2; set lsmean1; if form='T';
my2=lsmean;
id=1;
keep id my2 _name_;run;
proc sort data=lsmean2; by id;run;
data twoside; merge lsmean1 lsmean2 nol no2 error;
by id;
run;
data twoside;
set twoside;
by id;
retain n;
if first.id then n=1;
else n=n+1;
run;
data twoside;
set twoside;
by id;
format Gmref Gmtest 12.3 Ratio Intra_CV Power Lower Upper 8.2;
length Bioequivalence $20;
spool=mse*(0.5)*((1/n1)+(1/n2));
se=sqrt(spool);
Diff=exp(my2)- exp(my1);
Ratio=100*exp(my2-my1);
Intra_CV=100*sqrt(exp(mse)-1);
ct=tinv(0.05,df,0);
absct=abs(ct);
Lower=Round(100*exp((my2-my1)-(absct*se)),0.01);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Upper=Round(100*exp((my2-my1)+(absct*se)),0.01);
pt=tinv(0.025,df,0);
apt=abs(pt);
pw=(log(1.25)/se-apt);
Power=100*probt(pw,df);
Gmref=exp(my1); Gmtest=exp(my2);
if (Lower>=80.00)and(Upper<=125.00) then Bioequivalence="Yes"; else
Bioequivalence="No";
run;

proc print data=twoside noobs;
Title4 " 90% C.I. Equivalent to Schuirmann's Two One-Sided Tests ";
var _name_ GMref Gmtest n1 n2 df mse Diff Ratio Intra_CV Power Lower Upper
Bioequivalence;
run;

ods pdf close;
ods rtf close;
```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE TWO FORMULATION, TWO SEQUENCE,
TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY STATE DESIGN WITH GROUP ANOVA**

MODEL

```

Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No:-----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1  " SAS Version Used: Version &sysver  ";
FOOTNOTE2  '                                     ';
FOOTNOTE3  '                                     ';
FOOTNOTE4  j=1 'Prepared By Biostatistician:    ';
FOOTNOTE5  '                                     ';
FOOTNOTE6  '                                     ';
FOOTNOTE7  j=1 ' (Signature/Date)              ';

proc print data=one;
var subject seq form period group cmax Ctau auctau;
run;

proc print data=one;
var subject seq form period group tmax cmin ke thalf;
run;

proc print data=one;
var subject seq form period group Cavg Fluctuation Swing;
run;

proc print data=one;
var subject seq form period group Ke_first Ke_last npoints;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T Ctau=Ctau_T AUCtau=AUCtau_T ;
Drop form period group tmax cmin Cavg Fluctuation Swing ke thalf Ke_first
Ke_last npoints;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

run;
Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R Ctau=Ctau_R AUCtau=AUCtau_R ;
Drop form period group tmax cmin Cavg Fluctuation Swing ke thalf Ke_first
Ke_last npoints;
run;
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T Ctau_T AUCtau_T;
    output out=M_T
           mean=M_cmax_T mean=M_Ctau_T mean=M_AUCtau_T;
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R Ctau_R AUCtau_R;
    output out=M_R
           mean=M_cmax_R mean=M_Ctau_R mean=M_AUCtau_R;
run;
Data M_T_R;
merge M_T M_R;
B_cmax=100*(M_cmax_T/M_cmax_R);
B_Ctau=100*(M_Ctau_T/M_Ctau_R);
B_AUCtau=100*(M_AUCtau_T/M_AUCtau_R);
format B_cmax B_Ctau B_AUCtau 18.2;
Label B_cmax="Bioavailability of Cmax (%)"
      B_Ctau="Bioavailability of Ctau (%)"
      B_AUCtau="Bioavailability of AUCtau (%)"
      ;
keep B_cmax B_Ctau B_AUCtau;
run;
Data Ratio;
merge T_Data R_Data;
Ratio_Cmax=100*(cmax_T/cmax_R);
Ratio_Ctau=100*(Ctau_T/Ctau_R);
Ratio_AUCtau=100*(AUCtau_T/AUCtau_R);
format Ratio_Cmax Ratio_Ctau Ratio_AUCtau 15.2;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

Label Ratio_Cmax="Ratio Cmax (T/R) (%)"
      Ratio_Ctau= "Ratio Ctau (T/R) (%)"
      Ratio_AUCtau= "Ratio AUCtau (T/R) (%)"
      ;

run;

proc print data=Ratio label;
TITLE4  "Ratio Analysis";
Var Subject seq Ratio_Cmax Ratio_Ctau Ratio_AUCtau;
run;

proc print data=M_T_R label noobs;
TITLE4  "Ratio Analysis";
var B_cmax B_Ctau B_AUCtau;
run;

PROC SORT data=one;
      BY form;

Run;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
      CLASS form;
      TITLE4  "SUMMARY STATISTICS - FORMULATION ";
      VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS seq;
      TITLE4  "SUMMARY STATISTICS - SEQUENCE ";
      VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS period;
      TITLE4  "SUMMARY STATISTICS - PERIOD ";
      VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
      RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
      CLASS group;
      TITLE4  "SUMMARY STATISTICS - GROUP";
      VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
      RUN;

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS seq;
    BY form;
    TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
    VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
    RUN;

PROC MEANS data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
    CLASS period;
    BY form;
    TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";
    VAR Cmax Ctau Auctau Cmin tmax Cavg Fluctuation Swing ke thalf;
    RUN;

data two;
set one;
LCmax=log(Cmax);
LCtau=log(Ctau);
LAuctau =log(Auctau);
run;

/***** LCmax *****/

Proc Glm Data= two outstat=tanova;
    Title4 "ANOVA for log transformed Cmax ";
    class seq subject group form period;
    model LCmax=form group form*group period(group) seq seq*group
subject(seq*group)/ss1 ss3 clparm alpha=0.1;
    test h=seq e=subject(seq*group);
    test h=group e=subject(seq*group);
    lsmeans form/stderr pdiff out=lsmean;
    estimate 'R vs T' Form -1 1;
    ods output Estimates=ep;
Run;Quit;

Data error; set tanova;
    if _SOURCE_ = 'ERROR';
    mse=SS/DF; sse=SS; id=1;
    keep mse sse df id;
Run;

Proc Sort Data=error;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
if lower >= 80.00 and upper <= 125.00 then Bioequivalence='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort Data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;

```

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G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No. : BEQ/ST/SOP-016/01

```

Keep DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;

Run;

/***** LCTau *****/
Proc Glm Data= two outstat=tanova;
  Title4 "ANOVA for log transformed Ctau ";
  class seq subject group form period;
  model LCTau=form group form*group period(group) seq seq*group
subject(seq*group)/ss1 ss3 clparm alpha=0.1;
  test h=seq e=subject(seq*group);
  test h=group e=subject(seq*group);
  lsmeans form/stderr pdiff out=lsmean;
  estimate 'R vs T' Form -1 1;
  ods output Estimates=ep;
Run; Quit;

Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;
  Keep mse sse df id;

Run;

Proc Sort Data=error;
  by id;

Run;

Data test ;
set ep;
  length Bioequivalence $20;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
  id=1;

Run;

Proc Sort data=test;
  by id;

Run;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

Data final;
merge test error;
  by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Ctau;
merge final lsmean_R lsmean_T;
  pt=ttinv(0.05,DF,0);
  apt=abs(pt);
  pw=(log(1.25)/stderr-apt);
  Power=100*probt(pw,DF);
  Intra_cv=100*sqrt(exp(mse)-1);
  id=1;
  Gmref=exp(my1);
  Gmtest=exp(my2);
  Rename DEPENDENT=PK_Parameters;
  KEEP DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAuctau *****/
Proc Glim Data= two outstat=tanova;
  title4 "ANOVA for log transformed Auctau";
  class seq subject group form period;
  model LAuctau=form group form*group period(group) seq seq*group
subject(seq*group)/ss1 ss3 clparm alpha=0.1;
  test h=seq      e=subject(seq*group);
  test h=group    e=subject(seq*group);
  lsmeans form/stderr pdiff out=lsmean;
  estimate 'R vs T' Form -1 1;
  ods output Estimates=ep;
Run; Quit;

```

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G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No. : BEQ/ST/SOP-016/01

```
Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;
  keep mse sse df id;
Run;
Proc Sort Data=error;
  by id;
Run;
Data test ;
  set ep;
  length Bioequivalence $20;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
  id=1;
Run;
Proc Sort Data=test;
  by id;
Run;
Data final;
  merge test error;
  by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Auctau;
merge final lsmean_R lsmean_T;
  pt=tinv(0.025,DF,0);
  apt=abs(pt);
  pw=(log(1.25)/stderr-apt);
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Power=100*probt (pw, DF) ;
Intra_cv=100*sqrt (exp (mse) -1) ;
id=1;
Gmref=exp (my1) ;
Gmtest=exp (my2) ;
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;
Run;
Data CIALl;
set CI_Cmax CI_Ctau CI_Auctau;
format Gmref GMtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;
Run;
Proc Print Data=CIALL noobs;
Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";
var PK_Parameters Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;
Run;

Ods pdf close;
Ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR GRAPHS (THE TWO FORMULATION, TWO SEQUENCE, TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY STATE DESIGN)

```

/*****
/*   Study Number: ----- */
/*****
ods rtf file="D:\All Graphs.doc";
data data ;
  set data;
  keep subject trt c1-c26 t1-t26;
  label trt="Treatment";
run;
proc sort data=data;
  by subject trt;
run;
data a;
  set data;
  array c{26} c1-c26 ;array t{26} t1-t26;
  do st=1 to 26;
    cons=round(c{st},.0001);
    if (cons > 0)then lcon=log(c{st});
    else lcon=.;
    time=t(st);
    output;
  end;
  drop period seq;
  drop c1-c26 t1-t26 st;
run;
proc sort data=a;
  by subject;
run;
/*                               Linear Plot                               */
  goptions reset=all ;
  goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
  axis1 label=(a=90 'Concentration (ng/mL)') ;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
axis2 minor=(n=1) order=0.00      1.50      3.00      4.50      6.00
7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
19.50      21.00      22.50      24.00
```

;

proc gplot data=a;

label subject='Subject No.';

label time ='Time(Hour) ' ;

title 'Comparative Linear Plot of (Analyte name) Plasma Concentration
(ng/mL) Vs Time (Hour) ';

by subject;

plot const*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

*/

Semi Log Plot

/*;

goptions reset=all ;

goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5

ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;

axis1 label=(a=90 'Ln Concentration (ng/mL)') ;

axis2 minor=(n=1) order=0.00 1.50 3.00 4.50 6.00

7.50 9.00 10.50 12.00 13.50 15.00 16.50 18.00

19.50 21.00 22.50 24.00

;

proc gplot data=a;

label subject='Subject No.';

label time ='Time(Hour) ' ;

title 'Comparative Semi Log Plot of (Analyte name) Plasma
Concentration (ng/mL) Vs Time (Hour) ';

by subject;

plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

*/

Mean Graph

/*;

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

proc sort data=data;
  by trt;
run;

proc means data=data mean noprint ;
  var c1-c26 ;
  by trt;
  output out= b;
run;

data c;
  set b;
  subject= _stat_ ;
run;

data d; set c;
  drop _type_ _stat_ _freq_;
  if subject NE "MEAN" then delete;
run;

data e;
  set d;
  array c{26} c1-c26 ;
  do st=1 to 26;
    cons=round(c{st}, .00001);
    if (cons > 0) then lcon=log(c{st});
    else lcon=.;
    output;
  end;
  drop period seq;
  drop c1-c26 st;
run;

data f ;
  input time;
  cards;

```

;

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Reference SOP No. : BEQ/ST/SOP-016/01

run;

data g;

merge e f;

run;

```
*/                               Linear Plot                               /*;

    goptions reset=all ;
    goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Concentration (ng/mL)') ;
    axis2 minor=(n=1) order=0.00          1.50      3.00      4.50      6.00
    7.50      9.00      10.50      12.00      13.50      15.00      16.50      18.00
    19.50      21.00      22.50      24.00
```

;

proc gplot data=g;

label time ='Time(Hour) ' ;

title 'Comparative Linear Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour)(N=) ';

by subject;

plot cons*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

```
*/                               Semi Log Plot                               /*;
```

goptions reset=all ;

goptions htitle=1.5 colors=(black) ftitle='arial/bo' htext=1.5

ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;

axis1 label=(a=90 'Ln Concentration(ng/mL)') ;

axis2 minor=(n=1) order=0.00 1.50 3.00 4.50 6.00

7.50 9.00 10.50 12.00 13.50 15.00 16.50 18.00

19.50 21.00 22.50 24.00

;

proc gplot data=g;

label time ='Time(Hour) ' ;

title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma
Concentration (ng/mL) Vs Time (Hour)(N=) ';

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**Reference SOP No. : BEQ/ST/SOP-016/01**

```
by subject;

plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;

SYMBOL1 V=STAR C=blue I=JOIN width=2 height=1.8 bwidth=10 ;

SYMBOL2 V=circle C=BLACK I=JOIN width=2 height=1.8 bwidth=10 ;

run;

ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF PRE-DOSE CONCENTRATION FOR THE TWO
FORMULATION, TWO SEQUENCE, TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY
STATE DESIGN**

```
Ods pdf file='D:\Statistical Analysis -----'.pdf';
Ods rtf file='D:\Statistical Analysis -----'.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: ----- ';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1 " SAS Version Used: Version &sysver ";
FOOTNOTE2 '                                     ';
FOOTNOTE3 '                                     ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5 '                                     ';
FOOTNOTE6 '                                     ';
FOOTNOTE7 j=1 ' (Signature/Date)                  ';

Proc print data=inputdata;
run;

PROC MEANS data=inputdata MEAN STD CV maxdec=4 ;
CLASS Form subject ;
TITLE5      "SUMMARY STATISTICS - INTRA-SUBJECT STATISTICS ";
VAR Cpd;
RUN;

PROC MEANS data=inputdata N MEAN MEDIAN STD CV MIN MAX maxdec=4 ;
CLASS Form ;
TITLE5      "SUMMARY STATISTICS - FORMULATION ";
VAR Cpd;
RUN;

PROC MEANS data=inputdata N MEAN MEDIAN STD CV MIN MAX maxdec=4 ;
CLASS time;
TITLE5      "SUMMARY STATISTICS - TIME(IN DAYS)";
VAR Cpd;
RUN;

ods pdf close;
ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF PRE-DOSE CONCENTRATION FOR THE TWO FORMULATION, TWO SEQUENCE, TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY

STATE DESIGN WITH GROUP

```
Ods pdf file='D:\Statistical Analysis -----'.pdf';
Ods rtf file='D:\Statistical Analysis -----'.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: ----- ';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1 " SAS Version Used: Version &sysver ";
FOOTNOTE2 '                                     ';
FOOTNOTE3 '                                     ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:   ';
FOOTNOTE5 '                                     ';
FOOTNOTE6 '                                     ';
FOOTNOTE7 j=1 ' (Signature/Date)              ';
Proc print data=inputdata;
run;
PROC MEANS data=inputdata MEAN STD CV maxdec=4 ;
CLASS Form subject ;
TITLE5      "SUMMARY STATISTICS - INTRA-SUBJECT STATISTICS ";
VAR Cpd;
RUN;
PROC MEANS data=inputdata N MEAN MEDIAN STD CV MIN MAX maxdec=4 ;
CLASS Form ;
TITLE5      "SUMMARY STATISTICS - FORMULATION ";
VAR Cpd;
RUN;
PROC MEANS data=inputdata N MEAN MEDIAN STD CV MIN MAX maxdec=4 ;
CLASS Group;
TITLE5      "SUMMARY STATISTICS - GROUP ";
VAR Cpd;
RUN;
PROC MEANS data=inputdata N MEAN MEDIAN STD CV MIN MAX maxdec=4 ;
CLASS time;
TITLE5      "SUMMARY STATISTICS - TIME (IN DAYS)";
VAR Cpd;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

RUN;

ods pdf close;

ods rtf close;

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**Reference SOP No. : BEQ/ST/SOP-016/01**

SAS PROGRAM FOR GRAPHS (PRE-DOSE CONCENTRATION FOR THE TWO FORMULATION, TWO SEQUENCE, TWO PERIOD, MULTIPLE DOSE, 2 X 2 CROSSOVER STEADY STATE DESIGN)

```

/*****/
/*   Study Number: ----- */
/*****/

ods rtf file="D:\All Graphs.doc";

data data ;
  set data;
  keep subject trt c1-c3 t1-t3;
  label trt="Treatment";

run;

proc sort data=data;
  by subject trt;

run;

data a;
  set data;
  array c{3} c1-c3 ;array t{3} t1-t3;
  do st=1 to 3;
    cons=round(c{st},.0001);
    if (cons > 0)then lcon=log(c{st});
    else lcon=.;
    time=t(st);
    output;
  end;
  drop period seq;
  drop c1-c3 t1-t3 st;

run;

proc sort data=a;
  by subject;

run;

/*                               Linear Plot                               */
  goptions reset=all ;
  goptions htitle=2 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

axis1 label=(a=90 'Pre-Dose Concentration (ng/mL)') ;
axis2 minor=(n=1) order=5 6 7

;
proc gplot data=a;
    label subject='Subject No.';
    label time ='Time (Days)' ;
    title 'Comparative Linear Plot of (Analyte name) Plasma Pre-Dose
Concentration (ng/mL) Vs Time ' ;
    by subject;
    plot const*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=1.8 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=1.8 height=1.8 bwidth=10 ;

run;

*/                               Semi Log Plot                               /*;
    goptions reset=all ;
    goptions htitle=2 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Ln Pre-Dose Concentration(ng/mL)') ;
    axis2 minor=(n=1) order=5 6 7

;
proc gplot data=a;
    label subject='Subject No.';
    label time =' Time (Days)' ;
    title 'Comparative Semi Log Plot of (Analyte name) Plasma Pre-Dose
Concentration (ng/mL) Vs Time ' ;
    by subject;
    plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=1.8 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=1.8 height=1.8 bwidth=10 ;

run;

*/                               Mean Graph                               /*;

proc sort data=data;
    by trt;

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
proc means data=data mean noprint ;
  var c1-c3 ;
  by trt;
  output out= b;
run;
data c;
set b;
  subject= _stat_ ;
run;
data d; set c;
  drop _type_ _stat_ _freq_;
  if subject NE "MEAN" then delete;
run;
data e;
  set d;
  array c{3} c1-c3 ;
  do st=1 to 3;
    cons=round(c{st},.00001);
    if (cons > 0)then lcon=log(c{st});
    else lcon=.;
    output;
  end;
  drop period seq;
  drop c1-c3 st;
run;
data f ;
  input time;
  cards;
```

```
;
```

```
run;
```

```
data g;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

merge e f;

run;

*/                               Mean Linear Plot                               /*;

    goptions reset=all ;
    goptions htitle=2 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Pre-Dose Concentration (ng/mL)') ;
    axis2 minor=(n=1) order=5 6 7
;

proc gplot data=g;
    label time ='Time (Days)' ;
    title 'Comparative Linear Plot of (Analyte name) Mean Plasma Pre-Dose
Concentration (ng/mL) Vs Time (N= ) ' ;
    by subject;
    plot cons*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=1.8 height=1.8 bwidth=10 ;
    SYMBOL2 V=circle C=BLACK I=JOIN width=1.8 height=1.8 bwidth=10 ;

run;

*/                               Mean Semi Log Plot                               /*;

    goptions reset=all ;
    goptions htitle=2 colors=(black) ftitle='arial/bo' htext=1.5
ftext='arial/bo' VSIZE=4 in HSIZE=6 in ;
    axis1 label=(a=90 'Ln Pre-Dose Concentration(ng/mL)') ;
    axis2 minor=(n=1) order= 5 6 7
;

proc gplot data=g;
    label time =' Time (Days)' ;
    title 'Comparative Semi Log Plot of (Analyte name) Mean Plasma Pre-
Dose Concentration (ng/mL) Vs Time (N= ) ' ;
    by subject;
    plot lcon*time=trt/vaxis=axis1 haxis=axis2 ;
    SYMBOL1 V=STAR C=blue I=JOIN width=1.8 height=1.8 bwidth=10 ;

```

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**Reference SOP No. : BEQ/ST/SOP-016/01**

SYMBOL2 V=circle C=BLACK I=JOIN width=1.8 height=1.8 bwidth=10 ;

run;

ods rtf close;

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**Reference SOP No. : BEQ/ST/SOP-016/01****SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE SCALED-AVERAGE BIOEQUIVALENCE****APPROACH FOR PARTIAL REPLICATED CROSSOVER DESIGN**

```

/***** Scaled Average Bioequivalence Approach
(Partial Replicated Crossover Design) *****/
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: ----- ';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
Title4      ' Scaled-Average Bioequivalence Approach For Primary Pharmacokinetic
Parameter Cmax';
FOOTNOTE1 " SAS Version Used: Version &sysver ";
FOOTNOTE2 '                                     ';
FOOTNOTE3 '                                     ';
FOOTNOTE4 j=1 'Prepared By Biostatistician:   ';
FOOTNOTE5 '                                     ';
FOOTNOTE6 '                                     ';
FOOTNOTE7 j=1 ' (Signature/Date)              ';
proc print data=one;
var subject seq form period Cmax;
run;
proc sort data=one;
by form subject;
run;
data two;
set one;
LCmax=log(Cmax);
run;
Data R_Data;
set two;
if form="T" then delete;
keep subject seq form period LCmax;
run;
proc glm data=R_Data outstat=tanova noprint;
class subject period seq;
model LCmax=seq subject(seq) period;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
quit;
data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF;
keep mse;
run;
data Limit;
set error;
format Swr Swr_2 10.4 Intra_CV_R Lower Upper 8.2;
PK_Parameter="LnCmax";
Swr_2=mse;
Swr=sqrt(Swr_2);
Intra_CV_R=100*sqrt(exp(Swr_2)-1);
Lower=Round(100*exp(-0.760*Swr),0.01);
Upper=Round(100*exp(0.760*Swr),0.01);
if (Intra_CV_R>50) then do;
Lower=69.84;
Upper=143.19;
end;
keep PK_Parameter Swr Swr_2 Intra_CV_R Lower Upper;
Run;
Data limits;
set limit;
length method $80;
sd_r=Round(Swr,0.001);
if (sd_r>= 0.294) then do;Method="Scaled-Average Bioequivalence Approach is
Applicable";end;
if (sd_r < 0.294) then do;method="Unscaled-Average Bioequivalence Approach is
Applicable";end;
keep PK_Parameter Swr Swr_2 Intra_CV_R Lower Upper Method;
Run;
Proc print data=limits noobs;
Title5 " Statistical Results of Scaled-Average Bioequivalence Approach";
var PK_Parameter Swr Swr_2 Intra_CV_R Lower Upper Method;
run; ods pdf close; ods rtf close;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE UNSCALED-AVERAGE BIOEQUIVALENCE APPROACH FOR PARTIAL REPLICATED 4 WAY AND 3 WAY Crossover DESIGN WITH STANDARD ANOVA MODEL (UNDER SCALED-AVERAGE BIOEQUIVALENCE APPROACH)

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1  " SAS Version Used: Version &sysver      ";
FOOTNOTE2  '                                           ';
FOOTNOTE3  '                                           ';
FOOTNOTE4  j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5  '                                           ';
FOOTNOTE6  '                                           ';
FOOTNOTE7  j=1 ' (Signature/Date)                  ';

proc print data=one;
var subject seq form period Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period Res_area Ke_first Ke_last npoints;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
run;

Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period tmax ke thalf Res_area Ke_first Ke_last npoints;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T AUCt_T AUCinf_T;
    output out=M_T
        mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUCt_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;
Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
    R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
(%) "
    B_cmax="Bioavailability of Cmax (%)"
    B_AUCt="Bioavailability of AUCt (%)"
;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;
proc print data=M_T_R label noobs;
TITLE4 "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;
PROC SORT data=one;
    BY form;
Run;
PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
    TITLE4 "SUMMARY STATISTICS - FORMULATION ";
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS seq;
  TITLE4 "SUMMARY STATISTICS - SEQUENCE ";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS period;
  TITLE4 "SUMMARY STATISTICS - PERIOD ";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS seq;
  BY form;
  TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS period;
  BY form;
  TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;
set one;
LCmax=log(Cmax);
LAUCt=log(AUCt);
run;

/***** LCmax *****/

Proc Glim Data= two outstat=tanova;
  Title4 "ANOVA for log transformed Cmax ";
  class seq subject form period;
  model LCmax=form period seq subject(seq)/ssl ss3 clparm alpha=0.1;
  test h=seq e=subject(seq);
  lsmeans form/stderr pdiff out=lsmean;

```


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Reference SOP No. : BEQ/ST/SOP-016/01

```

estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run;Quit;
Data error; set tanova;
  if _SOURCE_ = 'ERROR';
  mse=SS/DF; sse=SS; id=1;
  keep mse sse df id;
Run;
Proc Sort Data=error;
  by id;
Run;
Data test ;
set ep;
  length Bioequivalence $100;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  Bioequivalence='Acceptance limits:Refer Widening limits from Scaled-Average
Bioequivalence Approach';
  id=1;
Run;
Proc Sort Data=test;
  by id;
Run;
Data final;
merge test error;
  by id;
Run;
Data lsmean_R; set lsmean; if form='R';
  my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
  my2=lsmean;id=1;keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCt *****/
Proc Glm Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";
class seq subject form period;
model LAUCt=form period seq subject(seq)/ssl ss3 clparm alpha=0.1;
test h=seq e=subject(seq);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
id=1;
Run;
Proc Sort data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_AUCT;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt (pw,DF);
Intra_cv=100*sqrt (exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
KEEP DEPENDENT Gmref Gmtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
Data CIALl;
set CI_Cmax CI_AUCT;
format Gmref Gmtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;
Run;
Proc Print Data=CIALL noobs;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided Test";

var PK_Parameters Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER

Bioequivalence;

Run;

Ods pdf close;

Ods rtf close;

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Reference SOP No. : BEQ/ST/SOP-016/01

**SAS PROGRAM FOR THE STATISTICAL ANALYSIS OF THE UNSCALED-AVERAGE
BIOEQUIVALENCE APPROACH FOR PARTIAL REPLICATED 4 WAY AND 3 WAY CROSSOVER
DESIGN WITH GROUP ANOVA MODEL MODEL (UNDER SCALED-AVERAGE BIOEQUIVALENCE
APPROACH)**

```
Ods pdf file='D:\Statistical Analysis of -----.pdf';
Ods rtf file='D:\Statistical Analysis of -----.doc';
Options ps=90 ls=100 PAGENO=1;
Title2      ' Protocol No: -----';
Title3      ' Statistical Data Processing of ----- Under ----- Condition ';
FOOTNOTE1  " SAS Version Used: Version &sysver      ";
FOOTNOTE2  '                                           ';
FOOTNOTE3  '                                           ';
FOOTNOTE4  j=1 'Prepared By Biostatistician:      ';
FOOTNOTE5  '                                           ';
FOOTNOTE6  '                                           ';
FOOTNOTE7  j=1 ' (Signature/Date)                  ';

proc print data=one;
var subject seq form period group Cmax Tmax AUCt AUCinf ke thalf;
run;

proc print data=one;
var subject seq form period group Res_area Ke_first Ke_last npoints;
run;

proc sort data=one;
by form subject;
run;

Data T_Data;
set one;
if form="R" then delete;
Rename cmax=cmax_T AUCt=AUCt_T AUCinf=AUCinf_T ;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
run;

Data R_Data;
set one;
if form="T" then delete;
Rename cmax=cmax_R AUCt=AUCt_R AUCinf=AUCinf_R;
Drop form period group tmax ke thalf Res_area Ke_first Ke_last npoints;
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
run;
proc univariate data=T_Data nextrobs=0 noprint;
    var cmax_T AUCt_T AUCinf_T;
    output out=M_T
        mean=M_cmax_T mean=M_AUCt_T mean=M_AUCI_T;
run;
proc univariate data=R_Data nextrobs=0 noprint;
    var cmax_R AUCt_R AUCinf_R;
    output out=M_R
        mean=M_cmax_R mean=M_AUCt_R mean=M_AUCI_R;
run;
Data M_T_R;
merge M_T M_R;
T_AUCt_AUCI=100*(M_AUCt_T/M_AUCI_T);
R_AUCt_AUCI=100*(M_AUCt_R/M_AUCI_R);
B_cmax=100*(M_cmax_T/M_cmax_R);
B_AUCt=100*(M_AUCt_T/M_AUCt_R);
format T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt 18.2;
Label T_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Test formulation (%)"
    R_AUCt_AUCI="Ratio of mean AUCt to mean AUCinf for Reference formulation
(%) "
    B_cmax="Bioavailability of Cmax (%)"
    B_AUCt="Bioavailability of AUCt (%)"
;
keep T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;
proc print data=M_T_R label noobs;
TITLE4 "Ratio Analysis";
var T_AUCt_AUCI R_AUCt_AUCI B_cmax B_AUCt;
run;
PROC SORT data=one;
    BY form;
Run;
PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX maxdec=6;
    CLASS form;
TITLE4 "SUMMARY STATISTICS - FORMULATION ";
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```

VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS seq;
  TITLE4 "SUMMARY STATISTICS - SEQUENCE ";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS period;
  TITLE4 "SUMMARY STATISTICS - PERIOD ";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS group;
  TITLE4 "SUMMARY STATISTICS - GROUP ";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS seq;
  BY form;
  TITLE4 "SUMMARY STATISTICS - SEQUENCE/FORMULATION";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

PROC MEANS Data=one N MEAN MEDIAN STD CV MIN MAX MAXDEC=6 FW=8;
  CLASS period;
  BY form;
  TITLE4 "SUMMARY STATISTICS - PERIOD/FORMULATION";
  VAR Cmax AUCt AUCinf tmax thalf Ke Res_area;

RUN;

data two;
set one;
LCmax=log(Cmax);
LAUCt=log(AUCt);
run;

/***** LCmax *****/

Proc Glim Data= two outstat=tanova;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Title4 "ANOVA for log transformed Cmax ";
class seq subject group form period;
model LCmax=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
test h=seq e=subject(seq*group);
test h=group e=subject(seq*group);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run;Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
keep mse sse df id;
Run;
Proc Sort Data=error;
by id;
Run;
Data test ;
set ep;
length Bioequivalence $20;
Ratio=100*exp(estimate);
lower=Round(100*exp(LowerCL),0.01);
upper=Round(100*exp(UpperCL),0.01);
Bioequivalence='Acceptance limits:Refer Widening limits from Scaled-Average
Bioequivalence Approach';
id=1;
Run;
Proc Sort Data=test;
by id;
Run;
Data final;
merge test error;
by id;
Run;
Data lsmean_R; set lsmean; if form='R';
```


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**Reference SOP No. : BEQ/ST/SOP-016/01**

```

my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_Cmax;
merge final lsmean_R lsmean_T;
pt=tinv(0.05,DF,0);
apt=abs(pt);
pw=(log(1.25)/stderr-apt);
Power=100*probt(pw,DF);
Intra_cv=100*sqrt(exp(mse)-1);
id=1;
Gmref=exp(my1);
Gmtest=exp(my2);
Rename DEPENDENT=PK_Parameters;
Keep DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;
Run;
/***** LAUCt *****/
Proc Glim Data= two outstat=tanova;
Title4 "ANOVA for log transformed AUCt ";
class seq subject group form period;
model LAUCt=form group form*group period(group) seq seq*group
subject(seq*group)/ssl ss3 clparm alpha=0.1;
test h=seq e=subject(seq*group);
test h=group e=subject(seq*group);
lsmeans form/stderr pdiff out=lsmean;
estimate 'R vs T' Form -1 1;
ods output Estimates=ep;
Run; Quit;
Data error; set tanova;
if _SOURCE_ = 'ERROR';
mse=SS/DF; sse=SS; id=1;
Keep mse sse df id;
Run;

```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Proc Sort Data=error;
  by id;
Run;
Data test ;
set ep;
  length Bioequivalence $100;
  Ratio=100*exp(estimate);
  lower=Round(100*exp(LowerCL),0.01);
  upper=Round(100*exp(UpperCL),0.01);
  if lower >= 80.00 and upper <= 125.00 then Bioequivalence ='Yes' ;else
Bioequivalence ='No';
  id=1;
Run;
Proc Sort data=test;
  by id;
Run;
Data final;
merge test error;
  by id;
Run;
Data lsmean_R; set lsmean; if form='R';
my1=lsmean; id=1; keep ID my1 ;
Run;
Data lsmean_T; set lsmean; if form='T';
my2=lsmean;id=1;keep id my2;
Run;
Data CI_AUCT;
merge final lsmean_R lsmean_T;
  pt=tinv(0.05,DF,0);
  apt=abs(pt);
  pw=(log(1.25)/stderr-apt);
  Power=100*probt(pw,DF);
  Intra_cv=100*sqrt(exp(mse)-1);
  id=1;
  Gmref=exp(my1);
  Gmtest=exp(my2);
```

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Reference SOP No. : BEQ/ST/SOP-016/01

```
Rename DEPENDENT=PK_Parameters;

KEEP DEPENDENT Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence ;

Run;

Data CIALl;

set CI_Cmax CI_AUCT;

format Gmref GMtest 16.3 MSE 10.6 RATIO LOWER UPPER POWER INTRA_CV 8.2;

Run;

Proc Print Data=CIALL noobs;

Title4 "90% Confidence Interval Equivalent to Schuirmanns's Two One Sided
Test";

var PK_Parameters Gmref GMtest MSE RATIO INTRA_CV POWER LOWER UPPER
Bioequivalence;

Run;

Ods pdf close;

Ods rtf close;
```


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STANDARD OPERATING PROCEDURE		
CONDUCTING AUDITS OF CLINICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	1 of 6

SITE OF DISTRIBUTION: Quality Assurance and Head – Bioequivalence.

Issue Date	Effective Date	Review Date
20/07/2016	25/07/2016	19/07/2019.

REVISION CARD

SR. NO.	REVISION NO.	ISSUED DATE	REASON (S) FOR REVISION	REVISION DATE
1.	00	13/04/2006	New SOP	12/05/2006
2.	01	12/05/2006	1. Changes in the Heading of SOP as 'Monitoring and Audit of Clinical Section' instead of 'Conducting Audit of Clinical Section' 2. Monitoring of Clinical Section by QA is incorporated.	24/07/2006
3.	02	24/07/2006	1. Removal of Monitoring, of Clinical section, by QA 2. Modification of Annexure No. 01, 'Checklist for Clinical Operations'	04/06/2007
4.	03	04/06/2007	1. Incorporation of format number 2. Separation of annexure	30/05/2009
5.	04	30/05/2009	1. Periodic Review 2. Modification in procedure 3. Deletion of old annexure and addition of all new annexure	25/06/2010
6.	05	25/06/2010	1. Deletion of section 4.8 2. Addition of new points to include the procedure for stamping of documents as section 4.8	30/05/2012
7.	06	30/05/2012	1. Periodic Review 2. Addition of three new points in 4.4 about online audit of temperature records, validation and calibration records 3. Addition of two new points in 4.5 about retrospective audit of data transfer sheet, actual time of blood collection table and demographic data 4. Modification in 4.7 to change title of FRM/QA/SOP-007-02 5. Modification in 4.8.3 to add master file 6. Addition of ECG in section 5. Abbreviation(s)	20/07/16
8.	07	20/07/16.	1. Periodic review 2. Modification of procedure and annexure 3. Renumbering of procedure	N/AP

Design. – Dept.	Prepared By	Checked By	Approved By	Authorised By
	Clinical - QA	Clinical - QA	Head - QA	Head - Bioequivalence
Sign and Date	 20/07/2016	 20/07/2016	 20/07/2016	 20/07/16
Name	Ms. Hemal S.	Mr. Khurshid S.	Dr. Sagar P.	Dr. Ashish M.

ANX/GN/SOP-001-01

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF CLINICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	2 of 6

1. OBJECTIVE:

To lay down the procedure for conducting audits of clinical section.

2. SCOPE:

This procedure is applicable to QA section and serves as a guideline for conducting audits of clinical section.

3. RESPONSIBILITY:

Quality Assurance staff: Conducts process audit

4. PROCEDURE:

4.1 **Study-based audits:** The purpose of study based audit is to ensure that studies are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

4.2 **Clinical Phases:** QA audit to be carried out in each phase of clinical activates. The phases of audit are as follows:

- Before the clinical phase of the study commences
(During this planning stage the essential documents as per regulatory requirement should be generated and should be on file before the study formally starts)
- During the clinical conduct of the study (In Process)
- After completion or termination of the study (Retrospective)

4.2.1 **Before the clinical phase of the study commences:** QA activities before the conduct of the study, include the following activities but not limited to;

- Protocol, CRF and ICF preparation [to check with the consistency of the SOP, regulatory requirement (if any) etc]
- Volunteer screening procedures, which includes the recruitment of volunteers according to the inclusion and exclusion criteria, specific requirements of the protocol, pathology, ECG and X-Ray records.
- Receipt of the investigational products
- Documentation and filing of the screening forms

4.2.2 **During the Clinical Conduct of the Study (In Process):** QA activities during the conduct of the study, include the following activities but not limited to;

- During the conduct of the study the check-in procedure which includes the consent process, physical examination during check-in activity, breath alcohol procedure, vital examination, medical examination, documentation of the check-in activity, informed

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF CLINICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	3 of 6

consent document signature, pre-dosing activity like pre-dose vital, and collection of pre-dose sample.

- Handling of investigational products.
- Monitoring of the dosing activity, post-study sample collection, sample centrifugation, separation and storage, meal distribution, vital monitoring, adverse event monitoring.
- Monitoring of the checkout activity for the compliance as per the protocol requirement, like sample collection, vital check, medical examination, ECG during post study etc.
- Any other activities as per protocol requirement eg. Glucose administration, glucose estimation, etc.

4.2.3 After Completion or Termination of the Study (Retrospective): QA activities after completion or termination of the study, include the following activities but not limited to;

- Conduct of quality reviews of CRFs and supplemental study documentation.
- Check all the study data for reliability and traceability.
- Verify the raw data generated during conduct of the clinical study for completeness, accuracy and validity ensuring that the detailed information of all the activities performed has been duly and promptly transcribed in the raw data and that all the activities performed allow reconstruction of the course of events.
- Verify that the study report accurately and completely reflects the data of the study.
- Ensure that any SOP/ Protocol deviation(s) occurred during the study have been duly mentioned in the final study report with the necessary corrective action taken, if any.
- Review of data transfer sheet for samples transferred to Bioanalytical section.
- Review of actual time of blood collection table and subject demographic data prior to its transfer to biostatistician.

4.2.4 Others: apart from study specific activities following document (not limited) to be reviewed at regular interval.

- Training of study personnel
- Temperature records of deep freezer
- Temperature and humidity records of humidity and stability chamber
- Validation and calibration records
- Cleaning records
- Preventive maintenance record

4.3 Audit Plan:

4.3.1 Prepare the audit plan for study-based audit after obtaining the plan for conduct of study activities from the principal investigator or section head; which provides an overview of the activities and timelines for the audit.

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF CLINICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	4 of 6

- 4.3.2 Retrospective audit (data/ report) will be done as and when data/ report are received from the respective section.
- 4.3.3 The contents of the audit plan might include:
- Brief details of the study to be audited
 - Approximate timelines for the conduct of the audit
 - Outline of specific auditing activities that will be conducted during the audit
 - Responsible auditor(s)
 - Responsible auditee(s)
- 4.3.4 For preparation of audit plan, refer SOP No. BEQ/QA/SOP-004, 'Scheduling of Audit Activities'.
- 4.4 **Audit Preparation:**
- 4.4.1 Prepare a checklist prior to execution of the audit. The checklist will vary as per process and study being audited.
- 4.4.2 Update/ review the checklist so as to be in line with protocol, GCP requirements and current SOPs.
- 4.4.3 Prepare a checklist prior to conduct of the audit for reference as per following template:
- For checking protocol, refer Annexure No. ANX/QA/SOP-005-01, 'Checklist for Protocol'.
 - For checking Informed Consent Form, refer Annexure No. ANX/QA/SOP-005-02, 'Checklist for Informed Consent Form'.
 - For screening, refer Annexure No. ANX/QA/SOP-005-03, 'Checklist for Screening of Enrolled Volunteers'.
 - For Receipt and Storage of Investigational Product, refer Annexure No. ANX/QA/SOP-005-04, 'Checklist for Receipt and Storage of Investigational Product'.
 - For in-process (online) audit of study, refer Annexure No. ANX/QA/SOP-005-05, 'Checklist for In-process Audit'.
 - For retrospective audit of study refer Annexure No. ANX/QA/SOP-005-06, 'Checklist for Retrospective Audit'.
- 4.5 **Conduct of the Audit**
- 4.5.1 During the conduct of the audit, check the relevant documents, activities and the procedures followed for carrying out each activity ensuring that all the activities are carried out in accordance to the protocol, relevant SOPs, GCP and the other applicable regulatory requirements.
- 4.5.2 Bring to notice of the concerned personnel the serious discrepancies found at the time of any activity, which may affect the integrity of the data and further outcome of the study.
- 4.5.3 Prepare the audit report based on the findings noted during the audit and based on checklist and submit it to the auditee for the necessary corrective actions.

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF CLINICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	5 of 6

- 4.5.4 For preparation of audit report, refer SOP No. BEQ/QA/SOP-007, 'Preparation and Generation of Audit Report'.

Note: During audit follow all rules for access, safety and hygiene so that the work is not disrupted.

4.6 Close-Out Meeting

- 4.6.1 After completion of the audit carry out a discussion with the concerned personnel and bring to notice all the shortcomings observed during the audit.
- 4.6.2 Prior to the discussion, spend sufficient time (approximately 15–30 minutes) preparing for the discussion by summarising all of their observations.
- 4.6.3 Feedback on audit findings should be given in a positive and constructive manner where possible to maintain motivation of the staff.

4.7 Stamping of Documents

- 4.7.1 In case of in process audit stamp, initial, date, and time (if applicable) the documents for which activities were witnessed by auditor.
- 4.7.2 In case of CRF, stamp, initial and date the first page of CRF.
- 4.7.3 In case of master file, raw data, if complete audit is done, stamp the index page of the files.
- 4.7.4 In case of logbook do not stamp the logbook.
- 4.7.5 In case of study specific ICFs stamp the first page of ICF audited.
- 4.7.6 In case of calibration stamp, initial and date the first page of calibration documents audited.
- 4.7.7 When stamping QA personnel shall:
- Ensure the legibility and durability of stamp impression and ensure that stamp(s) do not interlock with other stamp(s)
 - When voiding stamp impression, QA personnel will apply
 - i) A single line through the impression
 - ii) 'Void' immediately adjacent to the lined out impression
 - iii) Initial/ signature of person voiding the impression
 - iv) Date when impression is 'voided'

Note: Stamp all the above mentioned documents with 'Q.A Review' stamp in blue ink.

5. ABBREVIATION (S):

5.1	CCR	: Clinical Case Record
5.2	CRF	: Case Record Form
5.3	COA	: Certificate Of Analysis
5.4	CPU	: Clinical Pharmacology Unit
5.5	ECG	: Electrocardiogram
5.6	ICF	: Information Consent Form

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.			
STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF CLINICAL SECTION			
Supersedes	SOP No.:	Page No.:	
BEQ/QA/SOP-005/06	BEQ/QA/SOP-005/07	6 of 6	

- 5.7 PI : Principal Investigator
- 5.8 ME : Medical Examination
- 5.9 ML : Milli Litre
- 5.10 MO : Medical Officer
- 5.11 No. : Number
- 5.12 N/AP : Not Applicable
- 5.13 UPT : Urine Pregnancy Test

6. REFERENCE (S):

- 6.1 BEQ/QA/SOP-004, 'Scheduling of Audit Activities'
- 6.2 BEQ/QA/SOP-007, 'Preparation and Generation of Audit Report'

7. ANNEXURE (S):

- 7.1 Annexure No. ANX/QA/SOP-005-01, 'Checklist for Protocol'
- 7.2 Annexure No. ANX/QA/SOP-005-02, 'Checklist for Informed Consent Form'
- 7.3 Annexure No. ANX/QA/SOP-005-03, 'Checklist for Screening of Enrolled Volunteers'
- 7.4 Annexure No. ANX/QA/SOP-005-04, 'Checklist for Receipt and Storage of Investigational Product'
- 7.5 Annexure No. ANX/QA/SOP-005-05, 'Checklist for In-process Audit'
- 7.6 Annexure No. ANX/QA/SOP-005-06, 'Checklist for Retrospective Audit'

8. FORM (S):

N/AP

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

CHECKLIST FOR PROTOCOL

Sr. No	Contents	Yes	No	Comment(s)
1	1.0 TITLE PAGE			
2	2.0 LIST OF CONTENT			
3	3.0 ABBREVIATIONS			
4	4.0 CONTACT PERSONNEL			
5	5.0 FACILITIES			
6	6.0 DECLARATION			
7	6.1 Reviewer declaration			
8	6.2 Investigator Declaration			
9	7.0 SPONSOR'S APPROVAL			
10	8.0 PROTOCOL SYNOPSIS			
11	9.0 BACKGROUND			
12	9.1 Investigational Products			
13	9.2 Pharmacology			
14	9.3 Clinical Pharmacokinetics			
15	9.4 Indications and Uses			
16	9.5 Posology and method of Administration			
17	9.6 Adverse Reactions			
18	9.7 Precaution/warning/special warning			
19	9.8 Contraindications			
20	9.9 Study Rationale			
21	9.10 Study Population			
22	9.11 References			
23	10.0 STUDY OBJECTIVES AND PURPOSE			
24	10.1 Pharmacokinetics			
25	10.2 Safety			
26	11.0 STUDY DESIGN			
27	11.1 Design			
28	11.2 Evaluation Parameters			
29	11.2.1 Primary Bioavailability Variables			
30	11.2.2 Secondary Bioavailability Variables			
31	11.3 Procedures to Minimize / Avoid Bias			

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No	Contents	Yes	No	Comment(s)
32	11.4 Investigational Products, Dosing Regimen and Labelling			
33	11.4.1 Investigational Products			
34	11.4.2 Selection of Doses			
35	11.4.3 Justification of Choice Reference Product			
36	11.4.4 Supply of Investigational Products			
37	11.4.5 Dispensing and Labeling of Investigational Product			
38	11.5 Sequence and Duration of Study Periods			
39	11.5.1 Overall Study Plan			
40	11.5.2 Study Restrictions			
41	11.5.3 Procedures on Pre-Study and Study Day			
42	11.5.4 Blood Collection Schedule			
43	11.5.5 Total Blood Loss			
44	11.5.6 Handling of Blood Samples			
45	11.5.7 Dietary Restrictions During Study			
46	11.6 Termination of the Study			
47	11.7 Investigational Product Accountability (Receipt, Inventory and Return)			
48	11.8 Randomisation Procedures			
49	11.9 Source Data and Direct Recording In CRF			
50	12.0 SELECTION AND WITHDRAWAL OF SUBJECTS			
51	12.1 Inclusion Criteria			
52	10.3 Exclusion Criteria			
53	12.3 Subject's Withdrawal / Termination			
54	13.0 TREATMENT OF SUBJECTS			
55	13.1 Dose and Route of Administration			
56	13.2 Concomitant Medication			
57	13.3 Compliance			
58	14.0 ASSESSMENT OF BIOAVAILABILITY			
59	14.1 Efficacy Parameters			

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No.: BEQ/QA/SOP-005/07**

Sr. No	Contents	Yes	No	Comment(s)
60	14.2 Subjects With Pre-dose Concentration			
61	14.3 Data Deletion Due to Vomiting			
62	14.4 Drug Assay			
63	15.0 ASSESSMENT OF SAFETY PARAMETERS			
64	15.1 Pre-Study Screening			
65	15.2 Post-Study Examination			
66	15.3 Subjects Monitoring During the Study			
67	15.3.1 Vital signs, subject Questionnaire and Medical examination			
68	15.3.2 Adverse Events			
69	15.3.3 Adverse Event Documentation			
70	15.3.4 Reporting of Adverse Events			
71	16.0 PHARMACOKINETIC ANALYSIS AND STATISTICS			
72	16.1 Pharmacokinetic analysis			
73	16.2 Statistical Methods			
74	16.2.1 Plasma Concentrations			
75	16.2.2 Summary Statistics			
76	16.2.3 Analysis of Variance (ANOVA) For Primary Pharmacokinetic parameters			
77	16.2.4 Ratio Analysis For Primary Pharmacokinetic Parameters			
78	16.2.5 Power Test For Primary Pharmacokinetic Parameters			
79	16.2.6 Intra- Subject Variability For Primary Pharmacokinetic Parameters			
80	16.2.7 Confidence Intervals For Primary Pharmacokinetic Parameters			
81	16.2.8 Acceptance Criteria for Bioequivalence for Primary Pharmacokinetic Parameters			
82	16.2.9 Number of Subjects			
83	16.2.10 Justification for Design			

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No	Contents	Yes	No	Comment(s)
84	17.0 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS			
85	18.0 QUALITY CONTROL AND QUALITY ASSURANCE			
86	19.0 ETHICS			
87	19.1 Ethics Committee			
88	19.2 Ethical Conduct of the Study			
89	19.3 Informed Consent			
90	19.4 Compensation to Subjects			
91	20.0 INSURANCE AND FINANCING			
92	21.0 DATA HANDLING AND RECORD KEEPING			
93	22.0 PUBLICATION POLICY			
94	23.0 APPENDICES			

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

CHECKLIST FOR INFORMED CONSENT FORM

Sr. No.	Contents	Yes	No	Comment(s)
1.	ICF should be non-technical, practical and understandable to the volunteer.			
2.	A statement that the study involves research			
3.	An explanation of the purposes of the research			
4.	The expected duration of the subject's participation			
5.	A description of the procedures to be followed			
6.	Identification of any procedures which are experimental			
7.	A description of any reasonably foreseeable risks or discomforts to the subject			
8.	A description of any benefits to the subject or to others which may reasonably be expected from the research			
9.	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject			
10.	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained			
11.	For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained			
12.	An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject			
13.	A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled			
14.	Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent			
15.	Any additional costs to the subject that may result from participation in the research			
16.	The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject			
17.	A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
Reference SOP No.: BEQ/QA/SOP-005/07		

Sr. No.	Contents	Yes	No	Comment(s)
18.	The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.			
19.	The approximate number of subjects involved in the study			
20.	The anticipated prorated payment, if any, to the subject for participating in the study. A) Statement describing the financial compensation and medical management as under: - In the event of an injury occurring to the clinical study subject, such subject shall be provided free medical management as long as required. - In the event of trial related injury or death, the Sponsor or his representative, whosoever has obtained permission from the Licensing Authority for conduct of the clinical study, shall provide financial compensation for the injury or death. - The quantum of compensation decided by Licensing Authority in case of clinical study related injury or death within thirty days of the receipt of order from Licensing Authority will be paid by sponsor.			
21.	Description of follow-up procedure			
22.	Information regarding the dates of visit to facility.			
23.	All the technical terms simplified and should be easy to understand			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

CHECKLIST FOR SCREENING OF ENROLLED VOLUNTEERS

Sr. No.	Contents	Yes	No	Comment(s)
Screening of Enrolled Volunteers				
1.	Is the entry of in time and out time of volunteers made in register with time and sign as per "Format for Volunteer Entry-Exit Record"?			
2.	Is screening slip handed-over to enrolled volunteer?			
3.	Is eligibility of the volunteer for the screening from the volunteer database as well as from the Online Volunteer Information System (OVIS) checked?			
4.	Is the status of volunteer updated in "Volunteer Online Information Status for Screening"?			
5.	Is the wristband (mentioning, volunteer registration number and Initials) tied on the volunteer's wrist for identification?			
Obtaining Consent for Screening and HIV from the Volunteers				
1.	Is the copies of IEC approved screening ICF and 'Consent Form for HIV Testing' to the volunteers in the language they understand, distributed and documented in 'Screening Log'?			
2.	Is ample time to the volunteer provided to read ICF thoroughly?			
3.	Is the pre-counseling for HIV and the entire procedure of screening in simple language explained?			
4.	Is the query raised by the volunteers/ impartial witness/LAR (if any) clarified and discussed?			
5.	Are the volunteers (who are willing to participate voluntarily) gave consent by sign and date the 'Informed Consent for Screening'?			
6.	Is the separate consent for HIV test obtained?			
7.	Is volunteer illiterate and do not understand the language like English, Hindi or Marathi.			

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
	If yes: - Is the procedure informed and explained to the impartial witness? - Is the impartial witness explained the procedure of screening to the volunteer in the language known by him? - Is the impartial witness completed the details of volunteer along with his own details in the screening ICF? - Is volunteer's thumb impression or signature in the screening ICF (right thumb impression for male and left thumb impression for female) taken? Is signature of impartial witness in the screening ICF taken?			
Height, Weight and BMI (Body Mass Index)				
Height Recording				
1.	Is volunteer removes his footwear, while recording the height?			
2.	Is volunteer stand erect touching the wall beneath the stature meter?			
3.	Is stature meter tape pulled down gradually so that it touches the volunteer's head and the reading on meter tape observe?			
4.	Is the height recorded in Screening slip, 'Height - Weight and BMI Log Book' and under 'Demographics' of Screening Record?			
5.	Is volunteer removes his footwear, while recording the height?			
6.	Is volunteer stand erect touching the wall beneath the stature meter?			
7.	Is stature meter tape pulled down gradually so that it touches the volunteer's head and the reading on meter tape observe?			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

Sr. No.	Contents	Yes	No	Comment(s)
8.	Is the height recorded in Screening slip, 'Height - Weight and BMI Log Book' and under 'Demographics' of Screening Record?			
Weight Recording				
1.	Is the weight machine 'ON'?			
2.	Is the display showed a zero reading before taking the weight?			
3.	Is volunteer requested to remove footwear and empty all the pockets?			
4.	Is the volunteer requested to stand erect on the weighing scale and to look straight?			
5.	Is the display showed a stable reading and same has been recorded in Screening Slip, 'Height - Weight and BMI Log Book' and under 'Demographics' of Screening Record?			
BMI (Body Mass Index)				
1.	Is height and weight mentioned in screening slip entered in database?			
2.	Is volunteer's BMI calculated by Database System and transcribed to Height - Weight and BMI Log Book' and under 'Demographics' of Screening Record?			
Collection of Blood and Urine Samples				
1.	Is the requisition slip filled and authorized by medical officer for the laboratory test to be conducted			
2.	Is the volunteer escorted along with the requisition slip to concern person of pathology department?			
3.	After blood and urine samples are taken, is the entry made in screening slip?			
Vital Signs				
1.	Are volunteer's vital signs - radial pulse (for 1 minute), blood pressure, respiratory rate (for 1 minute) and temperature taken?			

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
2.	Are the readings recorded under Medical Examination' of Screening Record?			
3.	Are volunteer's vital signs - radial pulse (for 1 minute), blood pressure, respiratory rate (for 1 minute) and temperature taken?			
ECG				
1.	Is the ECG of the volunteer's recorded if vital signs are with in the acceptable range?			
2.	Is the volunteer requested to lie down in supine position on bed?			
3.	Is volunteer's chest, leg and forearms, uncovered and any metallic object such as a watch, coin, bracelet or necklace removed?			
4.	Is the person recording the ECG fed the necessary details before taking the print and initialed with date the ECG?			
5.	Is the entry made in respective ECG logbook?			
6.	Is the ECG referred to the medical officer trained in ECG reading to review the ECG and to provide his comments along with initial and date?			
7.	Is the ECG of the volunteer's recorded if vital signs are with in the acceptable range?			
Medical Examinations				
1.	Is the medical officer recorded the diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation, history of participation in a drug research study?			
2.	Is the medical officer recorded medical history of volunteer?			
3.	Is the medical officer conducted General and Systemic examination of the volunteer and recorded the same?			
X-Ray				
1.	Is the X-ray technician wearing a Lead Apron and TLD?			

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
2.	Is the X-ray machine and direct digitizer cleaned once in a month and recorded?			
3.	Is main door closed while shooting the X-ray?			
4.	Are main switch and the X-Ray machine switch 'ON'?			
5.	Is the X-ray plate put in the chest X-ray stand?			
6.	Is the X-ray tube of the machine kept six feet away from the chest stand?			
7.	Is the light of the tube switch on and the center of the light kept in the middle of the X-ray plate?			
8.	Is the volunteer removed clothes on his upper body before shooting of the X-ray? (Applicable only for male volunteer)			
9.	Is the volunteer wear a cotton gown before shooting of the X-ray? (Applicable only for female volunteer)			
10.	Is technician checked that volunteer does not have any metal things or ornaments on his upper body near chest portion?			
11.	Is volunteer stand near the X-ray plate, so that chest portion of the volunteer shall touch the X-ray plate?			
12.	Is the leads number on the marker as per the respective X-ray No., BEQ No and date arranged and then a marker on the right side of the plate put to recognize the right side of the chest X-ray?			
13.	Is the number of the X-ray film allocated as per the SOP?			
14.	Is the X-ray plate adjusted in such a way that the plate covers the whole chest portion of the volunteer?			
15.	Is the center of the X-ray tube adjusted in the middle of the back portion of the volunteer?			
16.	Is the machine adjusted for the exposure factors (mAs and KV) according to the fatness of the volunteer?			
17.	Is the volunteer requested to take a deep breath and hold the breath?			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

Sr. No.	Contents	Yes	No	Comment(s)
18.	Is the X-ray shooed immediately by the shooter, which is connected to the X-ray machine?			
19.	Is the volunteer told to take a breath and to leave the X-ray room thereafter?			
20.	Is the exposed cassette inserted into the cassette reader and x-ray picture taken on screen?			
21.	Is the displayed image saved to media on the viewer screen?			
22.	Are the details of the volunteer recorded in 'X-Ray Log Book'?			

Compensation

1.	Is the appropriate compensation given to the volunteer and documented with volunteer's signature and date?			

General

1.	Is the screening record or other required documents record all of the SOPs required information?			
2.	Is the data entry in the screening record and in all other required documents/logbooks; accurate; legible and complete?			
3.	Any change or correction to a data is dated, initialed, and explained (if necessary) and is not obscure the original entry?			
4.	Is the identity of volunteers verified prior to performing any screening activity with wristband and screening slip?			
5.	Are the equipments used calibrated and appropriately labeled?			
6.	Are the delegated staffs trained and competent enough to perform their duties?			
7.	Are the area cleaned?			

Audit Team		
Name	Signature	Date
1. _____	_____	_____

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
Reference SOP No.: BEQ/QA/SOP-005/07		

CHECKLIST FOR RECEIPT AND STORAGE OF INVESTIGATIONAL PRODUCT

Sr. No.	Contents	Yes	No	Comment(s)
RECEIPT OF INVESTIGATIONAL PRODUCT				
1.	Are the premises clean?			
2.	Check the environmental condition.			
3.	Is the specification of drug product on the label is crosschecked with the courier receipt, delivery challan etc.?			
4.	Is the integrity of the investigational product container and its packaging condition checked?			
5.	Are investigational products received for BA/BE studies are in sealed containers and properly labeled?			
6.	Are the COAs received along with the investigational product or at least prior to initiation of the study?			
7.	Is the label information on the container / pack verified with the information provided in the COA?			
8.	Is the quantity of retention samples for study sufficient as per the requirement of the respective regulatory agency?			
9.	Check the following for reference product : • Certificate of Analysis (COA) • Purchase Invoice • Shipment Record • Bill of Entry • Bin Card • Data Logger Record • (if attached during transportation)			
10.	Check the following for test product : • Certificate of Analysis (COA) • Bioequivalence Study Sample Requisition and Submission • Letter from Plant QA to PDR • Non Hazardous Certificate • Challan with Stamp • Data Logger Record • (if attached during transportation as per challan)			
11.	Is the line clearance obtained prior to counting of investigational product?			
12.	Are fresh hand gloves and mask worn while handling the investigational product?			
13.	Are sufficient no. of sealed containers is open at the time of receipt & remaining containers are in original sealed pack?			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

Sr. No.	Contents	Yes	No	Comment(s)
14.	Is fresh pair of gloves, butter paper and tray is used for counting each investigational product? (i. e. test and reference product).			
15.	Are the necessary details documented in relevant logbook?			
16.	On completion of counting, is the container / pack closed and kept in self-sealable zip lock bag and stapled?			
17.	Are any discrepancies observed? If yes then is it recorded in respective form?			
STORAGE OF INVESTIGATIONAL PRODUCT				
18.	Are the investigational products stored in labeled containers?			
19.	Are the investigational products stored in proper storage condition?			
20.	Is the storage condition documented as per the label claim or manufacturer / sponsor specification?			
21.	Are the necessary details documented in relevant logbook?			

Note:

- All the Investigational Products supplied for Bioequivalence studies should be in sealed containers.
- All the copies should be clear and readable.
- Each outer carton of the IP should be labeled with a statement 'For Clinical Trial Use Only'.
- Retention sample should be as per relevant regulatory requirements.

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

CHECKLIST FOR IN-PROCESS AUDIT

Sr. No.	Contents	Yes	No	Comment(s)
Informed Consent Process				
1.	Is the ICF distributed in the language understood by volunteer?			
2.	Is the ample time provided to the volunteers to read the ICF thoroughly?			
3.	Is an oral presentation given to the volunteers?			
4.	Is non-technical, practical and understandable language used during Informed consent process?			
5.	Are the pertinent aspects of the study informed to the volunteer?			
6.	Is the opportunity provided to the volunteers to enquire about the details of the study?			
7.	Is the query (if any) raised by volunteers clarified and discussed?			
8.	Is the ample time provided to the volunteers prior to obtaining ICF?			
9.	Is any volunteer coerce or unduly influenced to participate in the study?			
10.	Is consent from volunteers who are willing to participate in the study obtained by sign and date?			
11.	Is the uncontrolled copy of ICF issued to the volunteers?			
12.	Is 'Obtaining Study Specific ICF' form updated properly?			
13.	Is oral consent obtained for audio-video recording of ICF process?			
14.	Are all doubts and queries of volunteer cleared?			
Check in of Subjects				
1.	Are volunteers reported to the facility are healthy as per protocol requirement?			
2.	Is the entry of in time and out time of volunteers made in register and in 'Volunteer / Subject visit record' with time and sign?			

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
3.	Does identity of reported eligible volunteers checked by Name/ volunteer registration no. or by fingerprint and recorded in 'Volunteer Identity Verification Form'.			
4.	Does the cross participation of the volunteers in any other clinical trial in other organizations from on-line volunteers information system (OVIS).checked?			
5.	Does check in slip handed over to the respective volunteers?			
6.	Is study specific ICF obtained prior to initiation of any study related procedure?			
7.	Are the vol. has given a sample of their urine for conducting UPT (females) and test for drug of abuse?			
8.	Check for vol. testing negative for drug of abuse & UPT will be included			
9.	Is check in slip filled by concerned person for the respective activity?			
10.	Is the breath of the subject checked using breath alcohol analyzer & recorded into respective form?			
11.	Are vitals are taken & recorded into CRF.			
12.	Is on duty MO confirms the compliance of volunteers as per inclusion/Exclusion criteria, & records in CRF?			
13.	Is the ME of volunteers is done & recorded in CRF?			
14.	Is the check in slip is collected from volunteers & check in time entered in 'subject check in record' form?			
15.	Is the sub. no. allotted on first come first basis?			
16.	Is the identity card given to subject?			
17.	Are the details of subjects entered into 'master list of subject'?			
18.	Are physical check for prohibited items & belongings carried out?			
19.	Is the check in slip discarded on completion of check in procedure?			
20.	Are lockers allotted & uniforms & necessary toiletries are provided to subjects? Is it recorded into respective form & sign of volunteers are taken?			
21.	Are the volunteers enter in CPU after wearing uniform & completing all necessary formalities.			

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP No.: BEQ/QA/SOP-005/07**

Sr. No.	Contents	Yes	No	Comment(s)
Dispensing of Investigational Product				
1.	Does Register pharmacist carry out the dispensing activity?			
2.	Is the dispensing activity carried out within 72.00 hrs prior to administration of study investigational Product?			
3.	Is the dispensing activity carried out under supervision and in presence of quality assurance personnel?			
4.	Is the randomization scheduled obtained from Principal Investigator/ Co investigator?			
5.	Is the randomization seed used as per the SOP?			
6.	Is the information obtained about number of IPs to be dispensed based on the number of subjects as per the protocol?			
7.	Does CRA have given the Requisition for Dispensing and updated the Section 'A', 'Investigational Product Requisition for Dispensing'?			
8.	Are the labels for test and reference IP prepared on separate sheet mentioning total number of labels?			
9.	Are the labels prepared as per randomization?			
10.	Are the Contents of labels as per SOP?			
11.	Does The dispensing platform is clear from previous product, documents or materials and is ready to perform dispensing?			
12.	Ensure that the environmental conditions are within specified range in Humidity Chamber and Dispensing Area is maintained and documented.			
13.	Are all materials to be used for the dispensing of each product (containers, labels) and the dispensing record kept separately? (For each IP)			

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
14.	Are the labels and the dispensing record documents kept under lock and key till the start of dispensing activity?			
15.	Is fresh pair of hand gloves and face mask used during dispensing of each Investigational Product?			
16.	Does the QA has given line clearance before the removal of each IPs from chamber, after ensuring that the accessories and platform are clear of previous products, documents or materials not required to the planned activities, and that the accessories is clean and suitable for use. And recorded in 'Investigational Product Dispensing Form'			
17.	Is the dispensing activity of test carried out first as per randomization schedule?			
18.	Is the lid of dispensing container closed properly?			
19.	Does accountability of IP recorded in form, 'Investigational Product Accountability Form' and log book? (For each IP)			
20.	Does the reconciliation of dispensing labels at each stage i.e. before dispensing and after dispensing done and documented the same in Form 'Reconciliation of Dispensing Labels'? (For each IP)			
21.	Does each and every step were recorded sequentially in detail in 'Investigational Product Dispensing Checklist'?			
22.	Are the IP container(s) along with the dispensed IPs kept as per the storage condition?			
23.	Are the data entry in all forms and relevant logbooks; updated properly, accurate; legible and complete?			
Dosing				
1.	Are the premises clean?			

Macleods Pharmaceuticals Limited

Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
2.	Is appropriate number of glasses filled with appropriate volume of drinking water/ fluid available for each subject?			
3.	Does Adequate number of tongue depressors and functioned torch are available?			
4.	Required information for dropout/withdrawn subjects obtained prior to removal of IP?			
5.	Does the dosing container are received are temper proof?			
6.	Check the label on container as per SOP.			
7.	Is the dosing done under controlled environmental condition as specified in protocol?			
8.	Are the dosing sheets along with investigational products distributed as per quadrants?			
9.	Is the identity of subjects verified prior to dosing with Id card, wristband, dosing sheet and label?			
10.	Instructions regarding restriction (posture, water etc) given			
11.	Instructions regarding swallow the dose with the provided volume of water/ fluid given			
12.	Is the dosing done at scheduled time?			
13.	Is the dosing done in sitting position?			
14.	Is the amount of water/ fluid consumed completely?			
15.	Is the mouth check done after dosing?			
16.	Does medical officer supervise the dosing activity?			
17.	Is in-process documentation done?			
Restrictions				
1.	Are the fasting condition maintained and monitored?			
2.	Is pre and post-dose water restriction maintained and monitored?			
3.	Is the posture restriction maintained and monitored?			
4.	Is there any deviation? if yes, is it recorded.			

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.	
Reference SOP No.: BEQ/QA/SOP-005/07	

Sr. No.	Contents	Yes	No	Comment(s)
Sample collection				
1.	Is the blood samples collected in appropriate blood collection tubes containing suitable anticoagulant (as specified in protocol)?			
2.	Is 0.5 mL of normal saline injected after each collection?			
3.	Is the identity of subject checked before blood collection?			
4.	Is the tube ID checked before blood collection?			
5.	Are the samples collected after discarding 0.5 mL of blood from the tubing?			
6.	Are the samples collected at scheduled time?			
7.	Is there any time point deviation?			
8.	If yes, is deviation filed?			
9.	Is in-process documentation done in bleed sheet?			
Sample Separation and Storage				
1.	Are the samples centrifuged at set parameters as specified in protocol?			
2.	Is there delay in centrifugation after collection?			
3.	If yes, are the samples kept in cold condition?			
4.	Are the separated plasma aliquoted in duplicate/ or as per protocol in prelabelled polypropylene tubes?			
5.	Are the labels of blood collection tubes and plasma tubes crosschecked before transfer of separated plasma?			
6.	Are the plasma samples stored properly in deep freezer?			
7.	Is in-process documentation done in relevant forms/ logbooks?			

Macleods Pharmaceuticals Limited



Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
Vital signs and Subject Questionnaire				
1.	Is the vital signs and subject questionnaire done at scheduled time?			
2.	Is the vital signs parameters monitored as per protocol			
3.	Is in-process documentation done in CRF			
4.	Are the equipments used during vital monitoring are calibrated and label on equipment is updated?			
Serving Standardized Meal to the Study Subjects				
1.	Are the meals in hygienic condition?			
2.	Are the contents of meal provided to subject as per protocol?			
3.	Are the quantities of food as per requirement of protocol?			
4.	Is quality of meal satisfactory?			
5.	Is the meal provided at scheduled time?			
6.	Is in-process documentation done in 'Record of Standardized Meals'?			
Post Study Safety Assessment				
1.	Is Requisition slip for Blood / Urine Examination' prepared for subjects			
2.	Is blood sample collected as per approved protocol?			
3.	Is the vital signs and subject questionnaire done and recorded in case record form			
4.	Is the ECG of subjects done and reviewed by medical officer?			
5.	Is the Medical examination of subjects done and recorded in CRF?			
6.	Is adverse event resolved prior to safety assessment? (for withdrawn subjects)			
General				
Check for the availability of following documents.				
1.	Initiation of clinical operation			
2.	Master list of subjects			
3.	Subject check in record			

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
4.	Obtaining study specific ICF (Period I)			
5.	ICF (period I)			
6.	Screening Form			
7.	Breath alcohol records			
8.	Clinical Case Record (check in)			
9.	Item issue/ received form			
10.	Protocol training attendance form			
11.	Delegation of duties			
12.	Emergency medicine checklist			
13.	Equipment checklist			
14.	Emergency bag checklist			
15.	Inclusion criteria checklist			
16.	Exclusion criteria checklist			
17.	Are all the subjects (enrolled in the study) gave consent by sign and date the 'Informed Consent form' prior to start of any study related activity?			
18.	Is the data entry in the CRFs and in all other required forms/logs; accurate; legible and complete.			
19.	Any change or correction to a CRF is dated, initialed, and explained (if necessary) and is not obscure the original entry.			
20.	Are essential documents for the conduct of a clinical study available?			
21.	Does Study specific ICF file checked.			

Audit Team

Name

Signature

Date

1. _____

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G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

**Reference SOP NO.: BEQ/QA/SOP-005/07****CHECKLIST FOR RETROSPECTIVE AUDIT**

Sr. No.	Contents	Yes	No	Comment(s)
Maser file.				
1.	IEC approved Protocol			
2.	IEC approved ICFs (English, Hindi, Marathi)			
3.	Case Record Form (CRF)			
4.	Sample Case Record Form (CRF)			
5.	Subject Questionnaire (English and in translated languages)			
6.	Photocopy of Insurance Statement & Policy			
7.	Photocopy of Application Letter			
8.	IEC Approval Letter			
9.	Photocopy of IEC Composition			
10.	Correspondence with IEC			
11.	Photocopy of progress reports			
12.	Normal Value(s)/Range(s) for Laboratory			
13.	Accreditation of pathology laboratory			
14.	Photocopy of COA			
15.	Photocopy of Investigational Product(s) Receipt			
16.	Instructions for Handling of Investigational Product(s)			
17.	Photocopy of study Labels			
18.	Communication with Caterer			
19.	Correspondence with Sponsor			
20.	Translation / Back Translation Record			
21.	Correspondence with Back Translator			
22.	Back Translated copies			
23.	Correspondence with Biostatistician			
24.	Correspondence with Pathology Laboratory			
25.	Correspondence with Contracted Hospital			
26.	Correspondence with X-ray department			
27.	Photocopy of Curriculum Vitae			
28.	Monitoring Report			
29.	Literatures			
30.	FDA Form 1572 (If Applicable)			

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.



Reference SOP NO.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
31.	Communication with Analytical Investigator			
32.	Photocopy of actual time point of blood collection			
33.	Schedule for conduct of clinical study activities			
34.	Internal Correspondence			
Raw data				
1.	Initiation of Clinical Operations			
2.	Protocol discussion points and Delegation of Duties			
3.	Protocol Training and Delegation of Duties			
4.	Study Activity Plan			
5.	Emergency Medicine Check List			
6.	Equipment Check List			
7.	Emergency Bag Check List			
8.	Volunteer /subject visit record			
9.	Volunteer Identity Verification Form			
10.	Volunteer Online Information Status For Study Check in			
11.	ICF distribution and presentation record			
12.	Obtaining Study Specific ICF			
13.	Urine Test For Drugs of Abuse Record			
14.	Breath Alcohol Record			
15.	Check List for Tubes and Labels - Clinical			
16.	Checklist for Pharmacist to be filled for dispensing of IP			
17.	Investigational Product Dispensing Form			
18.	Investigational Product Accountability Form			
19.	Master List of Subject			
20.	Subject Check in Record			
21.	Recording of Temperature Relative Humidity during the Study			
22.	Recording of Temperature (if Applicable)			
23.	Record of Standardised Meals			
24.	Night/ Day Custodian			
25.	Details of material used for cannulation			
26.	Record of Cannula Insertion			
27.	Record of Cannula Removal			

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
28.	Separation and Storage of Clinical Samples			
29.	Checklist for Sample Collection and Storage Tubes			
30.	Volunteer blocking record on online volunteer information			
31.	Subject Check-out Record			
32.	Solution preparation (if applicable)			
33.	Volunteer Compensation for Standby /Not Eligible to Participate in Stand/ Follow-up			
34.	Volunteer compensation for travelling			
35.	Subject Questionnaire for Prohibited Item (If Applicable)			
36.	Subject Questionnaire for food intake (If Applicable)			
37.	Subject Compensation for the study			
38.	Transfer of clinical records (to analytical DF)			
39.	Compensation Slip			
40.	Protocol deviation form			
41.	Subject's Identity Cards			
42.	Note to File (If Any) <i>(In case of any incidence/ notes are to be recorded as a part of more information)</i>			
43.	Other Relevant Documents (including unused forms/ annexure or data of not participated volunteers)			
Case Record Forms (CRFs)				
Title page				
Instruction for CRF Documentation				
Screening CRF				
1.	Screening Record			
2.	Requisition Slip for Blood and Urine Examination			
3.	Laboratory Report			
4.	X-ray Report			
5.	ECG Report			
6.	Photocopy of ECG Report			
Study Specific CRF				
1.	Inclusion Criteria Checklist			
2.	Exclusion Criteria Checklist			

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Bioequivalence Department

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP NO.: BEQ/QA/SOP-005/07

Sr. No.	Contents	Yes	No	Comment(s)
3.	Investigational Product Administration Form			
4.	Bleed Sheet			
5.	Vitals and Subject Questionnaire			
6.	Clinical Case Record			
7.	Adverse Event (AE) Form (If Any)			
8.	Serious Adverse Event (SAE) Form (If Any)			
9.	Follow-up Conversation Form			
10.	Note to File			
Post Study Safety Assessment CRF				
1.	Safety Laboratory Parameter Investigation Form			
2.	Requisition Slip for Blood and Urine Examination			
3.	Laboratory Report			
4.	ECG Report			
5.	Photocopy of ECG Report			
6.	Subject withdrawal/ dropout record or study completion certificate			
General				
1.	Is the CRF or other required forms; record all of the protocol required information on each study subject?			
2.	Is the CRF for each subject compiled on completion of the study?			
3.	Is the data entry in the CRFs and in all other required forms/logs; accurate; legible and complete.			
4.	Any change or correction to a CRF is dated, initialed, and explained (if necessary) and is not obscure the original entry			
5.	Data reported on the CRF, that are derived from source documents, are consistent with the source documents or the discrepancies are explained.			
6.	Is each CRF reviewed by medical officer and verified by Principal Investigator/ co investigator?			
7.	Are essential documents for the conduct of a clinical study available?			

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093..

**Reference SOP NO.: BEQ/QA/SOP-005/07**

Sr. No.	Contents	Yes	No	Comment(s)
Other Relevant Documents				
Log books				
1.	ECG Log book (Screening)			
2.	ECG Log book (Safety)			
3.	X-Ray Log book			
4.	Sodium vapour lamp log book for light sensitive drug (IP receipt, dispensing, study day (IP removal, dosing, separation & storage), segregation, transfer of samples to analytical)			
5.	Emergency medicine stock and usage log book.(inventory, usage and dose, time of administration)			
6.	Height Weight and BMI Log book			
7.	Refrigerated centrifuge logbook			
8.	Deep freezer log book (below -50° C) (check the records till transfer of samples to analytical DF)			
9.	X- Ray CDs			
10.	Any other			
Clinical report and appendices				
1.	Data reported in report are derived from source documents, are consistent with the source documents or the discrepancies are explained.			
2.	Does report format is as per regulatory requirement			

Audit Team

Name

Signature

Date

1. _____

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STANDARD OPERATING PROCEDURE**CONDUCTING AUDITS OF BIOANALYTICAL SECTION****Supersedes****SOP No.:****Page No.:**

BEQ/QA/SOP-006/08

BEQ/QA/SOP-006/09

1 of 6

SITE OF DISTRIBUTION: Quality Assurance, Bioanalytical Documentation Room and Head – Bioequivalence

Issue Date	Effective Date	Review Date
11/04/2018	20/04/2018	10/04/2021

REVISION CARD

SR. NO.	REVISION NO.	ISSUED DATE	REASON (S) FOR REVISION	REVISION DATE
1.	00	13/04/2005	New SOP	14/12/2005
2.	01	14/12/2005	1. Modification of point 7.0 and 9.0 in Annexure No. 01 'Checklist for Bioanalytical Operations'.	24/07/2006
3.	02	24/07/2006	1. Modification of Annexure No. 01 'Checklist for Bioanalytical Operations'.	04/06/2007
4.	03	04/06/2007	1. Incorporation of format number 2. Briefly description of auditing of Bioanalytical section. 3. Separation of annexure	28/05/2009
5.	04	28/05/2009	1. Modification in sections 4.1, 4.2, 4.4 and 4.7 2. Deletion of 'GCP' from section 4.3 3. Addition of audit trail in section 4.5.1 and 4.5.3 4. Addition of new point as section 4.5.4 5. Modifications in Annexure No. ANX/QA/SOP-006-01, 'Checklist for Bioanalytical Operations'.	25/06/2010
6.	05	25/06/2010	1. Addition of new point to include procedure of stamping of documents as section 4.7. 2. Renumbering of section 4.7 to 4.8 and modification in note given under section 4.8	30/05/2012
7	06	30/05/2012	1. Periodic Review 2. Modification in responsibility 3. Minor modifications in 4.2, 4.3, 4.5.1 and 4.5.3 4. Modification in 4.4 to add new points for online audit and to delete of 'STP' and 'bioanalytics' 5. Deletion of 4.7.3 to remove study notebook stamping 6. Modification in 4.8 to change title of FRM/QA/SOP-007-02 and to add observations and findings listing 7. Additions in abbreviation(s) 8. Minor modifications in Annexure No. ANX/QA/SOP-006-01	15/03/2016
8	07	15/03/2016	1. Minor modifications in 4.2, 4.3 to add audit plan and analytical 2. Modification in 4.4 to delete about in process audit of updation of instrumental labels, solution preparation and addition of instrumental conditions and soft copy of	-

Design.-Dept.	Prepared By	Checked By	Approved By	Authorised By
	Bioanalytical - QA	Bioanalytical - QA	Head - QA	Head - Bioequivalence
Sign and Date	<i>Shondge</i> 04/04/18	<i>gkhemani</i> 04/04/2018	<i>Dr. Sagar P.</i> 04/04/18	<i>Dr. Ashish M.</i> 11/6/18
Name	Ms. Sheetal D.	Ms. Gauri K.	Dr. Sagar P.	Dr. Ashish M.

ANX/GN/SOP-001-01

MACLEODS

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CONDUCTING AUDITS OF BIOANALYTICAL SECTION

Page No.:

2 of 6

	Prepared By	Checked By	Approved By	Authorised By
Design.-Dept.	Bioanalytical - QA	Bioanalytical - QA	Head - QA	Head - Bioequivalence
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Name	Ms. Sheetal D.	Ms. Gauri K.	Dr. Sagar P.	Dr. Ashish M.

ANX/GN/SOP-001-01

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF BIOANALYTICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-006/08	BEQ/QA/SOP-006/09	3 of 6

1. OBJECTIVE:

To lay down a procedure for conducting audits of bioanalytical section.

2. SCOPE:

This procedure is applicable to the quality assurance section and serves as a guideline for conducting audits of bioanalytical section.

3. RESPONSIBILITY:

Quality Assurance staff: conducts audits of bioanalytical section

4. PROCEDURE:

- 4.1 Conduct audits of bioanalytical operations.
- 4.2 Conduct audit of method validation and study sample analysis based on the audit plan provided to the study director/ section head/ Analytical investigator.
- 4.3 Audit each bioanalytical operation in conformance to the MV protocol, analytical study protocol, STPs, relevant SOPs and in accordance with principles of Good Laboratory Practice (GLP) during the following phases:
 - In-process
 - Retrospective
- 4.4 Audit the in-process phase for the following activities:
 - 4.4.1 Instrument calibration:
 - Calibration is done as per respective EOP.
 - Availability of standard certificate.
 - Check whether the standard equipment used for calibration is within its validity period.
 - Check that the standard equipment used for calibration is itself calibrated in the range equal to or more than the test equipment parameters range calibrated.
 - All the results are within acceptable criteria.
 - Check the entries in the respective logbook.
 - 4.4.2 Method validation and study sample analysis
 - Instrumental analysis
 - Preparation of stock solution
 - Spiking of samples
 - Sample processing
 - Compliance to STP/ MV protocol
 - SOP/ Protocol deviations (if any)

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF BIOANALYTICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-006/08	BEQ/QA/SOP-006/09	4 of 6

- Review of raw data and chromatograms
- Logbook entries
- Soft copy of data (as and when required)

4.4.3 Issuance of subject samples for analysis

4.4.3.1 The quality assurance personnel shall be present at the time of issuance of subject samples for analysis by the custodian.

4.4.3.2 The quality assurance personnel shall check the availability of the Annexure No. ANX/AL/SOP-006-04, 'Requisition and tracking record for study samples' prior to the issuance of subject samples for analysis.

4.4.3.3 The quality assurance personnel shall verify the samples issued to the analyst against the requisition for the correctness of the samples issued and will do the initial and date in 'samples checked by' column in annexure no. ANX/AL/SOP-006-04, 'Requisition and tracking record for study samples'.

4.4.3.4 The quality assurance personnel shall also review the entry done in the respective logbook for the subject samples issued.

4.5 Audit the retrospective phase for the following activities:

4.5.1 During method validation, check the raw data, logbooks, chromatograms, audit trail, softcopy of MV data and its method validation report

4.5.2 Then check the standard testing procedure as per method validation report.

4.5.3 During sample analysis, check the data entry sheet (concentration data), raw data, logbooks, chromatograms, audit trail, softcopy of data, its report, ISR data and its report.

4.5.4 During instrument calibration check the raw data, chromatograms, logbooks, certificate of standards used during calibration and updation of calibration labels.

4.5.5 During reviewing soft copy, make entry in respective logbook

4.5.6 While reviewing System equilibrium injections, create a result table with ID "Date of equilibrium performed – SE - QA REVIEW "

4.5.7 While closing the already saved result table , save as the result table with ID "Already saved result table ID-QA REVIEW" with annotation "QA reviewer has reviewed the data"

4.6 Refer Annexure No. ANX/QA/SOP-006-01, 'Checklist for Bioanalytical Operations' while carrying out the audit.

4.7 Stamping of Document:

4.7.1 In process: In case of in-process audit stamp, initial, date and time (if applicable) the document(s) for which activity(s) were witnessed by auditor.

4.7.2 In case of retrospective audit stamp, initial and date the first form of the raw data form compiled for day wise activity.

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MACLEODS		
STANDARD OPERATING PROCEDURE		
CONDUCTING AUDITS OF BIOANALYTICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-006/08	BEQ/QA/SOP-006/09	5 of 6

- 4.7.3 In case of logbook there is no need to stamp.
- 4.7.4 In case of calibration data audit, stamp, initial, and date the first page of the set of documents audited.
- 4.7.5 When stamping QA personnel shall:
- Ensure the legibility and durability of stamp impression and ensure that stamp(s) do not interlock with other stamp(s).
 - When voiding stamp impression, QA personnel will apply
 - i) A single line through the impression
 - ii) 'Void' immediately adjacent to the lined out impression
 - iii) Initial/ signature of person voiding the impression
 - iv) Date when impression is 'voided'
- Note: Stamp all the above mentioned documents with 'Q.A Review' stamp in blue ink.
- 4.8 Issue the forms, FRM/QA/SOP-007-01 'Audit report' and Form No. FRM/QA/SOP-007-02 'Observation sheet' as per SOP No. BEQ/QA/SOP-007, 'Preparation and Generation of Audit Reports'. List down the observations and findings in the Form No. FRM/QA/SOP-007-02, 'Observation Sheet' and fill the necessary details in Form No. FRM/QA/SOP-007-01, 'Audit Report'. Submit it to section head/ Analytical investigator or his or her designee in case of method validation and calibration and to study director or his or her designee in case of study sample analysis for the corrective actions to be done.
- Note: Prepare a checklist prior to audit for reference, as per Annexure No. ANX/QA/SOP-006-01, 'Checklist for Bioanalytical Operations'. The audit of the various activities may not be limited to the checklist. Prepare the audit report based on the findings, noted during the audit conducted.

5. ABBREVIATION (S):

5.1	EOP	: Equipment Operating Procedure
5.2	ISR	: Incurred Sample Reanalysis
5.3	MV	: Method Validation
5.4	No.	: Number
5.5	N/AP	: Not applicable
5.6	QA	: Quality assurance
5.7	SOP	: Standard operating procedure
5.8	STP	: Standard testing procedure

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STANDARD OPERATING PROCEDURE		
CONDUCTING AUDITS OF BIOANALYTICAL SECTION		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-006/08	BEQ/QA/SOP-006/09	6 of 6

6. REFERENCE (S):

6.1 BEQ/QA/SOP-007, 'Preparation and Generation of Audit Reports'.

7. ANNEXURE (S):

7.1 Annexure No. ANX/QA/SOP-006-01, 'Checklist for Bioanalytical Operations'.

8. FORM (S):

N/AP

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-006/09

CHECKLIST FOR BIOANALYTICAL OPERATIONS

Sr. No.	Contents	Y/N or N/AP	Comments
I	IN-PROCESS AUDIT		
A	Instrumental conditions		
1	Is controlled copy of STP/protocol available		
2	Are entries made in instrument logbooks on which samples are being analysed		
3	Is correct column being used for analysis		
4	Are the chromatographic parameters(Acquisition method) set as mentioned in STP/protocol		
5	Are integration parameters in integration method set as mentioned in STP/protocol		
	If not then "Integration authorization form" available		
6	Is the instrument within the calibration duration		
7	Is the instrument being used properly identified with in-house i.d.		
8	Is sample transfer to auto sampler or analysis on instrument carried under yellow monochromatic light for light sensitive molecule.		
9	Is the mobile phase and rinsing solution properly labeled		
B	Preparation of stock solution		
1	Is analyst wearing protective gears		
2	Is waste container available		
3	Is controlled copy of STP/ protocol available		
4	Are the COA of the analytical standard available		
5	Is the analytical standard stored as per the storage conditions mentioned on the COA		
6	Are details on the label of the analytical container matching with the details on the certificate of analysis		
7	Is the analytical standard bottle / vial opened after it attains room temperature prior to weighing		
8	Is light sensitive analytical standard weighed under yellow monochromatic light.		
9	Are amber coloured glassware used for light sensitive analytical standard		
10	Is balance area and workstation clean		
11	Is the balance calibrated (daily /quarterly) before use and corresponding calibration entries checked in the logbook		
12	Is the air bubble at proper position		
13	Is internal calibration done before every weighing		
14	At the time of weighing is another personnel available to monitor the weighing activity- and cross-sign the weighing slip.		
15	Is the container of standard replaced to its respective storage place immediately after weighing activity is complete.		
16	Are entries made in respective logbooks which are used during processing		
C	Spiking of samples		
1	Is workstation clean		
2	Is controlled copy of STP/ protocol available		
3	Is analyst wearing protective gears		

Macleods Pharmaceuticals Limited**Bioequivalence Department**

G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.

Reference SOP No.: BEQ/QA/SOP-006/09

4	Is separate stock solution prepared for CC and QC by separate person		
5	Is spiking dilution of CC and QC prepared using at least two stock solution / dilution		
6	Is complete "Authorisation of CC range and QC range" form available		
7	Is concentrations in CC standard properly distributed		
8	Is calculation of concentration for preparation of spiking dilution done with validated excell		
9	Is selectivity and spiking solution check exercise is within acceptance limit before spiking		
11	Are pipette /Handystep used for spiking calibrated		
12	Are stock solution ,dilution and solutions used for spiking within stability period		
13	Are polypropylene tubes ,solutions properly labeled		
14	Is plasma completely thawed before usage		
15	Are matrix lots meeting the acceptance criteria of selectivity pooled together for bulk spiking		
16	Is less than or equal to 1% spiking dilution spiked in biological matrix		
17	Are entries made in respective logbooks which are used during spiking		
18	Is complete bulk spiking carried out under yellow monochromatic light for light sensitive molecule?		
19	Is waste disposed in proper container		
D	Sample processing		
1	Is workstation clean		
2	Is controlled copy of STP/ protocol available		
3	Is analyst wearing protective gears		
4	Is sequence printout available before retrieval of subject samples		
5	Is 'Sample processing' annexure available		
6	Are pipette /Handystep I.D. used for processing mentioned in 'sample processing' annexure		
7	Are pipette /Handystep used for processing calibrated		
8	Are stock solution ,dilution and solutions used for processing within stability period		
9	Are polypropylene tubes ,solutions properly labeled		
10	Are quality control samples interspersed in subject samples		
11	Is missing samples checked		
12	Are number of quality control samples fulfils minimum requirement		
13	Is analyst record each activity in 'sample processing' annexure		
14	At the time of aliquoting is another personnel available to monitor the activity		
15	Are samples processed as per STP		
16	Are entries made in respective logbooks which are used during processing		
17	Is waste disposed in proper container		
18	Is processing carried out under yellow monochromatic light for light sensitive molecule.		

Macleods Pharmaceuticals Limited**Bioequivalence Department**

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Reference SOP No.: BEQ/QA/SOP-006/09

II	RETROSPECTIVE AUDIT		
	Checklist for retrospective audit of method validation data / sample analysis		
1.	Is the analysis carried out referring the relevant method validation protocol / analytical study protocol/ STP		
2.	Are the complete raw data files, chromatogram files, audit trail files and the respective reports available?		
3.	Check the raw data forms for the following:		
3.1	Are the forms numbered and issued by QA?		
3.2	Are all entries done in black ink?		
3.3	Are any change or correction should be dated, initialed and explained (if necessary) and should not obscure the original entry?		
3.4	Is the overwriting initialed with date?		
3.5	Completeness of form		
3.6	Are there any blank spaces left?		
3.7	Check the calculations done for accuracy.		
4	Check the logbooks for the following:		
4.1	Are the entries complete?		
4.2	Are any change or correction should be dated, initialed and explained (if necessary) and should not obscure the original entry?		
4.3	Is the overwriting initialed with date?		
4.4	Are the entries in chronological order?		
4.5	Are the entries in accordance with the entries in raw data forms?		
5	Check the chromatograms for the following:		
5.1	Method acquisition printout: date of printing and parameters as per respective protocol/ STP.		
5.2	Sequence printout: date of printing, second sequence if reinjection done and the same entry is made in reinjection record form.		
	Is Corrected sequence printout (before injection) with remark in footer for correction		
5.3	Processing sequence printout: date of printing		
5.4	Result table printout with relevant parameters such as retention time, area, estimated concentration etc.		
	If Correction in sequence (after injection) then corrected during result table creation		
5.5	Check the chromatograms for proper integration		
5.6	Are all the chromatograms filed in a sequence?		
6	Audit trail		
6.1	Check the audit trail to ensure that any activity is performed on the availability of the personnel		
6.2	Ensure that any personnel is not involved in multiple activities at the same time		
6.3	Ensure via the audit trail the an analytical run is submitted only after loading of the samples in the autosampler		
6.4	Ensure via the audit trail that the analyst software is locked if the system remains ideal for more than five minutes		
6.5	Ensure via audit trail that no data is overwritten		
6.6	In case any data is modified, then ensure that the modification		

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Reference SOP No.: BEQ/QA/SOP-006/09

	is recorded in the audit trail with proper prompt.		
6.7	Is system activation and deactivation time mentioned in the instrument logbook similar to that captured in the audit trail		
6.8	Ensure that all activities recorded in the logbook are in line with the activities captured in the audit trail		
6.9	Check softcopy of the audit trail		
7	Reconstruction of the project/study		
7.1	From the sample processing forms check the activities done on each day and crosscheck randomly for the flow of activity from respective logbook entries.		
8	Column Record		
8.1	Is correct column as mentioned in the protocol / STP used during the analysis		
8.2	Is the issuance and return of column entry done in column logbook?		
9	System suitability		
9.1	Is the System suitability test done at all times?		
9.2	Is there any major malfunction of equipment used (check system logbook for daily maintenance) from date of initiation to end of project?		
9.3	Is the System suitability test carried out after major malfunction?		
9.4	Is there any interchange of system components (check system logbook for configuration change from date of initiation to end of project)?		
9.5	Is the System suitability test carried out after change of component?		
9.6	Is the system suitability complying with the acceptance criteria?		
9.7	Is the system suitability carried out if instrument goes in stand by mode?		
9.8	Is the system suitability carried out if gap of 60 minutes or more between system suitability and bioanalytical batch?		
9.9	Is the system suitability carried out if gap of 60 minutes or more between injections of two analytical batches is observed?		
9.10	Is the system suitability carried out if sequence is stopped in between due to instrument hardware error		
10	Analytical Standards		
10.1	Are the COA's available for all the analytical standards used?		
10.2	Are all the analytical standards within revalidation/ expiry date?		
10.3	Are the entries of purity of analytical standard in analytical standard record logbook in accordance with COA's?		
10.4	Are the analytical standards stored as per COA's?		
10.5	Crosscheck the logbook entries of analytical standards weighed in 1. Semi micro/ Ultra microbalance 2. Analytical standard log and 3. Raw data forms 4.0 Refrigerator / desiccator logbook		
11	Others		
11.1	Are all the equipments used for the study calibrated?		
11.2	Is the personnel handling a particular activity trained for the same?		
11.3	Determine whether adequate number of quality control samples were run with the study samples and whether these QC were		

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**Reference SOP No.: BEQ/QA/SOP-006/09**

	within the acceptance range.		
11.4	Whether all the samples were analysed, wherever applicable, with same calibration curve?		
11.5	Whether all activities and procedures are carried out as per the relevant SOPs?		
11.6	Whether the waste generated is disposed as per relevant SOP?		
11.7	Is the data reported in the method validation report / STP / study report in line with the source data		

√ : Compliance

X : Non-Compliance

Macleods Pharmaceuticals Limited



Bioequivalence Department

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STANDARD OPERATING PROCEDURE

CONDUCTING AUDITS OF PHARMACOKINETIC AND STATISTICAL PHASE

Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-015/01	BEQ/QA/SOP-015/02	1 of 3

SITE OF DISTRIBUTION: Quality Assurance and Head – Bioequivalence

Issue Date	Effective Date	Review Date
28/02/2017	07/03/2017	27/02/2020

REVISION CARD

SR. NO.	REVISION NO.	ISSUED DATE	REASON (S) FOR REVISION	REVISION DATE
1.	00	17/01/2013	New SOP	05/02/2015
2.	01	05/02/2015	1. Periodic review 2. Modification in responsibility to add statistician responsibility 3. Addition of new sub points under 4.1 about ensuring used statistical methods, analysis and report as 4.1.1 to 4.1.3 4. Addition of new sub point as 4.5.1 about ensuring consistency of results reported and renumbering of 4.5.1 – 4.5.3 to 4.5.2 – 4.5.4 5. Addition of new sub point as 4.6.1 for data consistency assurance and renumbering of 4.6.1 – 4.6.4 to 4.6.2 – 4.6.5	28/02/2017
3.	02	28/02/2017	1. Periodic review 2. Addition of new annexure for checklist and reference of same in 4.1 3. Minor modifications in 4.5.1, 4.5.3 and 4.5.4 4. Modification in 4.7 about audit report for better clarity	N/ AP

Design.-Dept.	Prepared By	Checked By	Approved By	Authorised By
	Clinical - QA	Bioanalytical - QA	Head - QA	Head - Bioequivalence
Sign and Date	27/02/2017	27/02/2017	27/02/2017	27/02/2017
Name	Mr. Khurshid S.	Ms. Gauri K.	Dr. Sagar P.	Dr. Ashish M.

ANX/GN/SOP-001-01

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.		
STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF PHARMACOKINETIC AND STATISTICAL PHASE		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-015/01	BEQ/QA/SOP-015/02	2 of 3

1. OBJECTIVE:

To lay down a procedure for conducting audits of statistical phase.

2. SCOPE:

This procedure is applicable to the quality assurance section and serves as a guideline for conducting audits of statistical phase.

3. RESPONSIBILITY:

Quality Assurance staff: conducts audits of statistical phase.

Statistician: Replies to audit findings, if any.

4. PROCEDURE:

- 4.1 Conduct audits of pharmacokinetic and statistical phase as per annexure No. ANX/QA/SOP-015-01, 'Checklist for Pharmacokinetic and Statistical Phase'.
 - 4.1.1 To ensure that the statistical methods used and an interpretation of the results are integrated in the report.
 - 4.1.2 To ensure that the statistical analysis reflects the analysis stated in the protocol.
 - 4.1.3 To ensure that the report conclusions are accurate representation of the results.
- 4.2 Receive the pharmacokinetic and statistical output.
- 4.3 Receive the randomization schedule.
- 4.4 Receive the draft of the report that covers the pharmacokinetic and statistical part of the study report.
- 4.5 Ensure the following:
 - 4.5.1 The results reported are consistent with the data collected, the total process from data collected to completion of the statistical report should be covered.
 - 4.5.2 Randomization in statistical output is same as that of the randomization schedule.
 - 4.5.3 The statistics is run as per the statistical plans mentioned in the approved protocol.
 - 4.5.4 Variables used for ANOVA is as per the approved protocol.
- 4.6 Check the pharmacokinetic and statistical part of the final report for following:
 - 4.6.1 Assure consistency with the data; check the PK and statistical summary and analysis required by the protocol to the statistical part of the report.
 - 4.6.2 The data is transcribed accurately from the pharmacokinetic and statistical output.
 - 4.6.3 The units mentioned on the tables and the graphs are accurate.
 - 4.6.4 The tables are appropriately titled and the graphs are labeled appropriately.
 - 4.6.5 The discussions are in line with the text.

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STANDARD OPERATING PROCEDURE CONDUCTING AUDITS OF PHARMACOKINETIC AND STATISTICAL PHASE		
Supersedes	SOP No.:	Page No.:
BEQ/QA/SOP-015/01	BEQ/QA/SOP-015/02	3 of 3

- 4.7 Prepare the audit report based on the findings noted during the audit and based on checklist and submit it to the auditee for the necessary corrective actions. For preparation of audit report, refer SOP No. BEQ/QA/SOP-007, 'Preparation and Generation of Audit Report'.
- 4.8 In case audit of statistical phase on any other type of study, review the data on similar line as mentioned above.

5. ABBREVIATION (S):

- 5.1 No. : Number
- 5.2 N/AP : Not applicable
- 5.3 QA : Quality assurance
- 5.4 SOP : Standard operating procedure
- 5.5 STP : Standard testing procedure

6. REFERENCE (S):

- 6.1 BEQ/QA/SOP-007, 'Preparation and Generation of Audit Reports'.

7. ANNEXURE (S):

- 7.1 Annexure No. ANX/QA/SOP-015-01, 'Checklist for Pharmacokinetic and Statistical Phase'.

8. FORM (S): N/AP

Macleods Pharmaceuticals Limited Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai 400 093.
Reference SOP No.: BEQ/QA/SOP-015/02

CHECKLIST FOR PHARMACOKINETIC AND STATISTICAL PHASE

Study No. _____	
Date of Audit: _____	

Sr. No.	Contents	Y/N/NA	Comment(s)
1.	Is the randomization in statistical output same as that of the randomization schedule?		
2.	Are the statistics run as per the statistical plans mentioned in the approved protocol?		
3.	Are the Variables used for ANOVA same as per the approved protocol?		
4.	In statistical part of the report, is the consistency of data assured?		
5.	In statistical part of the report, is the Pk and statistical summary checked?		
6.	Is the data transcribed accurately from the pharmacokinetic and statistical output in report?		
7.	Are the units mentioned on the tables and the graphs accurate in the report?		
8.	Are the tables appropriately titled and the graphs labeled appropriately in the report?		

Y: Yes, N: No, NA: Not Applicable

Additional /General Comments:

Audit Team		
Name	Signature	Date
1. _____	_____	_____

APPENDIX 16.1.11
PUBLICATIONS BASED ON THE STUDY
(Not Applicable)

APPENDIX 16.1.12

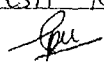
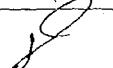
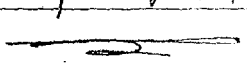
IMPORTANT PUBLICATIONS REFERENCED IN THE REPORT

CERTIFICATE OF ANALYSIS (MARKET SAMPLE FOR BE STUDY)

Page 1 of 2

Product	Euthyrox 200 (Levothyroxine Tablets 200 mcg)		
Lot No.	209740	A.R. No.	DPM16120023
Mfg. Date	-----	Exp. Date	11 / 2018
Mfg. by	Merck BV, Tupolevlaan 41 - 61, 1119 NW Schiphol-Rijik	Pack	Blister pack 30's
Date of Analysis	08/03/2017	Date of Report	14/03/2017
SPC No.	-----	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Observation
1	Description	To report	White, circular, flat tablets having break line on both sides and embossed with 'EM/200' on one side.
2	Identification (By HPLC)	The retention time of the Levothyroxine peak in the chromatogram of sample preparation should correspond to that of the Levothyroxine peak in the chromatogram of standard preparation as obtained in the test "Assay".	The retention time of the Levothyroxine peak in the chromatogram of sample preparation is correspond to that of the Levothyroxine peak in the chromatogram of standard preparation as obtained in the test "Assay".
3	Average Weight (mg)	To report	101.03
4	Dissolution (in 0.01 N Hydrochloric Acid containing 0.2 % sodium lauryl sulfate ; 500 ml; 50rpm;paddle;45 Min.; By HPLC ,as Levothyroxine sodium anhydrous [C ₁₅ H ₁₀ I ₄ NNaO ₄])	To report	1) 102 3) 96 5) 95 2) 80. 4) 88 6) 95

	Prepared By	Checked By	Approved By
Name	Ganesh Rokade	Devendrasing Rajput	Dipali Patil
Signature			
Date	14/03/2017	14/03/17	14/03/2017

Format No.: F/HOC070/08-00

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 CIN : U24239MH1989PLC052049

Works :
 Plot No. 2209, GIDC,
 Sarigam, Dist - Valsad,
 State : Gujarat - 396155, India.

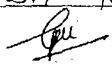
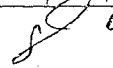
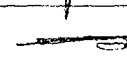
CERTIFICATE OF ANALYSIS (MARKET SAMPLE FOR BE STUDY)

Page 2 of 2

Product	Euthyrox 200 (Levothyroxine Tablets 200 mcg)		
Lot No.	209740	A.R. No.	DPM16120023
Mfg. Date	-----	Exp. Date	11 / 2018
Mfg. by	Merck BV, Tupolevlaan 41 - 61, 1119 NW Schiphol-Rijik	Pack	Blister pack 30's
Date of Analysis	08/03/2017	Date of Report	14/03/2017
SPC No.	-----	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Observation
5	UNIFORMITY OF DOSAGE UNITS (By Content Uniformity , by HPLC , as Levothyroxine sodium anhydrous [C ₁₅ H ₁₀ L ₄ NNaO ₄]) Acceptance Value	Less than or equal to 15.0	4.8
6	ASSAY (By HPLC, as Levothyroxine sodium anhydrous [C ₁₅ H ₁₀ L ₄ NNaO ₄] - mcg per tablet -% label claim	Not less than 190.0 and not more than 210.0 Not less than 95.0 and not more than 105.0	196.412 98.2

REMARK : The product complies / ~~does not comply~~ as per the above specification.

	Prepared By	Checked By	Approved By
Name	Ganesh Rokade	Devenraj Rajput	Dipak Patil
Signature			
Date	14/03/2017	14/03/17	14/03/2017

Formal No. : E/THQ/070/08-00

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CIN : U24239MH1989PLC052049

Works :
Plot No. 2209, GIDC,
Sarigam, Dist - Valsad,
State : Gujarat - 396155, India.

CERTIFICATE OF ANALYSIS (FINISHED PRODUCT)

Page 1 of 4

Product	LEVOTHYROXINE TABLETS 200 mcg	A.R. No.	FDP16100026
Batch No.	MLK602	Batch Size	150000 Tablets
Packing Batch No.	MLK602C	Packing Batch Size	17000 Tablets
Mfg. Date	10/2016	Exp. Date	09/2018
Date of Analysis	31-10-2016	Date of Report	17-03-2017
SPC No.	C/SPC/WP003134R/00	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Result
1	DESCRIPTION	Pink coloured, circular tablets, debossed with 'M66' on one side and breakline on the other side	Pink coloured, circular tablets, debossed with 'M66' on one side and breakline on the other side
2	IDENTIFICATION A. For levothyroxine - By HPLC -By TLC	The retention time of the Levothyroxine peak in the chromatogram of sample preparation should correspond to that of Levothyroxine peak in the chromatogram of the standard preparation as obtained in the test "Assay". The R_f value and appearance of a spot due to levothyroxine in the chromatogram obtained from sample preparation should corresponds to that of the levothyroxine spot in chromatogram obtained from standard preparation.	The retention time of the Levothyroxine peak in the chromatogram of sample preparation is correspond to that of Levothyroxine peak in the chromatogram of the standard preparation as obtained in the test "Assay". The R_f value and appearance of a spot due to levothyroxine in the chromatogram obtained from sample preparation is corresponds to that of the levothyroxine spot in chromatogram obtained from standard preparation.

	Prepared By	Checked By	Approved By
Name	Ganesh Rokade	Deendrasing Rajpatil	Dipak Patil
Signature			
Date	17/03/2017	17/03/17	17/03/2017

Format No. B/HQC070/04-00

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Website : www.macleodspharma.com
CIN : U94939MH1989PLC052049

 Works :
Plot No. 2207, GIDC,
Sangam, Dist. Valsad,
Gujarat - 396112, India


CERTIFICATE OF ANALYSIS (FINISHED PRODUCT)

Page 2 of 4

Product	LEVOTHYROXINE TABLETS 200 mcg	A.R. No.	FDP16100026
Batch No.	MLK602	Batch Size	150000 Tablets
Packing Batch No.	MLK602C	Packing Batch Size	17000 Tablets
Mfg. Date	10/2016	Exp. Date	09/2018
Date of Analysis	31-10-2016	Date of Report	17-03-2017
SPC No.	C/SPC/WP003134R/00	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Result
	B. For Colourants (FD & C Red 40 Al lake)	The appearance of the spot due to FD & C Red 40 Al lake in the chromatogram obtained in the sample preparation should correspond to that of the spot due to FD & C Red 40 Al lake obtained with the standard preparation when viewed in normal day light.	The appearance of the spot due to FD & C Red 40 Al lake in the chromatogram obtained in the sample preparation is correspond to that of the spot due to FD & C Red 40 Al lake obtained with the standard preparation when viewed in normal day light.
3	AVERAGE WEIGHT (mg)	125.0 ± 5.0 %	125.66
4	HARDNESS (N)	70 ± 30	Min:65 Max:80
5	LOSS ON DRYING (%w/w, determined on 1g of sample at 105°C for 3h)	Not more than 6	1.9
6	DISSOLUTION (in 0.01 N Hydrochloric Acid containing 0.2 % sodium lauryl sulfate ; 500 ml; 50rpm;paddle;45 Min.; By HPLC ,as Levothyroxine sodium anhydrous [C ₁₅ H ₁₀ I ₄ NNaO ₄])	Not less than 70 % (Q) of the labeled amount	1) 98 3) 105 5) 105 2) 96 4) 102 6) 98

	Prepared By	Checked By	Approved By
Name	Ganesh Rikale	Devendrasing Rajput	Dipak Patil
Signature			
Date	17/03/2017	17/03/2017	17/03/2017

Format No.: F/11QC070/04-00

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State : Gujarat - 396155, India


CERTIFICATE OF ANALYSIS (FINISHED PRODUCT)

Page 3 of 4

Product	LEVOTHYROXINE TABLETS 200 mcg	A.R. No.	FDP16100026
Batch No.	MLK602	Batch Size	150000 Tablets
Packing Batch No.	MLK602C	Packing Batch Size	17000 Tablets
Mfg. Date	10/2016	Exp. Date	09/2018
Date of Analysis	31-10-2016	Date of Report	17-03-2017
SPC No.	C/SPC/WP003134R/00	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Result
7	UNIFORMITY OF DOSAGE UNITS (By Content Uniformity, by HPLC, as Levothyroxine sodium anhydrous [C ₁₅ H ₁₀ I ₄ NNaO ₄]) -Acceptance Value (%) (For 10 dosage units) -Acceptance Value (%) (For 30 dosage units)	Less than or equal to 15.0 Less than or equal to 15.0 and no individual content of any dosage unit is less than 0.75 M and not more than 1.25 M	7.2
8	ORGANIC IMPURITIES (BY HPLC, %) -Liothyronine -Any unknown individual impurity -Total impurities (including liothyronine)	Not more than 2.0 Not more than 1.0 Not more than 4.0	0.32 0.16 0.84

	Prepared By	Checked By	Approved By
Name	Ganesh Rokade	Devender Singh Rajput	Dipak Patil
Signature			
Date	17/03/2017	17/03/17	17/03/2017

Format No.: F/HQC070/04-00

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 CIN : U24239MH1989PLC052049

 Work :
Plot No. 2209, GIDC,
Sangari, Dist. Valsad,
State : Gujarat - 396155, India.

CERTIFICATE OF ANALYSIS (FINISHED PRODUCT)

Page 4 of 4

Product	LEVOTHYROXINE TABLETS 200 mcg	A.R. No.	FDP16100026
Batch No.	MLK602	Batch Size	150000 Tablets
Packing Batch No.	MLK602C	Packing Batch Size	17000 Tablets
Mfg. Date	10/2016	Exp. Date	09/2018
Date of Analysis	31-10-2016	Date of Report	17-03-2017
SPC No.	C/SPC/WP003134R/00	STP No.	C/STP/WP003125/02

Sr.No.	Test	Specification	Result
9	ASSAY (By HPLC, as Levothyroxine sodium anhydrous $[C_{15}H_{10}I_4NNaO_4]$ - mcg per tablet -% label claim	Not less than 190.0 and not more than 210.0 Not less than 95.0 and not more than 105.0	203.471 101.7
10	MICROBIAL ENUMERATION TEST AND TEST FOR SPECIFIED MICROORGANISMS microbial enumeration tests -Total aerobic microbial count (cfu/g) -Total combined molds and yeast (cfu/g) Test for specified microorganism -Escherichia Coli	Not more than 10^3 Not more than 10^2 Should be absent	10 <10 Absent
11	SUBDIVISION OF TABLETS	Not more than one individual mass is outside limits of 85% to 115% of the average mass and no individual mass is outside the limit of 75% to 125% of the average mass.	Min :96.6 Max :105.1

REMARK : The product complies / does not comply as per the above specification.

	Prepared By	Checked By	Approved By
Name	Ganesh Kulkarni	Devendrasing Rajput	Dipak Patil
Signature			
Date	17/03/2017	17/03/17	17/03/2017

Format No.: F/HQC070/04-00

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 Website : www.macleodspharma.com
 CIN : U24239MH1989PLC059049

 Works :
 Plot No. 2209, GIDC,
 Sarigam, Dist - Valsad,
 State : Gujarat - 396155, India.

1. NAAM VAN HET GENEESMIDDEL

EUTHYROX 25/50/75/88/100/112/125/137/150/175/200, tabletten
25/50/75/88/100/112/125/137/150/175/200 microgram

2. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

EUTHYROX 25 microgram, tabletten : 25 µg levothyroxine natrium
EUTHYROX 50 microgram, tabletten : 50 µg levothyroxine natrium
EUTHYROX 75 microgram, tabletten : 75 µg levothyroxine natrium
EUTHYROX 88 microgram, tabletten : 88 µg levothyroxine natrium
EUTHYROX 100 microgram, tabletten : 100 µg levothyroxine natrium
EUTHYROX 112 microgram, tabletten : 112 µg levothyroxine natrium
EUTHYROX 125 microgram, tabletten : 125 µg levothyroxine natrium
EUTHYROX 137 microgram, tabletten : 137 µg levothyroxine natrium
EUTHYROX 150 microgram, tabletten : 150 µg levothyroxine natrium
EUTHYROX 175 microgram, tabletten : 175 µg levothyroxine natrium
EUTHYROX 200 microgram, tabletten : 200 µg levothyroxine natrium

Hulpstoffen: bevat lactose, zie rubriek 4.4.

Voor de volledige lijst van hulpstoffen, zie rubriek 6.1.

3. FARMACEUTISCHE VORM

Tabletten.

Wit, rond, vlak aan beide zijden, breuklijn aan beide zijden, met afgeronde rand. Aan de bovenkant staat per sterkte een inscriptie:

EUTHYROX 25	: EM 25
EUTHYROX 50	: EM 50
EUTHYROX 75	: EM 75
EUTHYROX 88	: EM 88
EUTHYROX 100	: EM 100
EUTHYROX 112	: EM 112
EUTHYROX 125	: EM 125
EUTHYROX 137	: EM 137
EUTHYROX 150	: EM 150
EUTHYROX 175	: EM 175
EUTHYROX 200	: EM 200

De tablet kan worden verdeeld in gelijke doses.

4. KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

Euthyrox 25 – 200 µg:

- Behandeling van euthyroïde struma, met name bij volwassenen als jodium niet geïndiceerd is

- Recidief profylaxe na kropresectie, afhankelijk van de postoperatieve hormoonstatus
- Substitutie bij hypothyroïdie
- Suppressiebehandeling bij schildkliercarcinoom

Euthyrox 25 - 100 µg:

- Substitutie tijdens de gelijktijdige behandeling met thyrostatica bij hyperthyroïdie

Euthyrox 100/150/200 µg:

- Diagnostisch gebruik bij schildkliersuppressieonderzoek

4.2 Dosering en wijze van toediening

Dosering

Om elke patiënt volgens zijn/haar individuele behoefte te kunnen behandelen, zijn er tabletten beschikbaar met een natriumlevothyroxinegehalte variërend van 25 tot 200 µg. Daardoor hoeven patiënten meestal maar één tablet per dag in te nemen.

De hieronder vermelde doseringen zijn richtlijnen.

De individuele dagelijkse dosis dient te worden vastgesteld aan de hand van laboratoriumtesten en klinische onderzoeken.

Omdat een aantal patiënten verhoogde concentratie T₄ en vrij T₄ concentratie vertoont, is de basale "schildklier stimulerend hormoon (TSH)-serumconcentratie" een meer betrouwbare basis voor de behandeling.

De schildklierhormoontherapie dient met een lage dosis gestart te worden en langzamerhand elke 2 tot 4 weken verhoogd te worden, totdat de volledige vervangingsdosis bereikt is.

Pediatrische patiënten

Voor pasgeborenen en jonge kinderen lijdend aan congenitaal hypothyroïdisme waar een snelle substitutie van belang is, dient de aanbevolen startdosis - 10 tot 15 microgram per kg lichaamsgewicht per dag - gedurende de eerste 3 maanden gegeven worden. Nadien moet de dosering per individu aangepast worden, gerelateerd aan de klinische uitkomsten, schildklierhormoon en de TSH-spiegel.

Bij oudere patiënten, bij patiënten met coronaire hartaandoeningen en bij patiënten met ernstige of langbestaande hypothyroïdie is bijzondere voorzichtigheid vereist bij aanvang van de behandeling met schildklierhormonen. Dit houdt in dat een lage startdosis (bijvoorbeeld 12,5 µg/dag) moet worden gegeven, die langzaam verhoogd wordt met lange intervallen (bijvoorbeeld een geleidelijke toename met 12,5 µg elke veertien dagen). De schildklierhormonen moeten regelmatig gecontroleerd worden. Een lagere dan de optimale dosering die volledige vervanging biedt, dient daarom te worden overwogen, met als gevolg een onvolledige correctie van de TSH-spiegel.

De ervaring heeft aangetoond dat bij patiënten met een laag gewicht en bij patiënten met een grote nodulaire struma, een lagere dosis voldoende is.

Indicatie	Aanbevolen dosis (µg natriumlevothyroxine/dag)			
Behandeling van euthyroïde krop	75 – 200			
Recidief profylaxe na kropresectie	75 – 200			
Substitutie bij hypothyroïdie bij volwassenen - startdosis - onderhoudsdosis	25 – 50 100 – 200			
Substitutie bij kinderen met verkregen hypothyroïdie - startdosis - onderhoudsdosis	12,5 – 50 100 – 150 µg/m ² lichaamsoppervlakte			
Substitutie tijdens de gelijktijdige behandeling met thyrostatica bij hyperthyroïdie	50 – 100			
Suppressiebehandeling bij schildkliercarcinoom	150 – 300			
Diagnostisch gebruik bij Schildkliersuppressie-onderzoek	Week 4 voor de test	Week 3 voor de test	Week 2 voor de test	Week 1 voor de test
Euthyrox 200 µg	---	---	1 tabl/dag	1 tabl/dag
Euthyrox 100 µg	---	---	2 tabl/dag	2 tabl/dag
Euthyrox 150 µg	½ tabl/dag	½ tabl/dag	1 tabl/dag	1 tabl/dag

Wijze van toediening

De dagelijkse doses kunnen in een eenmalige toediening gegeven worden.

Inname: eenmalige dagdosis 's ochtends op een lege maag, een half uur voor het ontbijt, bij voorkeur met wat vloeistof (bijvoorbeeld een half glas water).

Kinderen krijgen de gehele dosis ineens tenminste 30 minuten voor de eerste maaltijd van de dag. De tabletten moeten opgelost worden in wat water en de gevormde suspensie, die bereid moet worden op het moment dat die nodig is, moet met nog meer vloeistof ingenomen worden.

De duur van de behandeling is over het algemeen levenslang in het geval van substitutie bij hypothyroïdie en na strumectomie of thyroïdectomie en bij recidief profylaxe na kropresectie.

Gelijktijdige behandeling van hyperthyroïdie nadat een euthyreoïde toestand bereikt is, is geïndiceerd tijdens de periode dat een thyrostaticum gegeven wordt.

Voor benigne euthyroïde krop is een behandelingsduur van 6 maanden tot 2 jaar noodzakelijk. Om een terugkerende krop te voorkomen, wordt profylaxe met een lage dosis jodium (100 - 200 µg/dag) aangeraden na afname van de krogrooite. Als de medische behandeling gedurende deze periode onvoldoende blijkt, moet chirurgie of behandeling met radioactief jodium overwogen worden.

4.3 Contra-indicaties

- Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 vermelde hulpstoffen.

- Onbehandelde bijnierinsufficiëntie, onbehandelde hypofysaire insufficiëntie, en onbehandelde thyrotoxicose.
- De behandeling met Euthyrox mag niet gestart worden bij acuut myocardinfarct, acute myocarditis en acute pancarditis.
- Combinatietherapie van levothyroxine met een thyrostaticum is niet geïndiceerd tijdens de zwangerschap (zie rubriek 4.6).

4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik

Voor de start van de behandeling met schildklierhormonen of voor het uitvoeren van een schildkliersuppressie test dienen de volgende aandoeningen uitgesloten of behandeld te worden: coronaire insufficiëntie, angina pectoris, arteriosclerose, hypertensie, hypofysaire insufficiëntie (hypopituitarisme), bijnierinsufficiëntie, autonoom functionerende schildklier.

Bij aanvang van de behandeling met levothyroxine bij patiënten met een risico op psychotische stoornissen, wordt aanbevolen om te starten met een lage dosering levothyroxine en de dosering aan het begin van de behandeling geleidelijk te verhogen. Het wordt geadviseerd om de patiënt te monitoren. Bij het optreden van verschijnselen van psychotische stoornissen, dient aanpassing van de dosering van levothyroxine te worden overwogen.

Zelfs een door geneesmiddelen veroorzaakte lichte hyperthyroïdie moet bij patiënten met coronaire insufficiëntie, hartinsufficiëntie of tachycardiale aritmieën vermeden worden. Daarom dienen in dit geval regelmatig controles van de schildklierhormoonparameters te worden uitgevoerd.

In het geval van secundaire hypothyroïdie dient de oorzaak vastgesteld te worden voordat vervangingstherapie wordt gegeven en, indien nodig, moet vervangingstherapie van een gecompenseerde bijnierinsufficiëntie worden aangevallen.

Als het vermoeden van een autonoom functionerende schildklier bestaat, dient er voor de behandeling een TRH-test te worden uitgevoerd of dient er een suppressiescintigram te worden gemaakt.

Bij postmenopauzale vrouwen met hypothyroïdie en een toegenomen risico van osteoporose, dienen suprafysiologische serum-levothyroxine spiegels vermeden te worden en daarom dient de schildklierfunctie nauwlettend gecontroleerd te worden.

Levothyroxine dient niet in andere hyperthyroïdie toestanden gegeven te worden, behalve bij gelijktijdige aanvulling tijdens thyreostatica-behandeling van hyperthyroïdie.

Schildklierhormonen mogen niet gegeven worden voor gewichtsverlies. Bij euthyroïde patiënten veroorzaakt een behandeling met levothyroxine geen gewichtsverlies. Hoge doses kunnen ernstige of zelfs levensbedreigende bijwerkingen veroorzaken. Levothyroxine in hoge doses mag niet gecombineerd worden met bepaalde stoffen voor gewichtsverlies, zoals sympathomimetica (zie rubriek 4.9).

Als een behandeling met levothyroxine is ingesteld, dan wordt aangeraden om bij wijziging van het levothyroxine product, de dosering aan te passen aan de klinische respons van de patiënt en de laboratoriumuitslagen.

Bij gelijktijdige toediening van orlistat en levothyroxine kan hypothyreoïdie en/of een verminderde controle over hypothyreoïdie optreden (zie rubriek 4.5). Patiënten die levothyroxine gebruiken moet worden geadviseerd hun arts te raadplegen voordat de behandeling met orlistat wordt gestart, gestopt, of wordt aangepast, omdat orlistat en levothyroxine mogelijk op verschillende tijdstippen dienen te worden

ingenomen en de dosering van levothyroxine mogelijk dient te worden aangepast. Verder wordt aanbevolen om de patiënt te monitoren door de hormonale serumwaarden te controleren.

Euthyrox bevat lactose. Patiënten met zeldzame, aangeboren galactose intolerantieproblemen, Lapp-lactase deficiëntie of glucose-galactose-malabsorptie dienen dit geneesmiddel niet te gebruiken.

Voor diabetische patiënten en patiënten die anticoagulantitherapie ondergaan, zie rubriek 4.5 'Interacties met andere geneesmiddelen en andere vormen van interacties'.

4.5 Interacties met andere geneesmiddelen en andere vormen van interactie

Antidiabetische middelen:

Levothyroxine kan het effect verminderen van geneesmiddelen die de bloedsuikerspiegel verlagen. Om deze reden dienen de bloedglucosespiegels bij het begin van schildklierhormoontherapie regelmatig gecontroleerd te worden en dient, indien nodig, de dosering van het antidiabetische middel te worden aangepast.

Coumarinederivaten:

Het effect van anticoagulatetherapie kan worden versterkt, aangezien levothyroxine anticoagulerende middelen verdringt van het plasma-eiwit, wat het risico van een bloeding kan vergroten bijv. in CZS of maag-/darmbloedingen, vooral bij de oudere patiënten. Daarom is het noodzakelijk om bij de start van en gedurende de gelijktijdige behandeling de bloedstollingsparameters regelmatig te controleren. Indien nodig dient de dosering van het anticoagulerende middel aangepast te worden.

Proteaseremmers:

Proteaseremmers (bijv. ritonavir, indinavir, lopinavir) kunnen het effect van levothyroxine beïnvloeden. Nauwkeurige controle van de schildklierhormoonwaarden wordt aanbevolen. Indien noodzakelijk zal de dosering van levothyroxine aangepast moeten worden.

Fenytoïne:

Fenytoïne kan het effect van levothyroxine beïnvloeden door het verdringen van levothyroxine van de plasma-eiwitten met als gevolg een toename van de fT3 en fT4 fracties. Aan de andere kant verhoogt fenytoïne het levermetabolisme van levothyroxine. Daarom wordt een zorgvuldige controle van de schildklierhormoonparameters aanbevolen.

Galzuurbindende harsen:

Galzuurbindende harsen (bijv. cholestyramine of cholestipol) remmen de absorptie van natriumlevothyroxine. Daarom dient natriumlevothyroxine 4-5 uur voor toediening van dit soort middelen te worden ingenomen.

Aluminium, ijzer en calciumzouten:

Van aluminiumbevattende middelen (antacida, sucralfaat) is in relevante literatuur gemeld dat ze mogelijk het effect van levothyroxine verminderen. Middelen die levothyroxine bevatten dienen dan ook tenminste 2 uur voor het toedienen van aluminiumbevattende middelen te worden ingenomen. Hetzelfde geldt voor geneesmiddelen die ijzer en calciumzouten bevatten.

Salicylaten, dicoumarol, furosemide, clofibraat:

Salicylaten, dicoumarol, furosemide in hoge doses (250 mg), clofibraat en andere stoffen kunnen levothyroxine verdringen van het plasma-eiwit, wat uitmondt in een verhoogde vrije T₄ fractie.

Orlistat

Bij gelijktijdige inname van orlistat en levothyroxine kan hypothyreoïdie en/of een verminderde controle over hypothyreoïdie optreden. Een verminderde absorptie van jodiumzouten en/of levothyroxine zou hier de oorzaak van kunnen zijn.

Sevelameer:

Sevelameer kan de absorptie van levothyroxine verminderen. Daardoor wordt het aanbevolen om patiënten op veranderingen in de schildklierfunctie te controleren aan het begin of einde van een gelijktijdige behandeling. Indien nodig moet de levothyroxinedosis aangepast worden.

Thyrosinekinaseremmers:

Thyrosinekinaseremmers (bijv. imatinib, sunitinib) kunnen de werkzaamheid van levothyroxine verminderen. Daardoor wordt het aanbevolen om patiënten te controleren met betrekking tot verandering in de werking van de schildklier aan het begin of einde van een gelijktijdige behandeling. Indien nodig moet de levothyroxinedosis aangepast worden.

Propylthiouracil, glucocorticoïden, bètasympathicolytica, amiodaron en jodium houdende contrastmiddelen:

Deze stoffen remmen de perifere omzetting van T₄ in T₃. Amiodaron kan door het hoge jodgehalte zowel hyperthyroïdie als hypothyroïdie veroorzaken. Bijzondere voorzichtigheid is geboden in geval van nodulaire krop met mogelijk niet onderkende autonomie.

Sertraline, chloroquine/proguanil:

Deze stoffen verminderen de werkzaamheid van levothyroxine en verhogen de serum-TSH-spiegel.

Enzyminducerende geneesmiddelen:

Barbituraten en andere middelen met leverenzyminducerende eigenschappen kunnen de hepatische levothyroxineklaring vergroten.

Oestrogenen:

Vrouwen die anticonceptiva op basis van oestrogenen gebruiken, en postmenopauzale vrouwen die een hormonale substitutietherapie krijgen, hebben misschien meer levothyroxine nodig.

Sojabevattende producten:

Sojabevattende producten kunnen de intestinale absorptie van levothyroxine verminderen. Daarom dient de dosering van Euthyrox mogelijk te worden aangepast, vooral bij het begin of na beëindiging van een voeding met sojasupplementen.

4.6 Vruchtbaarheid, zwangerschap en borstvoeding

De behandeling met levothyroxine moet tijdens de zwangerschap en vooral tijdens borstvoeding consequent voortgezet worden. Tijdens de zwangerschap kan het zijn dat de dosis zelfs verhoogd moet worden. Aangezien de serumwaarde voor TSH al in de 4e zwangerschapsweek kan stijgen, moeten zwangere vrouwen die levothyroxine gebruiken elk trimester hun TSH-waarde laten meten, om te bevestigen dat de serumwaarde van de moeder voor TSH binnen de specifieke zwangerschapsreferentiegrenzen voor dat trimester ligt. Een verhoogde serumwaarde voor TSH moet bijgestuurd worden door een verhoging van de levothyroxinedosis. Aangezien de postpartumconcentraties voor TSH vergelijkbaar zijn met de waarden vóór de conceptie, moet de levothyroxinedosering onmiddellijk na de geboorte opnieuw ingesteld worden op de waarde vóór de zwangerschap. De TSH-spiegel moet 6–8 weken postpartum opnieuw gemeten worden.

Zwangerschap

De ontwikkeling van het kind is afhankelijk van de schildklierfunctie van de moeder. Thyroxine is noodzakelijk om een goede hersenontwikkeling van het kind te waarborgen. Daarom dient tijdens de zwangerschap een behandeling met schildklierhormonen te worden voortgezet. De doseringsbehoefte kan zelfs toenemen tijdens de zwangerschap. Tot op heden zijn er geen meldingen geweest van enig risico na uitgebreid gebruik tijdens de zwangerschap.

Borstvoeding

Euthyrox kan worden gebruikt tijdens lactatie. Levothyroxine wordt in lage concentraties via de moedermelk uitgescheiden. Zelfs bij hooggedoseerde levothyroxinetherapie is de hoeveelheid thyroxine die tijdens de lactatie uitgescheiden wordt in de moedermelk niet voldoende om bij het kind het ontwikkelen van hyperthyroïdie of suppressie van de TSH-secretie te veroorzaken.

Toepassing als adjuvans bij thyrostatica

Tijdens zwangerschap en lactatie moet Euthyrox niet tegelijk met medicatie voor de behandeling van hyperthyroïdie (thyrostatica) worden gegeven. Aangezien thyrostatica, in vergelijking tot levothyroxine, bij werkzame doseringen veel beter de placenta kunnen passeren, kan hypothyroïdie bij de foetus ontstaan. Omdat additionele toediening van levothyroxine de benodigde dosis van de thyrostatica kan verhogen, dient bij hyperthyroïdie tijdens de zwangerschap uitsluitend thyrostatica te worden gegeven.

4.7 Beïnvloeding van de rijvaardigheid en het vermogen om machines te bedienen

Euthyrox heeft geen invloed op de rijvaardigheid en op het vermogen machines te bedienen.

4.8 Bijwerkingen

De frequentiecategorie voor de onderstaande bijwerkingen is niet bekend (kan met de beschikbare gegevens niet worden bepaald).

Immuunsysteemaandoeningen	Overgevoeligheid Angio-oedeem

Bij overschrijding van de individuele tolerantielimiet van natriumlevothyroxine of bij overdosering kunnen de volgende klinische symptomen, kenmerkend voor hyperthyroïdie, zich voordoen, voornamelijk als de dosis te snel wordt verhoogd bij de aanvang van de behandeling

In dergelijke gevallen dient de dagelijkse dosis te worden verlaagd of de medicatie gedurende een aantal dagen te worden gestopt. De behandeling kan voorzichtig weer worden gestart als deze effecten verdwenen zijn.

Endocriene aandoeningen	Hyperthyreoidie Onregelmatige menstruatie
Zenuwstelselaandoeningen	Hoofdpijn Benigne intracraniale Hypertensie Tremor Rusteloosheid Insomnia
Hartaandoeningen	Aritmie Atriale fibrillatie Extrasystoles Tachycardie Hartkloppingen Angina pectoris
Maagdarmsstelselaandoeningen	Overgeven Diarree
Huid- en onderhuidaandoeningen	Hyperhidrose
Skeletspierstelsel- en bindweefselaandoeningen	Spierzwakte Spierspasmen
Algemene aandoeningen en toedieningsplaats- stoornissen	Overmatig blozen Pyrexie
Onderzoeken	Gewicht verlaagd

Melding van vermoedelijke bijwerkingen

Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl.

4.9 Overdosering

Een verhoogde T₃-spiegel is een meer betrouwbare aanwijzing voor een overdosering dan een verhoogde T₄- of vrij T₄ concentratie.

Bij overdosering vertoont de patiënt symptomen van een sterke toename van het basaal metabolisme.

Afhankelijk van de mate van overdosering wordt aangeraden de behandeling met de tabletten te stoppen en onderzoek uit te voeren.

Verscheidene gevallen van plotselinge dood door een hartaandoening zijn gemeld bij patiënten na jarenlang levothyroxine misbruik.

Symptomen die wijzen op duidelijke bètasymphaticomimetische effecten zoals tachycardie, angst, agitatie en hyperkinese, kunnen opgevangen worden met bètablokkers.

Bij extreme overdosering kan plasmaferese van nut zijn, maar zijn hemodialyse en hemoperfusie niet effectief en is peritoneale dialyse te weinig effectief.

Bij het overschrijden van het individuele tolerantieniveau zijn er geïsoleerde gevallen van toevallen gemeld bij patiënten met een aanleg hiervoor.

Overdosering van levothyroxine zou kunnen leiden tot symptomen van hyperthyreoïdie en tot acute psychose, met name bij patiënten met een risico op psychotische stoornissen.

5. FARMACOLOGISCHE EIGENSCHAPPEN

5.1 Farmacodynamische eigenschappen

Farmacotherapeutische categorie: schildklierhormonen, ATC-Code: H03A A01

Het effect van het synthetische levothyroxine in Euthyrox is gelijk aan dat van het natuurlijk voorkomend essentieel hormoon, uitgescheiden door de schildklier. Het wordt, net als het endogene hormoon, omgezet in T_3 in de perifere organen en ontwikkelt zijn specifieke effect via de T_3 -receptoren. Het lichaam kan geen onderscheid maken tussen endogeen en exogeen levothyroxine.

5.2 Farmacokinetische eigenschappen

Bij orale inname wordt levothyroxine bijna geheel in het bovenste deel van de dunne darm geabsorbeerd. Afhankelijk van de galenische vorm bedraagt de absorptie tot 80%. T_{max} is ongeveer 5 tot 6 uur.

Na orale toediening treedt het begin van de werking op na 3-5 dagen. Levothyroxine vertoont een extreem sterke binding van ongeveer 99,97% aan specifieke transporteiwitten. Deze eiwit-hormoonbinding is niet covalent en dus wordt het gebonden hormoon in het plasma continu en zeer snel uitgewisseld met de vrije hormoonfractie. Het verdeelingsvolume bedraagt ongeveer 10-12 l.

Door de hoge graad van eiwitbinding ondergaat levothyroxine geen hemodialyse of hemoperfusie.

De halfwaardetijd van levothyroxine bedraagt ongeveer 7 dagen. Bij hyperthyroïdie is dit korter (3-4 dagen). Bij hypothyroïdie is dit langer (ongeveer 9-10 dagen). De lever bevat 1/3 van het gehele extrathyroïdale levothyroxine. Dit is snel uitwisselbaar met het levothyroxine in het serum. Schildklierhormoon wordt voornamelijk gemetaboliseerd in de lever, nieren, hersenen en spieren. De metaboliëten worden uitgescheiden in de urine en de feces. De totale metabole levothyroxineklaring is ongeveer 1,2 l plasma per dag.

5.3 Gegevens uit het preklinisch veiligheidsonderzoek

Er zijn geen preklinische gegevens die van belang zijn voor de voorschrijver naast de gegevens die worden weergegeven in andere rubrieken van deze samenvatting van de productkenmerken.

6. FARMACEUTISCHE GEGEVENS

6.1 Lijst van hulpstoffen

Magnesiumstearaat (E 572)
Maïszetmeel
Croscarmellose natrium (E 468)
Gelatine (E 441)
Lactose monohydraat.

6.2 Gevallen van onverenigbaarheid

Niet bekend.

6.3 Houdbaarheid

3 jaar.

6.4 Speciale voorzorgsmaatregelen bij bewaren

Bewaren beneden 25°C. De blisterverpakking in de buitenverpakking bewaren ter bescherming tegen licht.

6.5 Aard en inhoud van de verpakking

50 of 90 tabletten in polypropyleenchloride/aluminium blisterverpakking of polyvinylchloride/aluminium blisterverpakking.

6.6 Speciale voorzorgsmaatregelen voor het verwijderen

Geen bijzondere instructies.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Merck BV
Tupolevlaan 41-61
1119 NW Schiphol-Rijk

8. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

EUTHYROX 25	: RVG 11718
EUTHYROX 50	: RVG 11344
EUTHYROX 75	: RVG 21494
EUTHYROX 88	: RVG 101391
EUTHYROX 100	: RVG 09009
EUTHYROX 112	: RVG 101393
EUTHYROX 125	: RVG 15468
EUTHYROX 137	: RVG 101394
EUTHYROX 150	: RVG 11345
EUTHYROX 175	: RVG 26173
EUTHYROX 200	: RVG 26174

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/HERNIEUWING VAN DE VERGUNNING

EUTHYROX 25 : RVG 11718
Datum van eerste verlening van de vergunning: 26 november 1986
Datum van laatste hernieuwing: 26 november 2016

EUTHYROX 50 : RVG 11344
Datum van eerste verlening van de vergunning: 4 november 1985
Datum van laatste hernieuwing: 4 november 2015

EUTHYROX 75 : RVG 21494
Datum van eerste verlening van de vergunning: 15 augustus 1997

Datum van laatste hernieuwing: 15 augustus 2012

EUTHYROX 100 : RVG 09009

Datum van eerste verlening van de vergunning: 15 december 1982

Datum van laatste hernieuwing: 15 december 2012

EUTHYROX 125 : RVG 15468

Datum van eerste verlening van de vergunning: 11 juni 1992

EUTHYROX 150 : RVG 11345

Datum van eerste verlening van de vergunning: 4 november 1985

Datum van laatste hernieuwing: 4 november 2015

EUTHYROX 175 : RVG 26173

EUTHYROX 200 : RVG 26174

Datum van eerste verlening van de vergunning: 11 juni 2001

Datum van laatste hernieuwing: 11 juni 2016

EUTHYROX 88 : RVG 101391

EUTHYROX 112 : RVG 101393

EUTHYROX 137 : RVG 101394

Datum van eerste verlening van de vergunning: 7 januari 2009

Datum van laatste hernieuwing: 7 januari 2014

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4, 4.5, 4.6 en 9: 15 oktober 2017

Public Assessment Report

Scientific discussion

Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets

(levothyroxine sodium)

NL/H/2700/001-011/DC

Date: 30 November 2015

This module reflects the scientific discussion for the approval of Levothyroxine Natrium Vale tablets. The procedure was finalised on 20 June 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets. The Marketing Authorisation Holder (MAH) is Vale Pharmaceuticals Limited.

Levothyroxine Natrium 25-200 micrograms is indicated for:

- Hypothyroidism
- Prophylaxis against goitre recurrence following resection of euthyroid goitre
- Benign, euthyroid goitre
- Suppression and replacement therapy in thyroid malignancy, especially post thyroidectomy.

Levothyroxine Natrium 25-200 micrograms is indicated for:

- Co-therapy in the antithyroid treatment of hyperthyroidism, once euthyroid status has been achieved.

Levothyroxine Natrium 100/150/200 micrograms is indicated for:

- Thyroid suppression test.

Levothyroxine Natrium Vale tablets, contain synthetic crystalline L-,3,3',5,5'-tetraiodothyronine sodium salt (levothyroxine (T4) sodium). Synthetic T4 is identical to that produced in the human thyroid gland.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Euthyrox 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets (NL License RVG 11718, 11344, 21494, 101391, 09009, 101393, 15468, 101394, 11345, 26173, 26174). In the Netherlands, the first marketing authorisation was granted in 1982, for Euthyrox 100 mcg tablets.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Slovenia, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Levothyroxine Natrium Vale tablets are:

25 mcg: white to off-white, round, tablets imprinted with 25 on one side and bisected on the other side to allow sub-division to achieve a 12.5 mcg dose.

50 - 200 mcg: white to off-white, round, flat, bevelled tablets imprinted with "L01, L02, L07, L10, L11, L12, L15, L17, L20 or L21" on one side and "50, 75, 88, 100, 112, 125, 137, 150, 175 or 200" on the other side.

The tablets are packed in high density polyethylene (HDPE) bottles, closed with white polypropylene (PP) screw caps with foil heat induction seals, and with a 1.0 g white polypropylene canister containing oxygen absorber. The canister (oxygen absorber) should remain inside the bottle during the in-use period.

The excipients are: microcrystalline cellulose PH101 (E460), pregelatinised maize starch, talc (E553b), colloidal anhydrous silica (E551), magnesium stearate (E470b).

These Levothyroxine tablets are in principle similar to the innovator Eltroxin tablets. In addition supplementary strengths are introduced. The current 50 mcg tablet has a tablet weight of 75.0 mg. The MAH introduced a new formulation with a weight of 75.0 mg instead of 150.0 mg for all other strengths i.e. all strengths across the range now have a tablet weight of 75.0 mg. The MAH conducted a bioequivalence study to compare the 75.0 mg formulation with the 150.0 formulation, using the 100 mcg strength. In addition, as Euthyrox is the innovator product in some CMS and Eltroxin is not, a bioequivalence study is submitted using Euthyrox as comparator. Next to these 2 studies a dose proportionality/bioavailability study was carried out using the 50, 100 and 200 µg Eltroxin tablets. The results of these studies are discussed under section IV.2 'Pharmacokinetics'.

All strengths were formulated with the same tablet mass 75.0 mg. Differences in the drug substance content between strengths were compensated for by slight mass changes in the microcrystalline cellulose.

II.2 Drug Substance

The active substance is levothyroxine sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to pale brownish-yellow, hygroscopic amorphous or crystalline powder, which is soluble in alkali hydroxides, very slightly soluble in ethanol and practically insoluble in water, chloroform, ethyl ether and acetone. The drug substance has one chiral center, the active ingredient is levothyroxine. The product does not exhibit polymorphism.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the additional requirement of the CEPs. Batch analytical data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer on 8 batches of the drug substance obtained from one manufacturer and 1 batch of the other supplier. Additional batch analysis data have been provided by this second manufacturer.

Stability of drug substance

The active substance from the first manufacturer is stable for 36 months when stored under the stated conditions. For the second supplier the active substance is stable for 24 months if stored at a temperature at 2-8 °C in the proposed package. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients justified and their functions have been explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified.

The aim of the product development was to extend the innovator formulation Eltroxin 50 µg and 100 µg tablets. The new range includes 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 µg tablet strengths.

The main bioequivalence study was performed on one batch (200 µg) with the same composition as the commercial batches. The reference product used for this bioequivalence study is Euthyrox 200 µg (Merck Germany, DE/H/0284/008/MR). The second study was a single dose pharmacokinetic and dose proportionality study of Eltroxin 50, 100 and 200 µg tablets at a dose of 600 µg. A third biostudy

was performed to compare the currently registered 100 µg Eltroxin product (with tablet mass 150 mg) to the proposed 100 µg product (with tablet mass 75 mg).

A biowaiver for the additional strengths was applied for. The MAH provided data to show similarity in dissolution profiles. The dissolution profiles were similar for most strengths and batches. For some strengths and under some of the test conditions, similarity of dissolution profiles was not demonstrated. However, some of these batches (50 µg and 200 µg strengths) were used in a dose proportionality bioequivalence study, which demonstrated bioequivalence. Further justification based on solubility characteristics was provided. In conclusion, dissolution similarity has been sufficiently demonstrated using an appropriate method, and a biowaiver for the additional strengths can be granted from a chemical-pharmaceutical point of view.

Breakability of the 25 µg tablet has been demonstrated according to the Ph. Eur. sub-division test for tablets. Overall, the pharmaceutical development has been described in sufficient detail.

Manufacturing process

The manufacturing process for levothyroxine sodium tablets includes preparation of a trituration of the drug substance with microcrystalline cellulose, mixing, sieving, blending and compressing. As the total amount of active substance present in the formulation is less than 2% the manufacturing process is considered as a non-standard process. The MAH applied a matrix approach and provided process validation data for the most critical 25 µg strength, for 2 inter-mediate strengths (88 µg and 100 µg), and the lowest & highest strengths (50 µg and 200 µg). For each of these strengths 3 batches were validated. This approach is considered acceptable and the provided validation data are considered satisfactory. In addition the MAH committed to validate the tablet strengths that have not been validated yet (75 µg, 112 µg, 125 µg, 137 µg, 150 µg and 175 µg) post authorisation.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, average mass, uniformity of mass, hardness, dimensions, friability, disintegration time, moisture content, HPLC assay, identification, related substances, content uniformity, uniformity of dosage units, dissolution, residual solvents, microbiological tests and subdivision of tablets (25 µg). The specifications are in line with the Ph. Eur. or USP. The test methods which are used in both release and shelf-life specifications have the same specification limits except for hardness and related substances. The analytical methods have been adequately described and validated. The stability indicating properties of the assay and related substances method has been demonstrated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specifications.

Stability of drug product

Full stability data on the product has been provided for three full-scaled batches of each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months) for the 25-50-100-150-200 µg strengths. For the remaining strengths a matrix approach has been applied; however, at 12-18-24 months full stability data is available. The batches were stored in 40 cc white multilayer HDPE bottle; polypropylene closure with induction seals liner and 1.0 g oxygen absorber.

Stability results showed that at accelerated conditions out of specifications were observed. For some tablet strengths at various conditions deviating results were found, and this resulted in 3 different storage conditions for the 11 tablet strengths. Nevertheless it is correct to base all storage conditions on actual stability data. Based on the available stability data above the proposed shelf-life of 2 years can be accepted.

The applicant provided in-use stability of limited in-use test periods: 67 days at 25°C/60% RH for the 25 µg strength (for tablets having been stored before for 24 months at 25°C/60% RH) and 30 days at 30°C/75% RH for 50 µg tablets (having been stored before for 18 months at 30°C/75% RH). Test parameters for 25 µg tablets were appearance, assay, related substances, dissolution and microbiological testing. Test parameters for the 50 µg tablets were appearance, assay, related substances, average hardness, friability, disintegration time, water content, dissolution and microbiological testing.

In the 50 µg/30 days study no deviating results were observed. Results after 67 days for the 25 µg tablets also meet the set specifications, although some assay and dissolution decrease and increase

for total impurities have been observed. The MAH committed to perform in-use stability studies on 28-, 50- and 100-tablet packs for the 25 µg and 200 µg validation batches. The following in-use stability claim is included in the SmPC: "After opening of the HDPE container the tablets should be used within 2 months". In view of the 112 tablet bottle as the maximum pack size, the minimum in use period would be 112 days. Additional in-use stability data in support of this period will be provided post authorisation.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. The raw materials used for the production of magnesium stearate are not of animal origin and do not come into direct contact with such materials.

II.4 Discussion on chemical, pharmaceutical and biological aspects

CMD(h) referral

Grounds for referral

The procedure was referred to the CMD(h) due to a different point of view between RMS and CMS regarding the required dissolution specification limits for these generic levothyroxine products to ensure that batches will show a batch to batch consistency based on the dissolution profiles of the biobatches, and thus to ensure a satisfactory *in-vivo* behaviour for all future commercial batches.

Outcome

The CMD(h) requested the CHMP's Quality Working Party (QWP) to provide a scientific opinion on the dissolution specifications required for these products. As the MAH has amended the dissolution specifications in line with the feedback of the QWP, the issue is considered resolved and agreement has been reached.

Quality conclusion

Overall, based on the submitted dossier, the member states consider that a proven chemical-pharmaceutical quality has been demonstrated for Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to validate the tablet strengths that have not been validated yet (75 µg, 112 µg, 125 µg, 137 µg, 150 µg and 175 µg).
- The MAH committed to test homogeneity on the final blend on all process validation batches of all product strengths, thereafter on the first 10 commercial batches of all product strengths. Subsequently this will be performed once a year, if the specific product strength is manufactured.
- The MAH committed to perform in-use stability studies on 28-, 50- and 100-count containers for the 25 µg and 200 µg validation batches. In view of the maximum pack size of 112 tablets, the minimum in use stability period of 112 days should be covered.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levothyroxine Natrium Vale is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Euthyrox tablets, which are available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview

on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levothyroxine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three pharmacokinetic studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted the following studies:

- A single dose bioequivalence study comparing Euthyrox 200 µg tablet (Merck Pharma GmbH, Germany) and Levothyroxine Natrium Vale 200 µg tablet, under fasting conditions.
- A single dose pharmacokinetic and dose proportionality study of Levothyroxine Natrium Vale 50, 100 and 200 µg tablets at a dose of 600 µg, under fasting conditions.
- A single dose bioequivalence study comparing the current Eltroxin 100 µg tablet (weight 150 mg) and the new 100 µg tablet formulation (tablet weight 75 mg), under fasting conditions.

The choice of the reference products in the bioequivalence studies is justified. As Eltroxin is not available as an innovator product in all of the CMS, a bioequivalence study is submitted using Euthyrox as comparator.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The studies under fasting conditions are justified as according the SmPC l-thyroxine should be taken on an empty stomach at least half an hour before breakfast. Therefore no food interaction study is needed. In all studies a 600 µg dose has been used to ensure that adequate levothyroxine plasma levels can be measured. This is agreed. Pharmacokinetic, statistical and bio-analytical methods used in the studies are acceptable. Both corrected and uncorrected data on total T4 and on total T3 were measured. However with regard to the endogenous l-thyroxine levels the statistical analysis and bioequivalence evaluation of the pharmacokinetic parameters should be performed on baseline-corrected data of total T4 only. Only these data are reported in the PAR.

The MEB has been assured that the studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Pharmacokinetic studies

Study I – bioequivalence study - 200 µg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 76 healthy subjects, 68 males and 8 females, aged 20-44 years. Each subject received a single dose of 600 mcg (3 x 200 mcg) of one of the 2 levothyroxine formulations. The tablet was orally administered with 240 ml water after an overnight fast. A

subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate.

Results

One subject was withdrawn in period I due to an adverse event (vomiting). One subject dropped out before dosing in period I and three subjects dropped out before check-in of period II for personal reasons. The remaining 71 subjects completed the study and were included in the analysis.

The statistical evaluation on baseline corrected total (free+bound) T4 of the 200 µg Euthyrox (Reference, B) and Levothyroxine Natrium Vale (Test, A) formulations is given below.

Table 1

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC _{0-t}	189.401	209.849	90.2556	86.8626	93.7812
C _{max}	6.890	7.839	87.9000	84.9950	90.9043

Table 5: (A vs. B) Geometric Means and 90% Confidence Interval for Total (bound+free) T4 (N=71)

**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Conclusion on the bioequivalence study

The 90% confidence intervals based on the calculated data of baseline corrected total (free+bound) levothyroxine (T4), for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80 – 125%. Based on the submitted bioequivalence study Levothyroxine Natrium Vale 200 mcg is considered bioequivalent to Euthyrox 200 mcg tablets.

Study II - 50, 100 and 200 mcg tablet dose proportionality study

A randomized, open label, balanced, three-treatment, three-period, three-sequence, single dose, crossover, pharmacokinetic and dose proportionality study under fasted conditions. Seventy-five healthy subjects, 63 males and 12 females, aged 19 – 44 years, were included in this study. Each subject received a single dose (total dose 600 µg) of the 50, 100 and 200 µg levothyroxine formulations. The doses were administered as 12 x 50 mcg, 6 x 100 mcg 3 x 200 mcg tablets. The formulations were taken with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. For each subject there were 3 dosing periods, separated by a washout period of 38 days.

Blood samples were taken at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate. The study under fasting conditions and the administration of a 600 mcg dose are justified.

Results

Four subjects dropped out and four subjects were withdrawn from the study:

- One subject in period I due to vomiting
- Three subjects before check-in at period II due to personal reasons
- One subject, in period II due to an adverse event (giddiness)
- One subject during check-in period III as the subject was positive in the drug abuse test (benzodiazepines)
- One subject before check-in at period III due to personal reasons
- One subject in period III due to vomiting.

The remaining 67 subjects completed the study and were included in the analysis.

The geometric mean and 90% confidence interval based for the pharmacokinetic parameters C_{max} and AUC₀₋₄ for baseline corrected total (bound+free) T4 for all 3 tablet strengths are presented below.

Data are given as A vs. B, C vs. B, A vs. C where:

A = Levothyroxine sodium) 50 mcg

B= Levothyroxine sodium) 100 mcg

C = Levothyroxine sodium) 200 mcg

Table 2a

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)		Lower Limit	Upper Limit
AUC ₀₋₄	179.369	160.330	111.8747	106.2184	117.8322
C _{max}	6.607	5.720	115.5029	109.8357	121.4624

Table 1: (A vs. B) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67).

**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Table 2b

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (C)	Reference (B)		Lower Limit	Upper Limit
AUC ₀₋₄	172.094	160.330	107.3372	101.9104	113.0531
C _{max}	6.275	5.720	109.7080	104.3252	115.3686

Table 2: (C vs. B) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67).

**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Table 2c

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (C)		Lower Limit	Upper Limit
AUC ₀₋₄	179.369	172.094	104.2273	98.9576	109.7775
C _{max}	6.607	6.275	105.2821	100.1164	110.7143

Table 3: (A vs. C) Geometric Means and 90% Confidence Interval for Baseline Corrected Total (bound+free) T4 (N=67)

**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

Conclusion on study II

Based on the statistical analysis of baseline corrected total (bound and free) T4, it is concluded that dose proportionality is demonstrated between Levothyroxine Natrium Vale 50 mcg tablets and 100 mcg tablets, between Levothyroxine Natrium Vale 200 mcg tablets and 100 mcg tablets and between Levothyroxine Natrium Vale 50 mcg tablets and 200 mcg tablets under fasting conditions.

Study III – Eltroxin 100 mcg current formulation vs. new Levothyroxine Natrium Vale 100 mcg formulation

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the Eltroxin 100 mcg tablet with the new 100 mcg levothyroxine sodium tablet formulation of Vale Pharmaceuticals Limited. The new formulation was developed with a tablet weight of 75.0 mg instead of the 150.0 mg current Eltroxin tablet.

Seventy-six healthy subjects, 52 males and 24 females, aged 20–44 years, were included in this study. Each subject received a single dose (total dose 600 mcg) of the 100 mcg levothyroxine formulations. The tablets were administered in solid form with 240 ml water after an overnight fast. A subsequent fasting period was applied for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were taken at -0.5 and -0.25 h prior to dosing, at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 48 hours after administration of the products.

The study design is considered adequate. The study under fasting conditions and the administration of a 600 mcg dose are justified.

Results

One subject dropped out before dosing of period I due to personal reasons. The remaining 75 subjects completed the study and were included in the analysis.

The statistical evaluation on baseline corrected total (free+bound) T4 of the current Eltroxin 100 mcg (Reference, B) and Levothyroxine Natrium Vale 100 mcg formulation applied for (Test, A) is given below.

Table 3

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)		Lower Limit	Upper Limit
AUC ₀₋₄	163.141	152.120	107.2450	100.1410	114.8529
C _{max}	5.710	5.463	104.5217	98.4222	110.9993

Table 4: (A vs. B) Geometric Means and 90% Confidence Interval for Total (bound+free) T4 (N=75)

*Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.

Conclusion on study III

Based on the pharmacokinetic parameters of baseline corrected total (free+bound) levothyroxine (T4), the current Eltroxin 100 µg and the new levothyroxine Natrium Vale 100 µg tablets are bioequivalent.

Biowaiver

The MAH applied for a biowaiver for the 25 mcg, 75 mcg, 88 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg and 175 mcg strengths. Dissolution similarity between strengths has been sufficiently demonstrated using an appropriate method. The justification for a biowaiver is acceptable in view of the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan

The MAH has not submitted a risk management plan, which was acceptable at the time of submission of this application. The member states considered that the regulatory requirements for the pharmacovigilance system description were adequately fulfilled.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Euthyrox. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. Dose proportionality of the Levothyroxine Natrium Vale 50, 100 and 200 µg tablets has been demonstrated at a dose of 600 µg. Bioequivalence has also been shown between the current Eltroxin 100 µg tablet and the new 100 µg tablet formulation. Based on the data submitted, the member states concluded that this generic formulation can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. In both test rounds at least 90% of all

participants were able to find the information. Of these participants, more than 90% were able to answer the questions correctly. There were no revisions suggested to the PIL. The readability report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levothyroxine Natrium Vale 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg and 200 mcg tablets have a proven chemical-pharmaceutical quality and are generic forms of Euthyrox tablets. Euthyrox is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

This application was discussed with the chair of the Board on 8 January, 5 March, 16 April and 3 June 2014. The Board agrees with the QWP's opinion regarding the limits of the dissolution specification. The MEB maintained its positive position regarding this application.

Agreement between member states was reached during a CMD(h) referral. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levothyroxine Natrium Vale with the reference product, and have therefore granted a marketing authorisation. The CMD(h) referral procedure was finalised with a positive outcome on 20 June 2014. In the Netherlands the marketing authorisation was granted on 24 November 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Minor change in the manufacturing process; Change in the specification parameters and/or limits of the finished product; Change in test procedure for the finished product; Change in supplier of packaging components or devices.	NL/H/2700/001-011/IA/001/G	IA/G	17-3-2015	16-4-2015	Approval	No
Change in test procedure for the finished product.	NL/H/2700/001-011/IB/002	IB	26-3-2015	27-4-2015	Approval	No
Name change in NL, AT, CZ, DE, DK, IE, NO, PO and SK.	NL/H/2700/001-011/IB/004	IB	9-7-2015	29-10-2015	Approval	No
Address change of the MAH in AT, BE, ES, FI, FR, IE, IT, LU, NO, PT and SE.	NL/H/2700/001-011/IA/005	IA	31-8-2015	16-9-2015	Approval	No

APPENDIX 16.2

SUBJECT DATA LISTINGS

APPENDIX 16.2.1
DISCONTINUED SUBJECTS
(Not Applicable)

APPENDIX 16.2.2

PROTOCOL DEVIATIONS

TABLE NO. 01
SUBJECT DEMOGRAPHICS

Vol. Reg. No.	Sub. No.	Date of screening	Sex	Age (Yrs)	Height (Meters)	Weight (Kg)	BMI (Kg/m ²)	Diet (V/MX)	h/o Tobacco Use (Y/N/PT)	Intake of Abusive / Recreational Drugs (Y/N)	Alcohol Intake (Y/N/PD)	h/o Blood Donation (Y/N)	h/o Participation in a Drug Research Study (Y/N)	History of allergy (Food, Medicine etc,) (Y/N)
BEQ-18872	01	30/03/18	M	37	1.72	87.3	29.51	MX	N	N	N	N	Y**	N
BEQ-4651	02	30/03/18	M	41	1.69	63.7	22.30	MX	N	N	N	N	Y**	N
BEQ-22047	03	22/03/18	M	35	1.70	79.8	27.61	MX	N	N	N	N	Y**	N
BEQ-9543	04	31/03/18	M	37	1.69	80.0	28.01	MX	N	N	N	N	Y**	N
BEQ-30488	05	31/03/18	M	43	1.67	63.4	22.73	MX	N	N	N	N	Y**	N
BEQ-21341	06	16/03/18	M	32	1.66	75.4	27.36	MX	N	N	N	N	Y**	N
BEQ-28073	07	30/03/18	M	35	1.68	59.5	21.08	MX	N	N	N	N	Y**	N
BEQ-30510	08	01/04/18	M	33	1.65	67.7	24.87	MX	N	N	N	N	N	N
BEQ-23283	09	01/04/18	M	28	1.65	54.6	20.06	MX	PT	N	N	N	Y**	N
BEQ-23897	10	30/03/18	M	33	1.71	61.3	20.96	MX	N	N	N	N	Y**	N
BEQ-19335	11	31/03/18	M	27	1.77	65.1	20.78	MX	N	N	N	N	Y**	N
BEQ-18886	12	31/03/18	M	24	1.67	55.8	20.01	MX	N	N	N	N	Y**	N
BEQ-27715	13	31/03/18	M	28	1.65	54.7	20.09	MX	N	N	N	N	Y**	N
BEQ-26391	14	28/03/18	M	21	1.84	67.2	19.85	MX	N	N	N	N	N	N
BEQ-26962	15	21/03/18	M	34	1.68	68.2	24.16	V	N	N	N	N	Y**	N
BEQ-30496	16	31/03/18	M	26	1.55	53.3	22.19	MX	N	N	N	N	N	N
BEQ-30500	17	31/03/18	M	26	1.64	53.4	19.85	V	N	N	N	N	Y**	N
BEQ-30498	18	31/03/18	M	29	1.69	61.8	21.64	MX	N	N	N	N	N	N
BEQ-19761	19	02/04/18	M	35	1.63	60.6	22.81	MX	N	N	N	N	Y**	N
BEQ-22590	20	02/04/18	M	25	1.74	69.8	23.05	MX	N	N	N	N	Y**	N
BEQ-26842	21	31/03/18	M	22	1.64	68.8	25.58	MX	N	N	N	N	N	N

Vol. Reg. No.	Sub. No.	Date of screening	Sex	Age (Yrs)	Height (Meters)	Weight (Kg)	BMI (Kg/m ²)	Diet (V/MX)	h/o Tobacco Use (Y/N/PT)	Intake of Abusive / Recreational Drugs (Y/N)	Alcohol Intake (Y/N/PD)	h/o Blood Donation (Y/N)	h/o Participation in a Drug Research Study (Y/N)	History of allergy (Food, Medicine etc,) (Y/N)
BEQ-30512	22	01/04/18	M	21	1.62	67.6	25.76	MX	PT	N	N	N	N	N
BEQ-28272	23	31/03/18	M	26	1.69	67.8	23.74	V	N	N	N	N	Y**	N
BEQ-30523	24	02/04/18	M	36	1.78	77.8	24.55	MX	N	N	N	N	N	N
BEQ-16974	25	02/04/18	M	35	1.71	74.2	25.38	MX	N	N	N	N	Y**	N
BEQ-30520	26	02/04/18	M	37	1.63	72.6	27.33	MX	N	N	N	N	Y**	N
BEQ-30517	27	02/04/18	M	44	1.65	65.1	23.91	V	N	N	N	N	Y**	N
BEQ-19531	28	03/04/18	M	40	1.63	74.9	28.19	MX	N	N	N	N	Y**	N
BEQ-12307	29	03/04/18	M	39	1.73	81.6	27.26	MX	N	N	N	N	Y**	N
BEQ-24855	30	27/03/18	M	27	1.68	59.2	20.98	V	N	N	N	N	Y**	N
Number				30	30	30	30							
Median				33.00	1.68	67.40	23.40							
Mean				31.9	1.681	67.07	23.720							
Standard Deviation				6.55	0.0555	9.015	2.9387							
Minimum				21	1.55	53.3	19.85							
Maximum				44	1.84	87.3	29.51							

Abbreviations:

Y: Yes Y*: Blood donated more than 90 days

Y**: Indicates participation in the previous drug research study more than 90 days

h/o: History of V: Vegetarian

MX: Mixed (Veg and Non-Veg)

N: No

M: Male

PD: Previous Drinker PT: Previous Tobacco User

LIST OF TABLE

Table No.	Title	Page
1.	Individual and mean pre-dose serum concentration of levothyroxine in (ng/mL) of Reference Product	3 of 53 to 4 of 53
2.	Individual and mean pre-dose serum concentration of levothyroxine in (ng/mL) of Test Product	5 of 53 to 6 of 53
3.	Individual and mean post dose serum concentration of non-baseline-corrected-levothyroxine in (ng/mL) of Reference Product	7 of 53 to 10 of 53
4.	Individual and mean post dose serum concentration of non-baseline-corrected-levothyroxine in (ng/mL) of Test Product	11 of 53 to 14 of 53
5.	Individual and mean post dose serum concentration of baseline-corrected-levothyroxine in (ng/mL) of Reference Product	15 of 53 to 18 of 53
6.	Individual and mean post dose serum concentration of baseline-corrected-levothyroxine in (ng/mL) of Test Product	19 of 53 to 22 of 53
7.	Hemolysed Samples	23 of 53

LIST OF FIGURES

Figure No.	Title	Page
1 – 60	Comparative linear & semi log plots of baseline-corrected-levothyroxine serum concentration (ng/mL) vs time (Hours) for each subject	24 of 53 to 53 of 53

TABLE NO. 1

INDIVIDUAL AND MEAN PRE-DOSE SERUM CONCENTRATION OF LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	-0.50 -0.25	-0.03		Average
1	RT	R	1	71.22	73.33	72.05	72.20
2	RT	R	1	50.98	55.50	58.65	55.04
3	TR	R	2	74.01	73.91	75.79	74.57
4	TR	R	2	72.81	73.77	76.75	74.44
5	TR	R	2	71.46	71.46	72.94	71.95
6	RT	R	1	45.66	44.87	44.96	45.16
7	TR	R	2	59.68	55.78	59.61	58.36
8	RT	R	1	75.75	76.81	75.17	75.91
9	TR	R	2	67.80	68.11	70.85	68.92
10	RT	R	1	70.76	70.86	66.03	69.22
11	TR	R	2	51.82	50.59	49.83	50.75
12	RT	R	1	85.88	82.68	83.06	83.87
13	TR	R	2	90.62	92.27	91.67	91.52
14	TR	R	2	65.84	65.86	64.41	65.37
15	TR	R	2	57.25	59.22	61.62	59.36
16	RT	R	1	44.79	47.85	47.62	46.75
17	RT	R	1	76.11	73.20	76.39	75.23
18	RT	R	1	66.07	68.48	69.29	67.95
19	RT	R	1	80.01	78.74	81.10	79.95
20	RT	R	1	83.23	80.29	82.40	81.97
21	TR	R	2	60.82	62.85	61.59	61.75
22	RT	R	1	76.58	77.54	78.51	77.54
23	TR	R	2	79.71	94.66	82.75	85.71
24	TR	R	2	72.31	68.35	69.97	70.21

TABLE NO. 1. Continued on next page...

CONTINUED TABLE NO. 1

INDIVIDUAL AND MEAN PRE-DOSE SERUM CONCENTRATION OF LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	-0.50	-0.25	-0.03	Average
25	RT	R	1	85.92	83.38	87.11	85.47
26	TR	R	2	70.07	65.51	68.04	67.87
27	RT	R	1	89.28	87.56	87.64	88.16
28	TR	R	2	64.40	62.50	63.86	63.59
29	TR	R	2	66.56	64.96	68.37	66.63
30	RT	R	1	81.92	81.23	79.67	80.94
N				30	30	30	----
Arithmetic Mean				70.311	70.404	70.923	----
S.D.				12.1950	12.3440	11.7272	----
Minimum				44.79	44.87	44.96	----
Maximum				90.62	94.66	91.67	----
C.V.%				17.34	17.53	16.54	----

TABLE NO. 2
INDIVIDUAL AND MEAN PRE-DOSE SERUM CONCENTRATION OF LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	-0.50 -0.25	-0.03		Average
1	RT	T	2	73.20	71.26	70.30	71.59
2	RT	T	2	70.04	71.59	71.65	71.09
3	TR	T	1	77.99	75.50	76.29	76.59
4	TR	T	1	76.27	76.70	74.38	75.78
5	TR	T	1	76.97	73.89	74.73	75.20
6	RT	T	2	44.97	46.20	45.19	45.45
7	TR	T	1	64.52	64.76	64.26	64.51
8	RT	T	2	77.37	79.93	78.31	78.54
9	TR	T	1	74.99	80.67	77.13	77.60
10	RT	T	2	69.68	69.82	71.25	70.25
11	TR	T	1	53.53	53.49	52.41	53.14
12	RT	T	2	77.05	74.61	81.48	77.71
13	TR	T	1	86.65	87.21	88.27	87.38
14	TR	T	1	65.53	65.71	66.96	66.07
15	TR	T	1	60.55	61.19	65.68	62.47
16	RT	T	2	44.29	45.48	48.01	45.93
17	RT	T	2	76.54	75.07	81.85	77.82
18	RT	T	2	51.03	52.30	53.81	52.38
19	RT	T	2	75.96	76.12	79.60	77.23
20	RT	T	2	81.63	81.48	78.84	80.65
21	TR	T	1	67.58	66.33	67.09	67.00
22	RT	T	2	86.31	82.30	88.52	85.71
23	TR	T	1	74.30	75.68	85.22	78.40
24	TR	T	1	69.18	73.26	72.35	71.60

TABLE NO. 2. Continued on next page...

CONTINUED TABLE NO. 2

INDIVIDUAL AND MEAN PRE-DOSE SERUM CONCENTRATION OF LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	-0.50	-0.25	-0.03	Average
25	RT	T	2	65.43	67.77	71.88	68.36
26	TR	T	1	80.54	78.40	76.75	78.56
27	RT	T	2	96.82	90.76	95.77	94.45
28	TR	T	1	63.22	62.51	62.87	62.87
29	TR	T	1	63.40	62.92	61.50	62.61
30	RT	T	2	69.05	67.98	68.69	68.57
N				30	30	30	----
Arithmetic Mean				70.486	70.363	71.701	----
S.D.				11.8400	11.0122	11.8219	----
Minimum				44.29	45.48	45.19	----
Maximum				96.82	90.76	95.77	----
C.V.%				16.80	15.65	16.49	----

TABLE NO. 3

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
1	RT	R	1	72.36	124.21	140.74	144.84	132.25	133.33	130.97	137.85	136.80	123.07
2	RT	R	1	63.65	86.24	89.63	91.30	87.75	84.04	83.08	89.96	92.20	88.09
3	TR	R	2	77.44	119.48	121.38	121.19	120.15	133.81	127.19	127.21	120.85	114.60
4	TR	R	2	74.94	90.29	119.45	124.98	132.22	136.77	132.15	140.51	137.82	129.81
5	TR	R	2	73.42	103.40	126.58	130.89	128.72	133.43	140.41	139.98	148.71	136.42
6	RT	R	1	57.94	81.71	101.49	100.19	103.11	101.66	95.25	94.39	97.16	82.59
7	TR	R	2	65.49	106.87	129.87	130.99	126.30	118.23	115.52	122.71	118.60	111.90
8	RT	R	1	82.70	94.48	125.85	132.43	140.16	137.81	133.66	134.17	135.42	135.78
9	TR	R	2	72.57	115.62	135.81	138.57	140.70	151.16	146.04	152.68	151.82	140.84
10	RT	R	1	71.01	95.99	124.42	129.42	132.57	134.42	140.31	141.58	150.03	144.10
11	TR	R	2	56.43	74.68	87.43	89.98	95.58	108.19	108.28	96.83	98.51	92.48
12	RT	R	1	82.58	123.16	143.96	141.90	152.53	143.59	139.76	142.23	148.51	137.40
13	TR	R	2	91.48	117.43	138.88	175.60	187.83	197.60	205.24	207.01	197.93	189.79
14	TR	R	2	70.62	97.06	115.19	128.08	126.01	119.77	122.71	117.36	132.00	126.21
15	TR	R	2	64.26	105.94	124.03	126.23	114.58	120.02	114.50	123.59	125.40	123.25
16	RT	R	1	47.85	83.27	93.20	91.13	95.48	98.20	95.74	102.38	116.66	107.04
17	RT	R	1	76.88	129.12	147.90	144.98	143.25	135.63	143.66	142.93	145.39	126.46
18	RT	R	1	76.10	103.36	125.00	119.16	121.67	107.58	115.32	112.35	110.87	105.57
19	RT	R	1	88.70	142.47	145.48	143.65	146.67	146.90	138.60	144.90	140.53	128.99
20	RT	R	1	97.35	146.07	149.89	158.50	158.06	151.69	162.87	160.14	154.70	134.81
21	TR	R	2	62.88	70.50	74.72	104.33	117.24	126.46	120.39	125.86	126.21	126.66
22	RT	R	1	80.12	89.57	95.31	109.65	125.65	126.90	126.63	126.76	137.25	134.97
23	TR	R	2	90.62	125.85	128.65	152.21	135.84	140.42	129.23	131.95	128.96	117.27
24	TR	R	2	71.21	105.94	132.32	131.69	122.29	130.80	133.02	132.03	130.01	121.87

TABLE NO. 3. Continued on next page...

CONTINUED TABLE NO. 3

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.	00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
1	RT	R	1	122.21	122.16	119.34	114.42	121.15	102.39	116.11	111.85	102.42	109.61	101.81	
2	RT	R	1	93.75	88.87	80.29	82.62	81.32	80.04	78.73	89.33	85.28	80.08	77.14	
3	TR	R	2	116.80	115.02	113.80	112.49	115.40	98.69	108.41	114.42	104.78	101.66	99.50	
4	TR	R	2	114.24	113.57	113.25	110.73	112.45	100.04	113.09	113.00	111.21	105.90	102.15	
5	TR	R	2	125.79	124.00	122.74	117.09	121.55	105.35	123.19	114.33	113.82	113.28	109.40	
6	RT	R	1	85.61	89.82	84.73	80.40	84.90	76.23	86.21	79.82	78.53	77.04	72.84	
7	TR	R	2	109.93	108.58	102.61	98.99	106.05	92.68	99.61	98.50	89.74	96.82	84.10	
8	RT	R	1	126.63	124.03	122.83	122.18	124.80	114.79	120.25	112.72	118.35	111.73	109.87	
9	TR	R	2	122.74	132.60	119.45	120.79	119.29	105.35	115.53	123.64	123.95	121.30	119.95	
10	RT	R	1	122.21	130.67	127.57	125.48	126.55	112.21	122.73	116.90	120.72	112.50	99.93	
11	TR	R	2	91.43	85.01	78.07	81.27	86.36	69.01	77.21	80.26	82.05	73.83	74.53	
12	RT	R	1	136.78	129.32	122.85	120.80	124.01	119.22	121.05	129.37	112.79	110.03	105.24	
13	TR	R	2	185.70	190.80	173.93	169.34	164.99	141.82	156.60	161.55	147.86	137.74	127.62	
14	TR	R	2	113.74	112.39	108.70	112.81	115.57	96.20	104.26	101.91	102.85	96.22	93.83	
15	TR	R	2	126.82	124.45	113.96	113.53	112.79	100.31	105.77	111.19	103.00	101.80	94.51	
16	RT	R	1	108.86	105.00	90.48	95.60	93.69	84.20	87.16	86.91	81.24	79.76	72.70	
17	RT	R	1	128.73	131.06	118.03	125.56	119.72	110.31	120.39	121.30	123.34	115.83	102.93	
18	RT	R	1	107.37	107.92	92.79	104.48	98.36	87.22	91.73	96.94	91.85	89.74	85.31	
19	RT	R	1	133.73	132.19	122.49	117.75	114.66	107.53	125.82	128.43	112.54	116.81	100.31	
20	RT	R	1	144.34	140.43	143.62	133.38	131.18	122.77	129.98	120.83	125.60	124.37	105.95	
21	TR	R	2	125.42	115.99	123.31	111.16	110.03	107.44	98.53	111.30	106.15	94.11	84.62	
22	RT	R	1	127.90	126.06	122.34	113.20	124.96	104.98	115.38	103.36	107.12	113.35	104.30	
23	TR	R	2	127.40	123.41	127.10	121.24	118.41	99.29	119.55	122.35	111.51	104.22	105.11	
24	TR	R	2	114.03	116.32	117.69	118.95	108.35	102.67	106.01	100.98	106.25	106.03	93.47	

TABLE NO. 3. Continued on next page...

CONTINUED TABLE NO. 3

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
25	RT	R	1	89.75	104.19	123.37	116.67	131.92	129.41	135.66	134.78	146.66	136.13
26	TR	R	2	67.96	76.05	105.31	126.78	135.65	122.34	130.67	123.96	126.83	119.72
27	RT	R	1	118.35	171.40	185.06	179.51	181.31	173.75	176.73	171.59	157.24	155.79
28	TR	R	2	62.95	71.84	75.52	75.13	78.48	85.78	99.25	100.68	113.47	111.05
29	TR	R	2	68.37	99.65	129.37	127.46	127.04	130.15	140.48	143.41	149.42	152.09
30	RT	R	1	86.02	124.96	156.92	150.69	159.13	139.39	149.14	150.34	149.17	145.49
N				30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				75.400	106.027	123.091	127.938	130.005	129.974	131.082	132.404	134.171	126.675
S.D.				14.0540	23.6510	24.7232	24.2180	24.2844	23.1558	24.2725	24.0168	21.2978	21.2486
Minimum				47.85	70.50	74.72	75.13	78.48	84.04	83.08	89.96	92.20	82.59
Maximum				118.35	171.40	185.06	179.51	187.83	197.60	205.24	207.01	197.93	189.79
C.V.%				18.64	22.31	20.09	18.93	18.68	17.82	18.52	18.14	15.87	16.77

TABLE NO. 3. Continued on next page...

CONTINUED TABLE NO. 3

INDIVIDUAL AND POST DOSE SERUM CONCENTRATION OF MEAN NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
25	RT	R	1	139.32	129.96	123.90	126.00	128.63	110.54	114.80	127.50	117.85	106.94	114.50
26	TR	R	2	115.26	109.68	106.09	108.79	104.86	102.91	105.05	108.17	102.12	94.95	91.04
27	RT	R	1	155.75	157.98	149.08	154.21	146.40	147.33	147.01	140.55	146.81	130.47	126.11
28	TR	R	2	103.78	98.81	95.08	97.50	94.37	85.68	91.75	95.20	87.58	81.43	84.68
29	TR	R	2	140.50	135.52	126.19	129.62	122.14	115.76	104.81	108.18	111.09	99.46	97.42
30	RT	R	1	138.52	130.35	130.48	129.94	126.09	113.58	125.20	122.31	116.42	117.98	104.71
N				30	30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				123.510	121.732	116.426	115.677	115.301	103.885	111.064	111.770	108.161	104.166	98.186
S.D.				19.7090	20.5778	20.1820	18.8461	17.5457	16.8868	18.0491	17.4562	16.9791	15.8376	14.4774
Minimum				85.61	85.01	78.07	80.40	81.32	69.01	77.21	79.82	78.53	73.83	72.70
Maximum				185.70	190.80	173.93	169.34	164.99	147.33	156.60	161.55	147.86	137.74	127.62
C.V.%				15.96	16.90	17.33	16.29	15.22	16.26	16.25	15.62	15.70	15.20	14.74

TABLE NO. 4

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
1	RT	T	2	75.09	103.64	122.67	128.90	128.23	133.37	129.45	125.58	127.56	119.88
2	RT	T	2	70.46	89.50	106.27	105.42	101.08	116.56	112.31	116.41	114.53	109.88
3	TR	T	1	85.61	116.24	124.23	120.70	115.52	117.37	118.43	119.81	113.85	115.76
4	TR	T	1	78.94	97.11	107.12	112.38	107.91	110.14	113.02	106.20	110.53	101.21
5	TR	T	1	79.23	104.63	132.23	141.53	142.09	138.80	129.46	138.28	143.96	128.94
6	RT	T	2	57.76	73.22	88.28	87.60	88.92	87.29	89.66	83.06	94.34	88.57
7	TR	T	1	66.23	85.43	107.33	119.42	125.00	117.04	116.59	120.14	124.28	118.92
8	RT	T	2	92.76	123.81	128.88	139.38	134.66	131.52	130.73	132.69	139.07	126.17
9	TR	T	1	91.16	126.82	136.22	139.95	137.05	135.96	136.70	134.81	135.73	135.95
10	RT	T	2	78.52	94.49	110.69	114.79	111.78	114.33	116.23	121.08	134.01	121.08
11	TR	T	1	57.09	70.75	83.92	86.87	92.39	99.28	103.09	106.52	103.25	104.78
12	RT	T	2	84.58	119.73	132.94	130.69	147.72	136.02	135.89	138.83	139.69	141.23
13	TR	T	1	96.36	107.21	125.30	141.74	149.31	167.66	162.11	157.20	169.75	156.42
14	TR	T	1	68.65	76.60	90.87	105.76	106.47	103.71	110.93	109.04	122.12	107.18
15	TR	T	1	65.62	79.51	96.72	111.58	112.50	115.89	120.80	125.02	120.33	115.64
16	RT	T	2	51.50	86.29	101.15	101.04	87.85	86.07	90.11	89.22	93.71	85.19
17	RT	T	2	81.87	113.70	127.15	142.38	146.15	140.53	146.74	146.94	142.93	129.19
18	RT	T	2	57.94	69.99	77.59	82.85	88.06	90.10	96.97	96.07	96.59	95.61
19	RT	T	2	84.35	115.93	125.63	130.30	128.63	120.06	123.74	130.88	131.09	125.05
20	RT	T	2	82.85	116.09	132.65	146.14	149.99	149.54	143.03	145.37	142.04	133.30
21	TR	T	1	79.94	90.80	90.77	97.35	90.96	94.61	104.39	113.45	123.31	107.26
22	RT	T	2	91.36	106.83	110.72	126.13	150.13	147.76	147.73	146.07	149.08	141.24
23	TR	T	1	79.88	97.39	113.44	112.44	122.73	117.87	117.36	132.04	135.80	130.68
24	TR	T	1	73.49	98.05	120.66	121.64	120.79	124.82	126.39	122.38	118.14	116.53

TABLE NO. 4. Continued on next page...

CONTINUED TABLE NO. 4

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
1	RT	T	2	118.38	110.14	106.26	98.50	111.25	100.10	105.46	102.27	106.30	102.55	98.93
2	RT	T	2	108.53	104.01	95.30	95.01	94.02	90.98	86.45	93.79	93.72	78.80	88.41
3	TR	T	1	107.59	107.36	113.01	112.34	110.25	95.76	107.35	107.67	106.59	101.06	94.94
4	TR	T	1	99.34	103.07	97.06	102.64	100.61	92.17	99.11	101.07	101.80	95.66	85.44
5	TR	T	1	127.02	128.83	118.51	106.35	117.76	107.87	122.62	116.36	114.12	109.08	101.35
6	RT	T	2	80.73	85.05	80.33	75.07	77.35	71.40	75.13	76.27	69.62	73.50	69.42
7	TR	T	1	108.68	108.43	98.07	103.46	104.62	102.65	100.65	107.16	103.52	96.80	82.74
8	RT	T	2	122.96	116.75	125.37	123.71	116.13	112.84	107.78	118.71	119.66	112.26	107.82
9	TR	T	1	118.95	111.29	110.87	112.56	111.99	101.83	119.32	114.72	106.04	107.86	98.80
10	RT	T	2	111.99	110.29	117.56	108.99	108.74	97.11	104.82	102.55	103.51	99.97	92.85
11	TR	T	1	97.09	93.21	87.95	88.51	91.60	80.54	86.80	83.22	90.45	75.13	80.24
12	RT	T	2	133.68	128.02	132.31	129.76	130.40	102.25	118.02	119.84	114.23	99.49	99.61
13	TR	T	1	161.62	144.94	140.54	138.75	146.35	130.19	132.14	132.14	129.65	123.63	112.79
14	TR	T	1	100.64	103.26	99.56	110.22	108.18	91.47	103.15	102.40	97.66	90.83	85.22
15	TR	T	1	111.63	110.31	108.44	106.16	102.43	91.80	103.02	104.10	105.15	97.79	93.45
16	RT	T	2	89.15	82.06	80.86	78.21	76.74	68.53	71.06	79.48	77.61	67.05	66.86
17	RT	T	2	123.06	124.15	115.72	118.96	123.24	114.08	113.82	117.11	115.49	116.01	107.00
18	RT	T	2	93.97	94.38	89.66	88.55	86.71	72.24	80.47	85.81	81.80	72.25	72.86
19	RT	T	2	127.02	126.00	117.00	111.62	108.99	98.70	109.10	114.19	104.66	109.96	104.53
20	RT	T	2	140.94	136.57	132.33	133.16	131.38	114.74	123.32	125.89	122.23	116.78	103.88
21	TR	T	1	105.36	103.36	99.43	101.85	111.68	90.85	99.30	98.37	98.16	89.70	83.20
22	RT	T	2	137.55	134.10	137.94	122.63	101.64	109.40	114.09	108.57	117.52	106.66	98.56
23	TR	T	1	112.28	116.18	104.82	111.29	111.69	112.75	114.16	116.09	112.30	103.99	111.42
24	TR	T	1	123.98	122.11	119.01	117.24	109.82	105.03	112.47	104.77	105.57	103.86	101.47

TABLE NO. 4. Continued on next page...

CONTINUED TABLE NO. 4

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
25	RT	T	2	69.40	96.73	102.51	98.58	103.91	114.52	113.83	107.97	119.30	111.28
26	TR	T	1	74.29	89.18	96.45	111.06	135.07	116.68	123.82	108.99	120.38	107.03
27	RT	T	2	101.00	147.94	175.07	169.93	164.00	167.35	167.98	163.95	172.43	153.49
28	TR	T	1	65.52	85.13	92.29	95.66	107.74	87.26	97.49	99.41	104.75	94.87
29	TR	T	1	68.82	109.20	128.84	127.47	129.10	134.44	133.21	135.39	143.51	124.30
30	RT	T	2	72.09	102.55	120.83	131.69	132.72	140.27	131.29	129.40	135.51	126.55
N				30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				76.079	99.816	113.647	119.379	121.949	121.894	122.983	123.407	127.386	119.106
S.D.				12.1683	18.1900	20.2757	20.3997	21.5333	21.9994	19.1763	19.3513	19.5140	17.5145
Minimum				51.50	69.99	77.59	82.85	87.85	86.07	89.66	83.06	93.71	85.19
Maximum				101.00	147.94	175.07	169.93	164.00	167.66	167.98	163.95	172.43	156.42
C.V.%				15.99	18.22	17.84	17.09	17.66	18.05	15.59	15.68	15.32	14.70

TABLE NO. 4. Continued on next page...

CONTINUED TABLE NO. 4

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF NON-BASELINE-CORRECTED -LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
25	RT	T	2	106.79	107.75	106.42	102.64	104.27	93.87	103.79	98.28	102.00	94.68	99.33
26	TR	T	1	110.60	108.47	105.07	112.21	107.60	101.84	107.94	110.32	105.91	97.62	96.47
27	RT	T	2	152.25	150.15	153.24	139.27	143.39	132.16	137.13	137.59	135.61	122.41	120.46
28	TR	T	1	104.99	87.88	92.24	92.32	91.97	83.70	93.62	88.32	88.30	82.99	74.98
29	TR	T	1	120.20	116.85	122.71	117.89	126.11	107.06	110.99	108.82	103.91	97.66	90.05
30	RT	T	2	119.98	125.13	120.40	116.83	121.03	104.24	117.03	111.55	108.39	104.33	96.25
N				30	30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				115.89 8	113.33 7	110.93 3	109.22 3	109.59 8	99.272	106.00 4	106.24 8	104.71 6	98.345	93.978
S.D.				17.758 4	16.648 3	17.746 5	15.834 4	16.497 3	15.074 9	15.340 6	14.542 9	14.195 7	14.610 8	13.072 8
Minimum				80.73	82.06	80.33	75.07	76.74	68.53	71.06	76.27	69.62	67.05	66.86
Maximum				161.62	150.15	153.24	139.27	146.35	132.16	137.13	137.59	135.61	123.63	120.46
C.V.%				15.32	14.69	16.00	14.50	15.05	15.19	14.47	13.69	13.56	14.86	13.91

TABLE NO. 5

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
1	RT	R	1	0.16	52.01	68.54	72.64	60.05	61.13	58.77	65.65	64.60	50.87
2	RT	R	1	8.61	31.20	34.59	36.26	32.71	29.00	28.04	34.92	37.16	33.05
3	TR	R	2	2.87	44.91	46.81	46.62	45.58	59.24	52.62	52.64	46.28	40.03
4	TR	R	2	0.50	15.85	45.01	50.54	57.78	62.33	57.71	66.07	63.38	55.37
5	TR	R	2	1.47	31.45	54.63	58.94	56.77	61.48	68.46	68.03	76.76	64.47
6	RT	R	1	12.78	36.55	56.33	55.03	57.95	56.50	50.09	49.23	52.00	37.43
7	TR	R	2	7.13	48.51	71.51	72.63	67.94	59.87	57.16	64.35	60.24	53.54
8	RT	R	1	6.79	18.57	49.94	56.52	64.25	61.90	57.75	58.26	59.51	59.87
9	TR	R	2	3.65	46.70	66.89	69.65	71.78	82.24	77.12	83.76	82.90	71.92
10	RT	R	1	1.79	26.77	55.20	60.20	63.35	65.20	71.09	72.36	80.81	74.88
11	TR	R	2	5.68	23.93	36.68	39.23	44.83	57.44	57.53	46.08	47.76	41.73
12	RT	R	1	0.00	39.29	60.09	58.03	68.66	59.72	55.89	58.36	64.64	53.53
13	TR	R	2	0.00	25.91	47.36	84.08	96.31	106.08	113.72	115.49	106.41	98.27
14	TR	R	2	5.25	31.69	49.82	62.71	60.64	54.40	57.34	51.99	66.63	60.84
15	TR	R	2	4.90	46.58	64.67	66.87	55.22	60.66	55.14	64.23	66.04	63.89
16	RT	R	1	1.10	36.52	46.45	44.38	48.73	51.45	48.99	55.63	69.91	60.29
17	RT	R	1	1.65	53.89	72.67	69.75	68.02	60.40	68.43	67.70	70.16	51.23
18	RT	R	1	8.15	35.41	57.05	51.21	53.72	39.63	47.37	44.40	42.92	37.62
19	RT	R	1	8.75	62.52	65.53	63.70	66.72	66.95	58.65	64.95	60.58	49.04
20	RT	R	1	15.38	64.10	67.92	76.53	76.09	69.72	80.90	78.17	72.73	52.84
21	TR	R	2	1.13	8.75	12.97	42.58	55.49	64.71	58.64	64.11	64.46	64.91
22	RT	R	1	2.58	12.03	17.77	32.11	48.11	49.36	49.09	49.22	59.71	57.43
23	TR	R	2	4.91	40.14	42.94	66.50	50.13	54.71	43.52	46.24	43.25	31.56
24	TR	R	2	1.00	35.73	62.11	61.48	52.08	60.59	62.81	61.82	59.80	51.66

TABLE NO. 5. Continued on next page...



CONTINUED TABLE NO. 5

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
1	RT	R	1	50.01	49.96	47.14	42.22	48.95	30.19	43.91	39.65	30.22	37.41	29.61
2	RT	R	1	38.71	33.83	25.25	27.58	26.28	25.00	23.69	34.29	30.24	25.04	22.10
3	TR	R	2	42.23	40.45	39.23	37.92	40.83	24.12	33.84	39.85	30.21	27.09	24.93
4	TR	R	2	39.80	39.13	38.81	36.29	38.01	25.60	38.65	38.56	36.77	31.46	27.71
5	TR	R	2	53.84	52.05	50.79	45.14	49.60	33.40	51.24	42.38	41.87	41.33	37.45
6	RT	R	1	40.45	44.66	39.57	35.24	39.74	31.07	41.05	34.66	33.37	31.88	27.68
7	TR	R	2	51.57	50.22	44.25	40.63	47.69	34.32	41.25	40.14	31.38	38.46	25.74
8	RT	R	1	50.72	48.12	46.92	46.27	48.89	38.88	44.34	36.81	42.44	35.82	33.96
9	TR	R	2	53.82	63.68	50.53	51.87	50.37	36.43	46.61	54.72	55.03	52.38	51.03
10	RT	R	1	52.99	61.45	58.35	56.26	57.33	42.99	53.51	47.68	51.50	43.28	30.71
11	TR	R	2	40.68	34.26	27.32	30.52	35.61	18.26	26.46	29.51	31.30	23.08	23.78
12	RT	R	1	52.91	45.45	38.98	36.93	40.14	35.35	37.18	45.50	28.92	26.16	21.37
13	TR	R	2	94.18	99.28	82.41	77.82	73.47	50.30	65.08	70.03	56.34	46.22	36.10
14	TR	R	2	48.37	47.02	43.33	47.44	50.20	30.83	38.89	36.54	37.48	30.85	28.46
15	TR	R	2	67.46	65.09	54.60	54.17	53.43	40.95	46.41	51.83	43.64	42.44	35.15
16	RT	R	1	62.11	58.25	43.73	48.85	46.94	37.45	40.41	40.16	34.49	33.01	25.95
17	RT	R	1	53.50	55.83	42.80	50.33	44.49	35.08	45.16	46.07	48.11	40.60	27.70
18	RT	R	1	39.42	39.97	24.84	36.53	30.41	19.27	23.78	28.99	23.90	21.79	17.36
19	RT	R	1	53.78	52.24	42.54	37.80	34.71	27.58	45.87	48.48	32.59	36.86	20.36
20	RT	R	1	62.37	58.46	61.65	51.41	49.21	40.80	48.01	38.86	43.63	42.40	23.98
21	TR	R	2	63.67	54.24	61.56	49.41	48.28	45.69	36.78	49.55	44.40	32.36	22.87
22	RT	R	1	50.36	48.52	44.80	35.66	47.42	27.44	37.84	25.82	29.58	35.81	26.76
23	TR	R	2	41.69	37.70	41.39	35.53	32.70	13.58	33.84	36.64	25.80	18.51	19.40
24	TR	R	2	43.82	46.11	47.48	48.74	38.14	32.46	35.80	30.77	36.04	35.82	23.26

TABLE NO. 5. Continued on next page...

CONTINUED TABLE NO. 5

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
25	RT	R	1	4.28	18.72	37.90	31.20	46.45	43.94	50.19	49.31	61.19	50.66
26	TR	R	2	0.09	8.18	37.44	58.91	67.78	54.47	62.80	56.09	58.96	51.85
27	RT	R	1	30.19	83.24	96.90	91.35	93.15	85.59	88.57	83.43	69.08	67.63
28	TR	R	2	0.00	8.25	11.93	11.54	14.89	22.19	35.66	37.09	49.88	47.46
29	TR	R	2	1.74	33.02	62.74	60.83	60.41	63.52	73.85	76.78	82.79	85.46
30	RT	R	1	5.08	44.02	75.98	69.75	78.19	58.45	68.20	69.40	68.23	64.55
N				30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				4.920	35.481	52.545	57.392	59.459	59.428	60.536	61.858	63.625	56.129
S.D.				6.1428	17.7356	18.8418	16.8510	15.9814	15.3604	16.1620	16.0827	14.1260	14.7009
Minimum				0.00	8.18	11.93	11.54	14.89	22.19	28.04	34.92	37.16	31.56
Maximum				30.19	83.24	96.90	91.35	96.31	106.08	113.72	115.49	106.41	98.27
C.V.%				124.86	49.99	35.86	29.36	26.88	25.85	26.70	26.00	22.20	26.19

TABLE NO. 5. Continued on next page...

CONTINUED TABLE NO. 5

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF REFERENCE PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
25	RT	R	1	53.85	44.49	38.43	40.53	43.16	25.07	29.33	42.03	32.38	21.47	29.03
26	TR	R	2	47.39	41.81	38.22	40.92	36.99	35.04	37.18	40.30	34.25	27.08	23.17
27	RT	R	1	67.59	69.82	60.92	66.05	58.24	59.17	58.85	52.39	58.65	42.31	37.95
28	TR	R	2	40.19	35.22	31.49	33.91	30.78	22.09	28.16	31.61	23.99	17.84	21.09
29	TR	R	2	73.87	68.89	59.56	62.99	55.51	49.13	38.18	41.55	44.46	32.83	30.79
30	RT	R	1	57.58	49.41	49.54	49.00	45.15	32.64	44.26	41.37	35.48	37.04	23.77
N				30	30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				52.964	51.186	45.880	45.131	44.755	33.339	40.518	41.224	37.615	33.620	27.640
S.D.				12.1797	13.4526	12.1901	11.0316	9.8504	10.0805	9.5544	9.0137	9.4714	8.5608	6.9543
Minimum				38.71	33.83	24.84	27.58	26.28	13.58	23.69	25.82	23.90	17.84	17.36
Maximum				94.18	99.28	82.41	77.82	73.47	59.17	65.08	70.03	58.65	52.38	51.03
C.V.%				23.00	26.28	26.57	24.44	22.01	30.24	23.58	21.87	25.18	25.46	25.16

TABLE NO. 6

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
1	RT	T	2	3.50	32.05	51.08	57.31	56.64	61.78	57.86	53.99	55.97	48.29
2	RT	T	2	0.00	18.41	35.18	34.33	29.99	45.47	41.22	45.32	43.44	38.79
3	TR	T	1	9.02	39.65	47.64	44.11	38.93	40.78	41.84	43.22	37.26	39.17
4	TR	T	1	3.16	21.33	31.34	36.60	32.13	34.36	37.24	30.42	34.75	25.43
5	TR	T	1	4.03	29.43	57.03	66.33	66.89	63.60	54.26	63.08	68.76	53.74
6	RT	T	2	12.31	27.77	42.83	42.15	43.47	41.84	44.21	37.61	48.89	43.12
7	TR	T	1	1.72	20.92	42.82	54.91	60.49	52.53	52.08	55.63	59.77	54.41
8	RT	T	2	14.22	45.27	50.34	60.84	56.12	52.98	52.19	54.15	60.53	47.63
9	TR	T	1	13.56	49.22	58.62	62.35	59.45	58.36	59.10	57.21	58.13	58.35
10	RT	T	2	8.27	24.24	40.44	44.54	41.53	44.08	45.98	50.83	63.76	50.83
11	TR	T	1	3.95	17.61	30.78	33.73	39.25	46.14	49.95	53.38	50.11	51.64
12	RT	T	2	6.87	42.02	55.23	52.98	70.01	58.31	58.18	61.12	61.98	63.52
13	TR	T	1	8.98	19.83	37.92	54.36	61.93	80.28	74.73	69.82	82.37	69.04
14	TR	T	1	2.58	10.53	24.80	39.69	40.40	37.64	44.86	42.97	56.05	41.11
15	TR	T	1	3.15	17.04	34.25	49.11	50.03	53.42	58.33	62.55	57.86	53.17
16	RT	T	2	5.57	40.36	55.22	55.11	41.92	40.14	44.18	43.29	47.78	39.26
17	RT	T	2	4.05	35.88	49.33	64.56	68.33	62.71	68.92	69.12	65.11	51.37
18	RT	T	2	5.56	17.61	25.21	30.47	35.68	37.72	44.59	43.69	44.21	43.23
19	RT	T	2	7.12	38.70	48.40	53.07	51.40	42.83	46.51	53.65	53.86	47.82
20	RT	T	2	2.20	35.44	52.00	65.49	69.34	68.89	62.38	64.72	61.39	52.65
21	TR	T	1	12.94	23.80	23.77	30.35	23.96	27.61	37.39	46.45	56.31	40.26
22	RT	T	2	5.65	21.12	25.01	40.42	64.42	62.05	62.02	60.36	63.37	55.53
23	TR	T	1	1.48	18.99	35.04	34.04	44.33	39.47	38.96	53.64	57.40	52.28
24	TR	T	1	1.89	26.45	49.06	50.04	49.19	53.22	54.79	50.78	46.54	44.93

TABLE NO. 6. Continued on next page...

CONTINUED TABLE NO. 6

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
1	RT	T	2	46.79	38.55	34.67	26.91	39.66	28.51	33.87	30.68	34.71	30.96	27.34
2	RT	T	2	37.44	32.92	24.21	23.92	22.93	19.89	15.36	22.70	22.63	7.71	17.32
3	TR	T	1	31.00	30.77	36.42	35.75	33.66	19.17	30.76	31.08	30.00	24.47	18.35
4	TR	T	1	23.56	27.29	21.28	26.86	24.83	16.39	23.33	25.29	26.02	19.88	9.66
5	TR	T	1	51.82	53.63	43.31	31.15	42.56	32.67	47.42	41.16	38.92	33.88	26.15
6	RT	T	2	35.28	39.60	34.88	29.62	31.90	25.95	29.68	30.82	24.17	28.05	23.97
7	TR	T	1	44.17	43.92	33.56	38.95	40.11	38.14	36.14	42.65	39.01	32.29	18.23
8	RT	T	2	44.42	38.21	46.83	45.17	37.59	34.30	29.24	40.17	41.12	33.72	29.28
9	TR	T	1	41.35	33.69	33.27	34.96	34.39	24.23	41.72	37.12	28.44	30.26	21.20
10	RT	T	2	41.74	40.04	47.31	38.74	38.49	26.86	34.57	32.30	33.26	29.72	22.60
11	TR	T	1	43.95	40.07	34.81	35.37	38.46	27.40	33.66	30.08	37.31	21.99	27.10
12	RT	T	2	55.97	50.31	54.60	52.05	52.69	24.54	40.31	42.13	36.52	21.78	21.90
13	TR	T	1	74.24	57.56	53.16	51.37	58.97	42.81	44.76	44.76	42.27	36.25	25.41
14	TR	T	1	34.57	37.19	33.49	44.15	42.11	25.40	37.08	36.33	31.59	24.76	19.15
15	TR	T	1	49.16	47.84	45.97	43.69	39.96	29.33	40.55	41.63	42.68	35.32	30.98
16	RT	T	2	43.22	36.13	34.93	32.28	30.81	22.60	25.13	33.55	31.68	21.12	20.93
17	RT	T	2	45.24	46.33	37.90	41.14	45.42	36.26	36.00	39.29	37.67	38.19	29.18
18	RT	T	2	41.59	42.00	37.28	36.17	34.33	19.86	28.09	33.43	29.42	19.87	20.48
19	RT	T	2	49.79	48.77	39.77	34.39	31.76	21.47	31.87	36.96	27.43	32.73	27.30
20	RT	T	2	60.29	55.92	51.68	52.51	50.73	34.09	42.67	45.24	41.58	36.13	23.23
21	TR	T	1	38.36	36.36	32.43	34.85	44.68	23.85	32.30	31.37	31.16	22.70	16.20
22	RT	T	2	51.84	48.39	52.23	36.92	15.93	23.69	28.38	22.86	31.81	20.95	12.85
23	TR	T	1	33.88	37.78	26.42	32.89	33.29	34.35	35.76	37.69	33.90	25.59	33.02
24	TR	T	1	52.38	50.51	47.41	45.64	38.22	33.43	40.87	33.17	33.97	32.26	29.87

TABLE NO. 6. Continued on next page...

CONTINUED TABLE NO. 6

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00
25	RT	T	2	1.04	28.37	34.15	30.22	35.55	46.16	45.47	39.61	50.94	42.92
26	TR	T	1	0.00	10.62	17.89	32.50	56.51	38.12	45.26	30.43	41.82	28.47
27	RT	T	2	6.55	53.49	80.62	75.48	69.55	72.90	73.53	69.50	77.98	59.04
28	TR	T	1	2.65	22.26	29.42	32.79	44.87	24.39	34.62	36.54	41.88	32.00
29	TR	T	1	6.21	46.59	66.23	64.86	66.49	71.83	70.60	72.78	80.90	61.69
30	RT	T	2	3.52	33.98	52.26	63.12	64.15	71.70	62.72	60.83	66.94	57.98
N				30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				5.392	28.966	42.797	48.529	51.098	51.044	52.132	52.556	56.535	48.256
S.D.				3.9730	11.5670	14.2158	13.3110	13.4811	14.2185	11.1734	11.6491	11.9663	10.1766
Minimum				0.00	10.53	17.89	30.22	23.96	24.39	34.62	30.42	34.75	25.43
Maximum				14.22	53.49	80.62	75.48	70.01	80.28	74.73	72.78	82.37	69.04
C.V.%				73.68	39.93	33.22	27.43	26.38	27.86	21.43	22.16	21.17	21.09

TABLE NO. 6. Continued on next page...

CONTINUED TABLE NO. 6

INDIVIDUAL AND MEAN POST DOSE SERUM CONCENTRATION OF BASELINE-CORRECTED-LEVOTHYROXINE IN (ng/mL) OF TEST PRODUCT

Subject No.	Sequence	Formulation	Period	5.50	6.00	8.00	10.00	12.00	18.00	24.00	30.00	36.00	48.00	72.00
25	RT	T	2	38.43	39.39	38.06	34.28	35.91	25.51	35.43	29.92	33.64	26.32	30.97
26	TR	T	1	32.04	29.91	26.51	33.65	29.04	23.28	29.38	31.76	27.35	19.06	17.91
27	RT	T	2	57.80	55.70	58.79	44.82	48.94	37.71	42.68	43.14	41.16	27.96	26.01
28	TR	T	1	42.12	25.01	29.37	29.45	29.10	20.83	30.75	25.45	25.43	20.12	12.11
29	TR	T	1	57.59	54.24	60.10	55.28	63.50	44.45	48.38	46.21	41.30	35.05	27.44
30	RT	T	2	51.41	56.56	51.83	48.26	52.46	35.67	48.46	42.98	39.82	35.76	27.68
N				30	30	30	30	30	30	30	30	30	30	30
Arithmetic Mean				45.048	42.486	40.083	38.373	38.748	28.421	35.153	35.397	33.866	27.495	23.127
S.D.				10.3532	9.2492	10.4591	8.3050	10.4652	7.3122	7.7315	6.7708	5.9118	7.0821	6.0232
Minimum				23.56	25.01	21.28	23.92	15.93	16.39	15.36	22.70	22.63	7.71	9.66
Maximum				74.24	57.56	60.10	55.28	63.50	44.45	48.46	46.21	42.68	38.19	33.02
C.V.%				22.98	21.77	26.09	21.64	27.01	25.73	21.99	19.13	17.46	25.76	26.04

TABLE NO. 7
HEMOLYSED SAMPLES

Subject No.	Period	Hemolysed Samples Time Points (Hours)
16	1	8.00
28	1	18.00
02	2	-0.50
07	2	-0.50
15	2	4.00
21	2	-0.03
22	2	-0.03
23	2	12.00

Figure 1

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=1

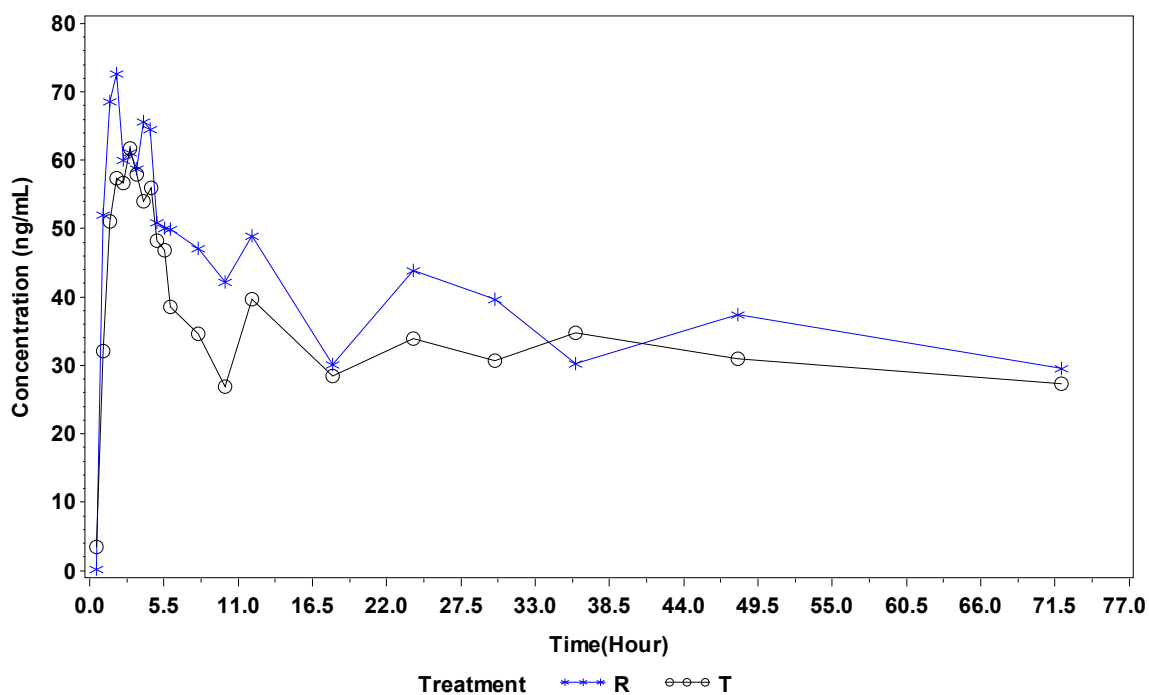


Figure 2

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=1

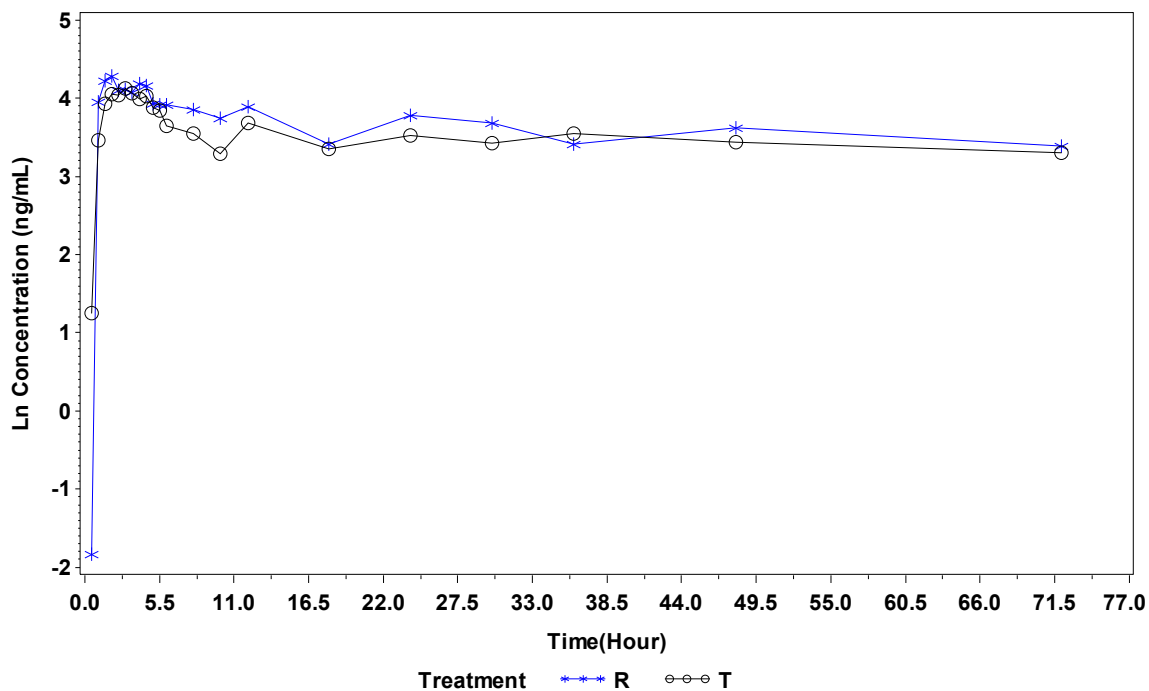


Figure 3

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=2

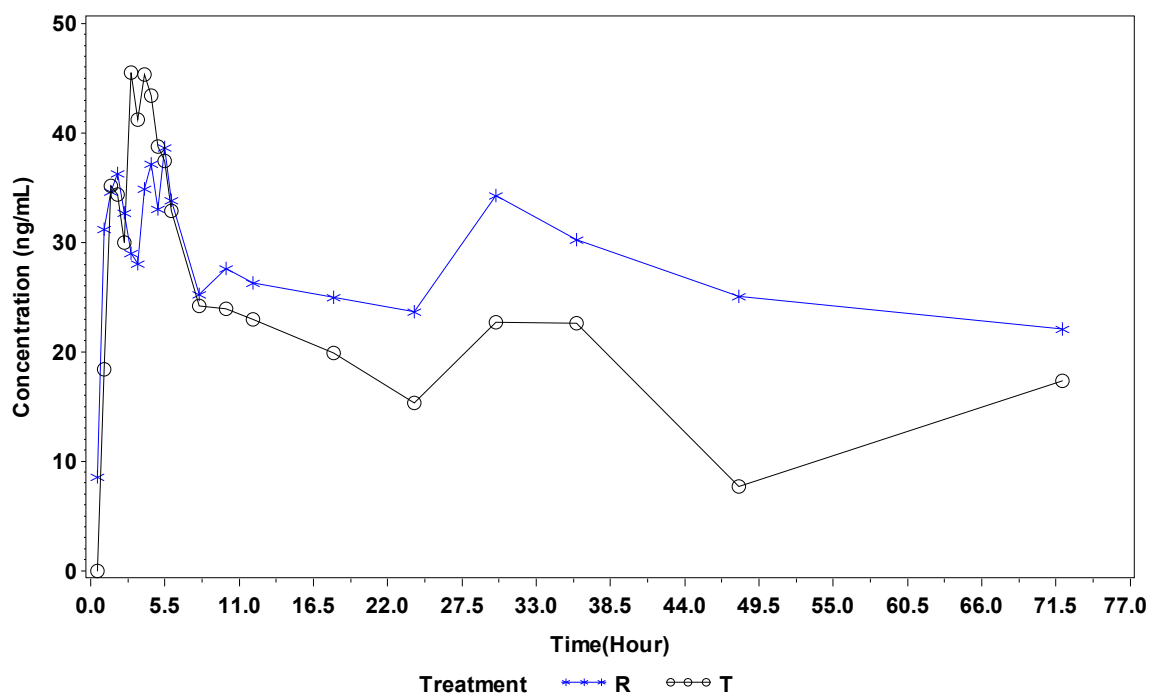


Figure 4

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=2

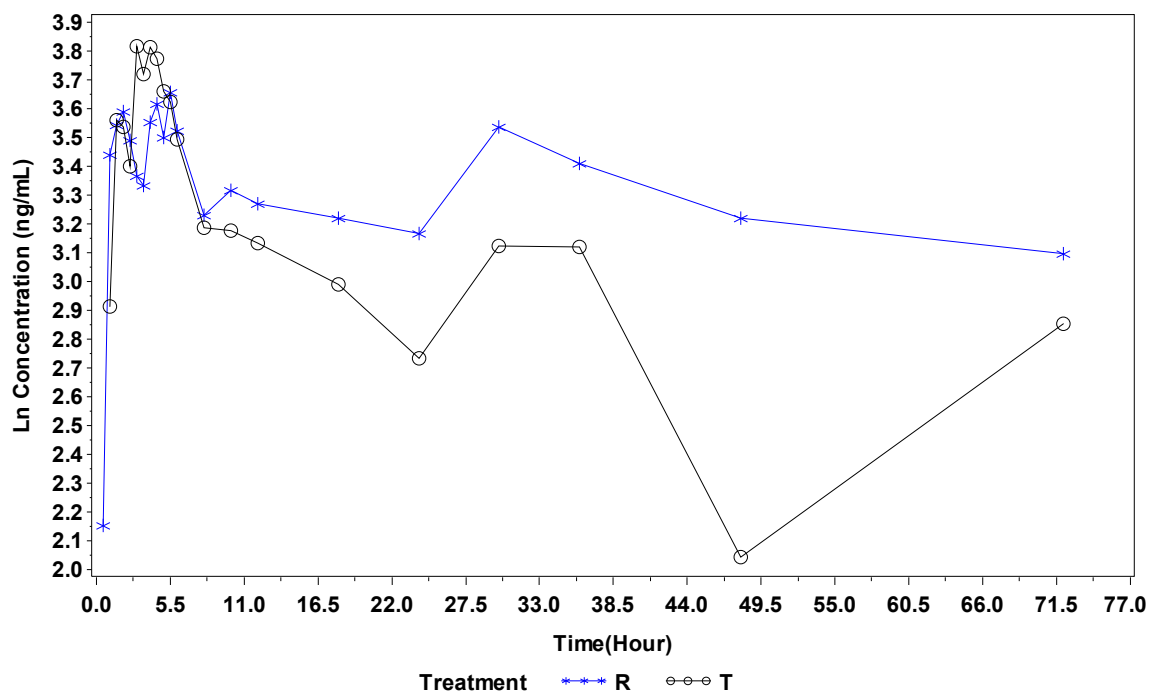


Figure 5

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=3

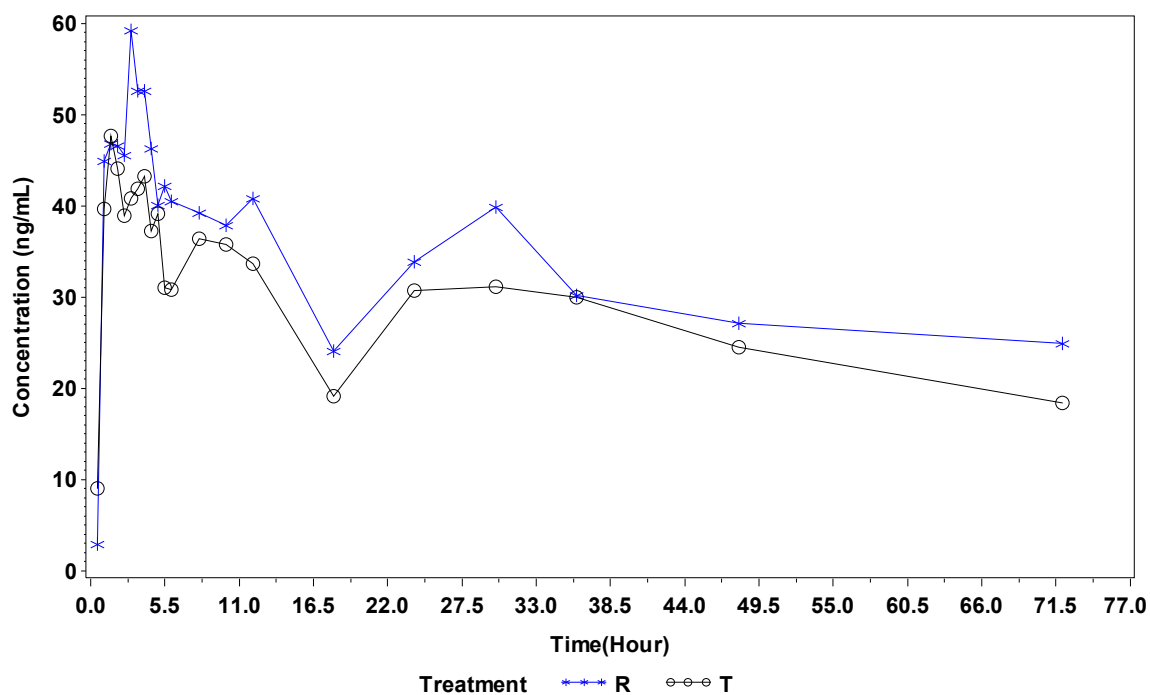


Figure 6

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=3

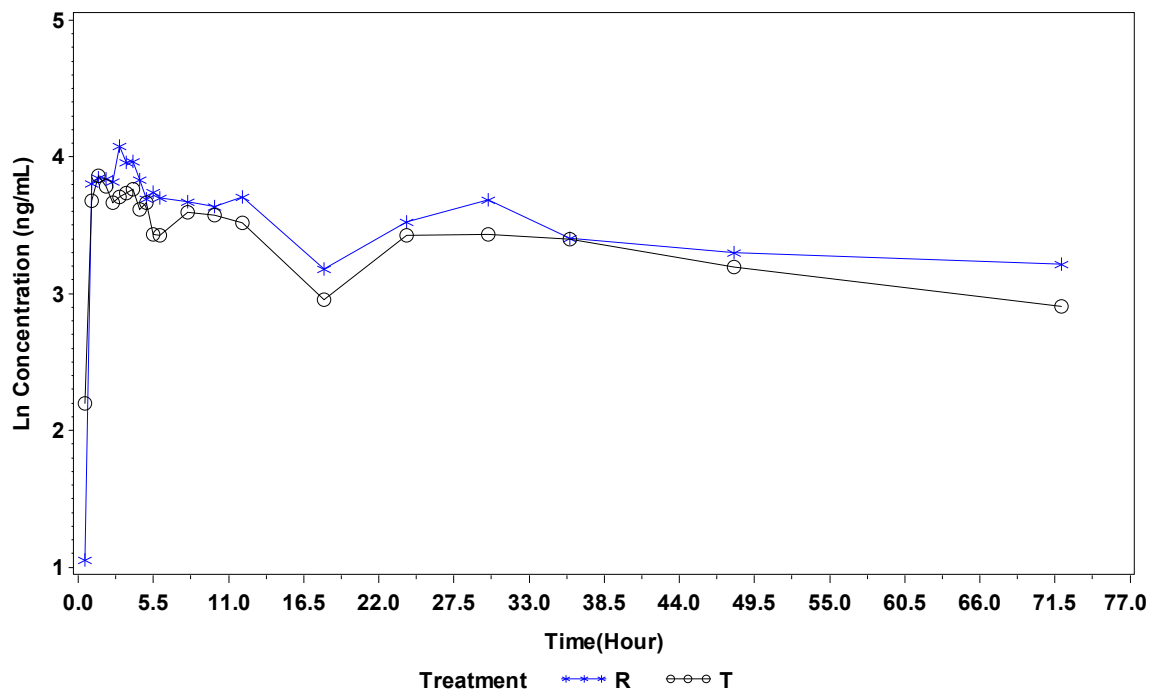


Figure 7

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=4

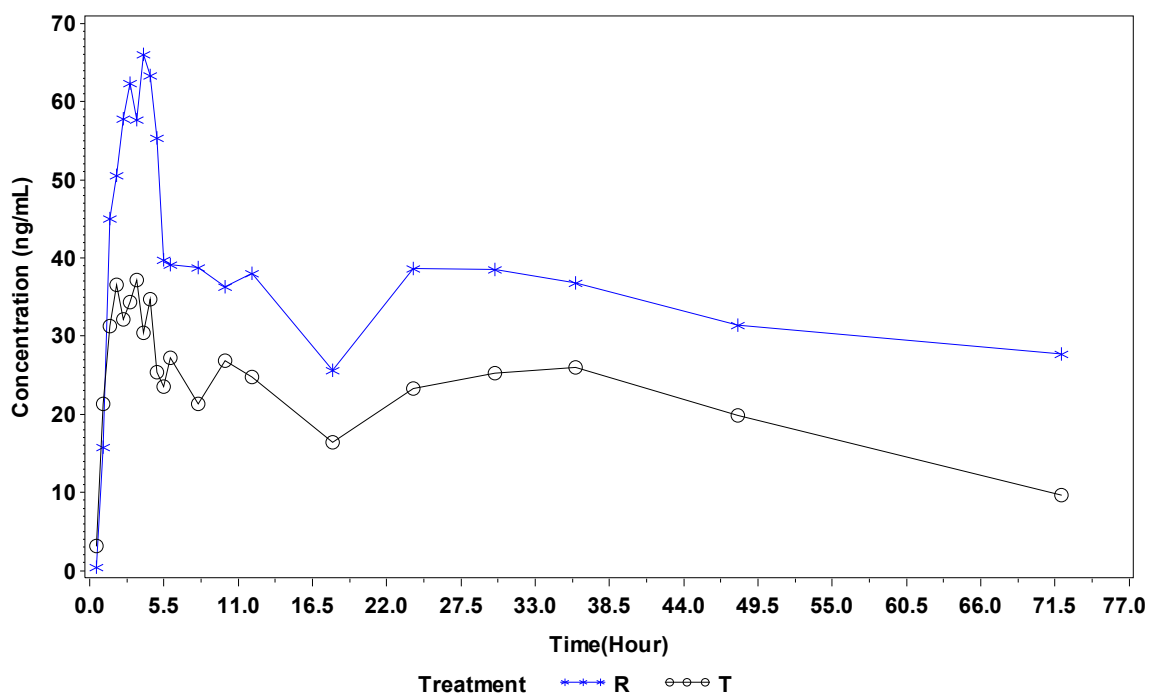


Figure 8

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=4

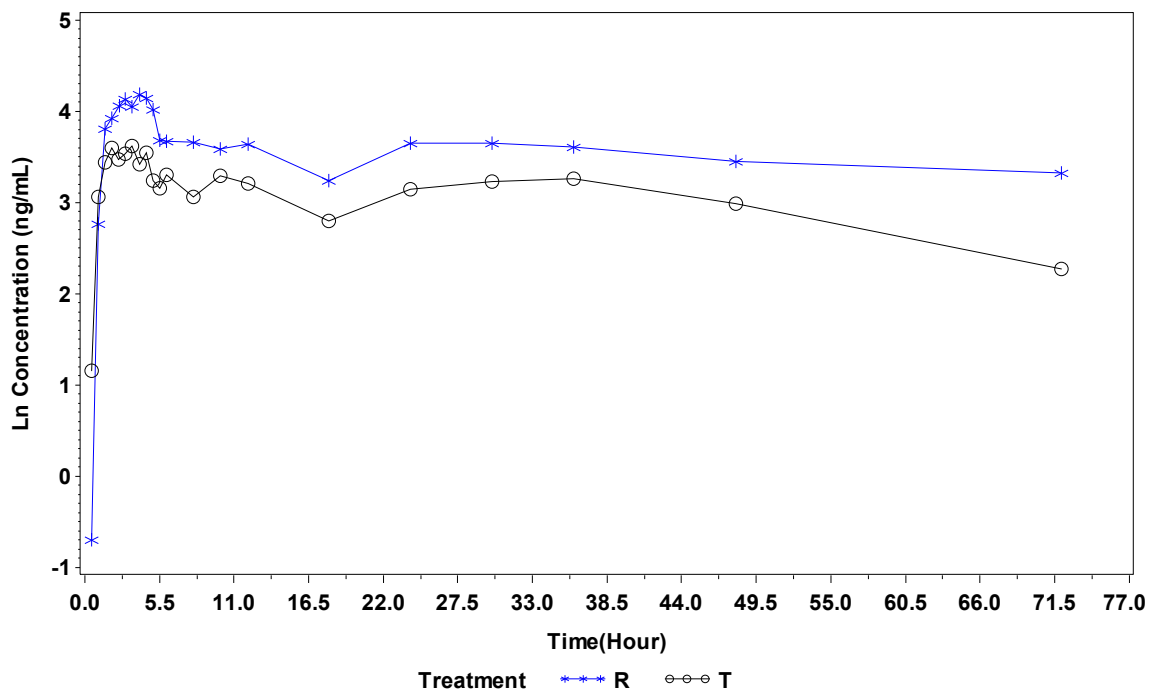


Figure 9

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=5

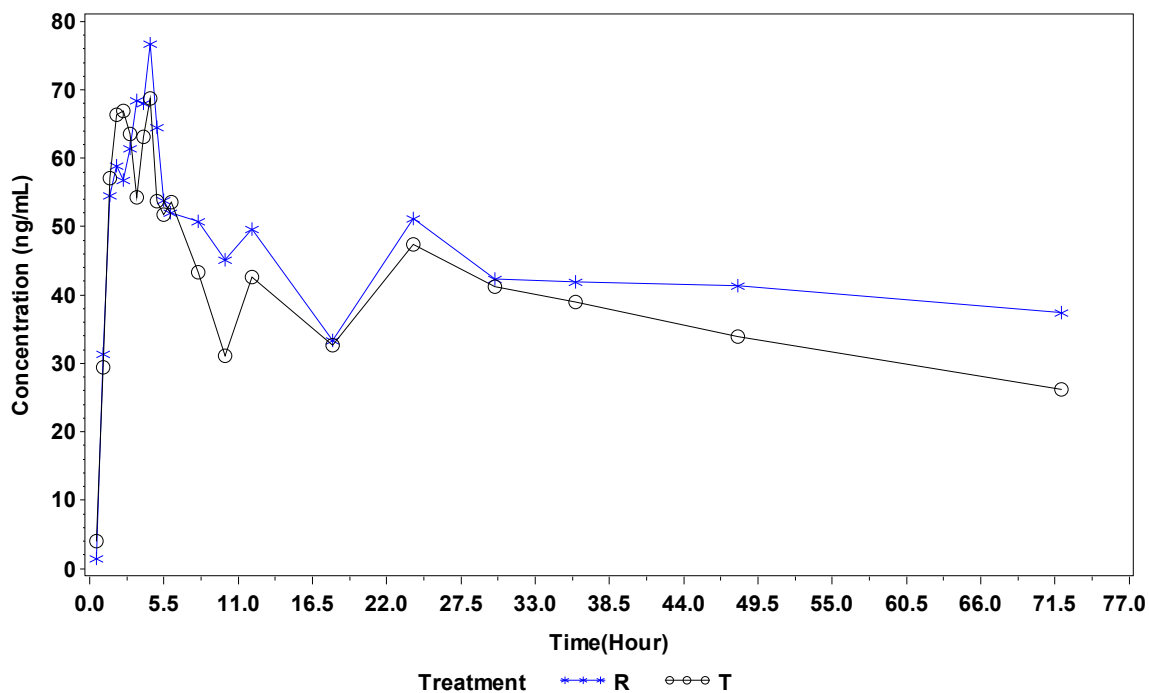


Figure 10

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=5

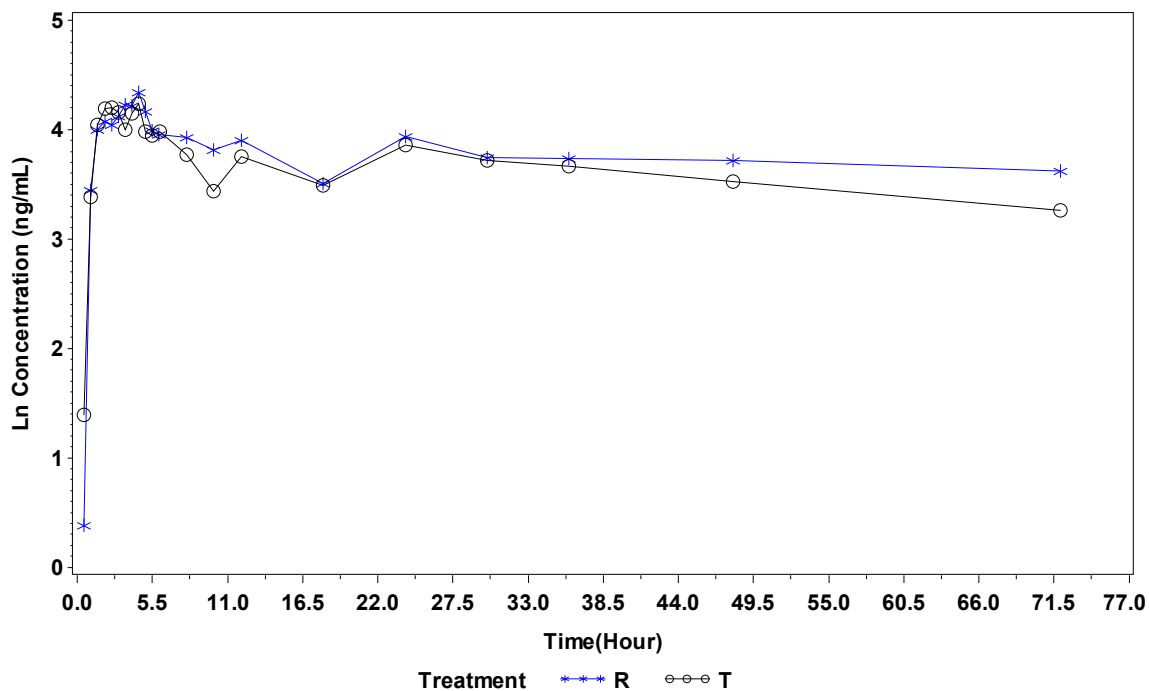


Figure 11

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=6

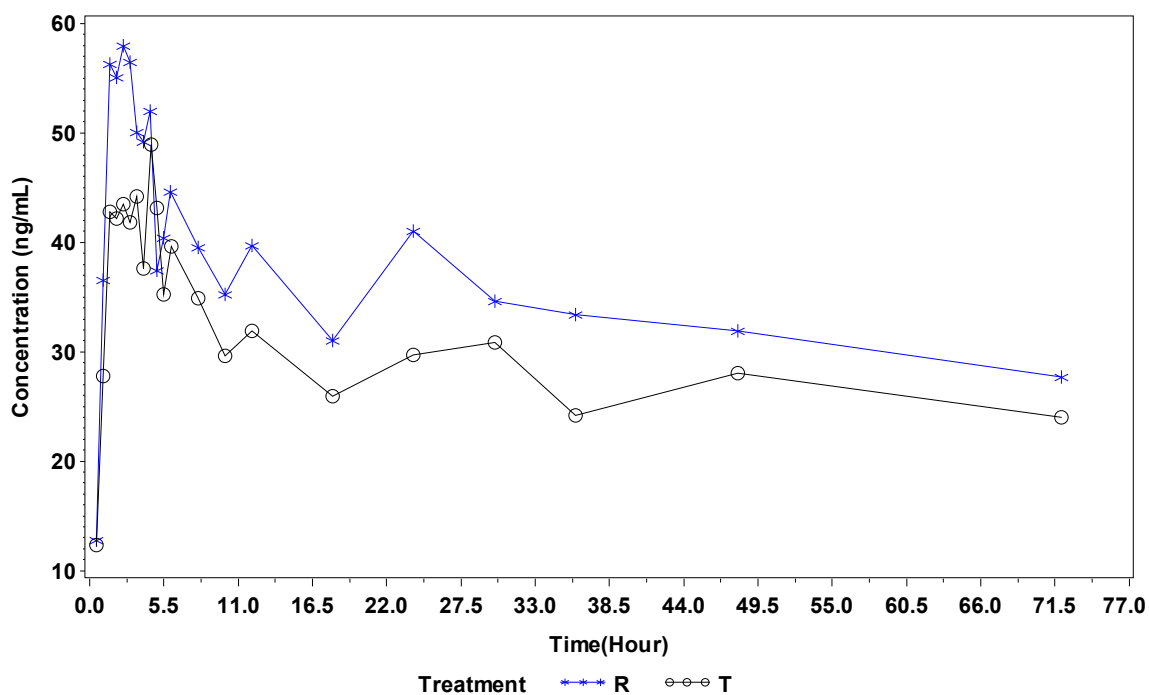


Figure 12

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=6

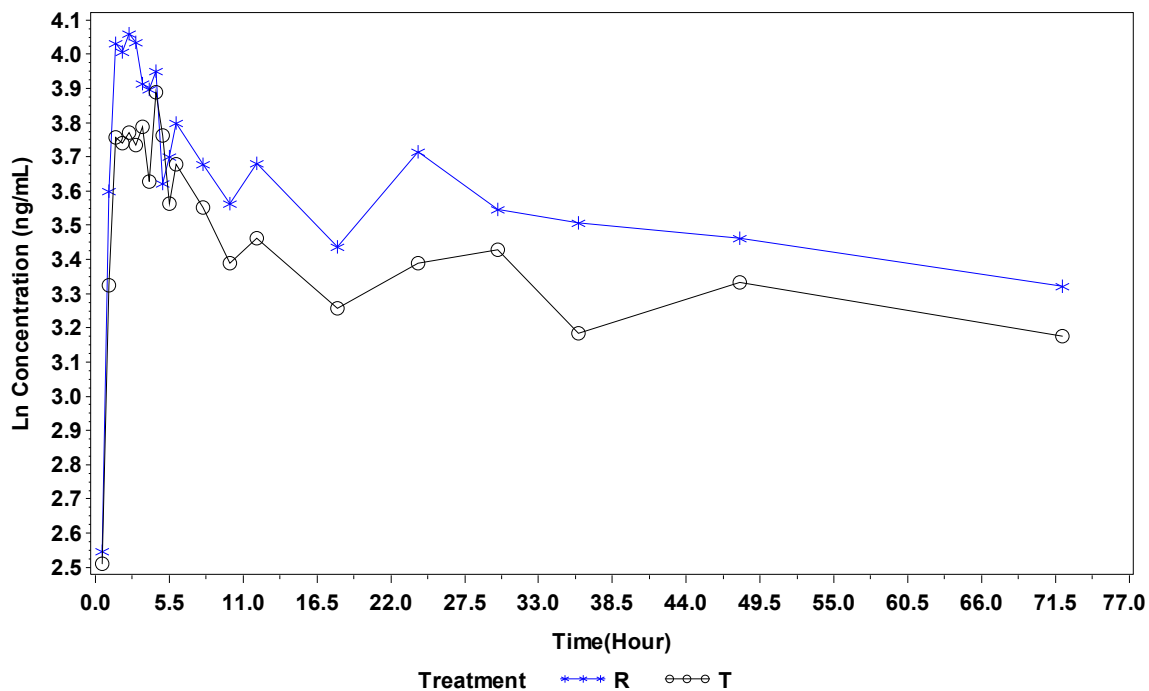


Figure 13

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=7

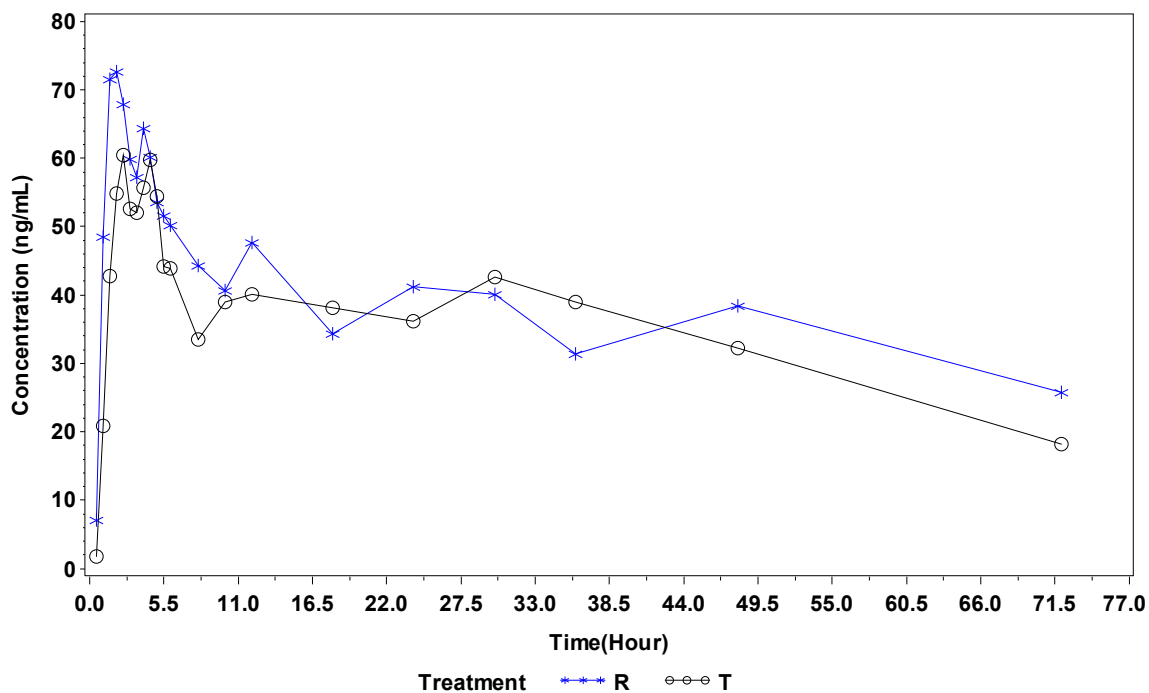


Figure 14

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=7

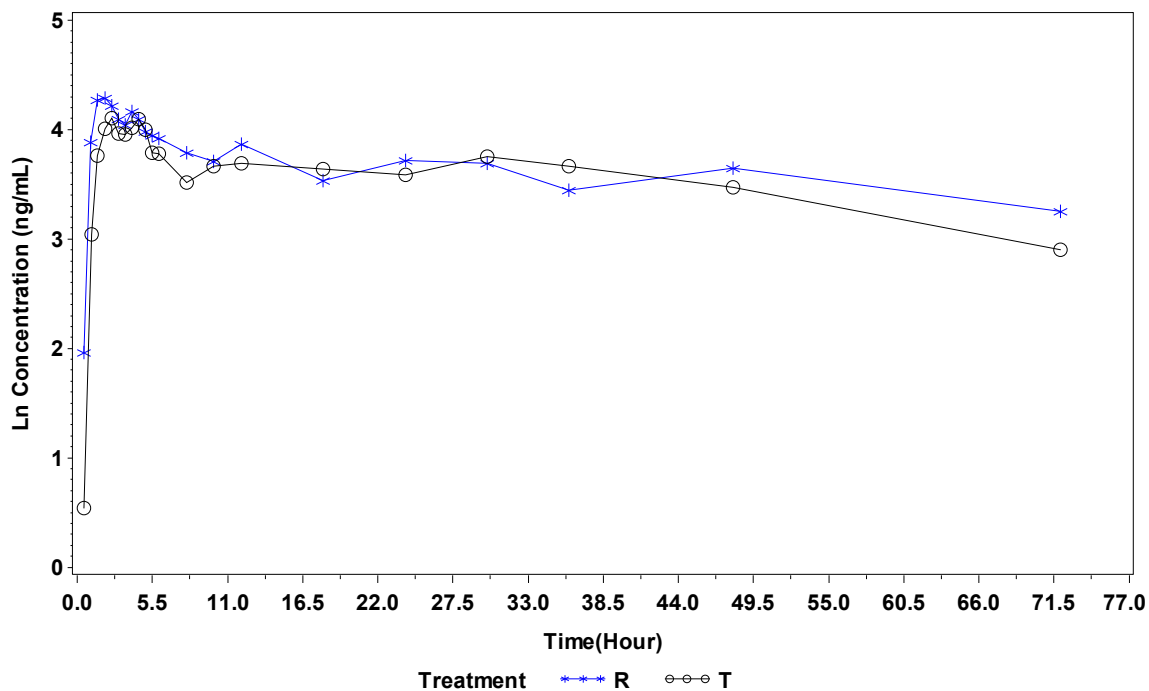


Figure 15

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=8

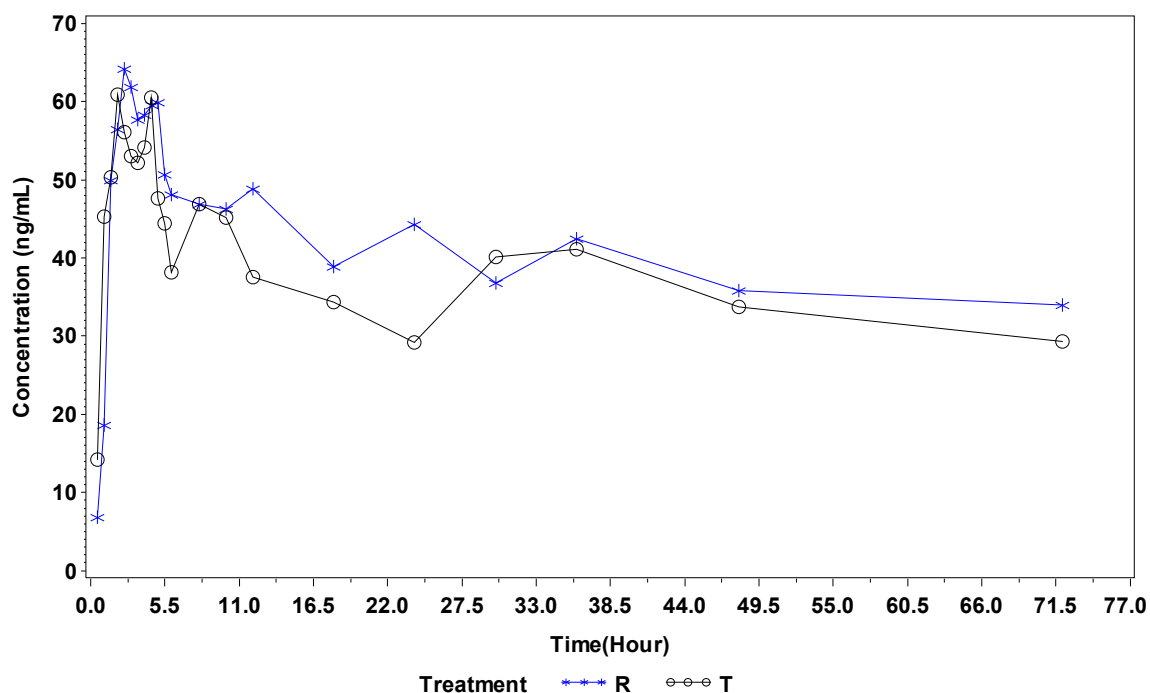


Figure 16

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=8

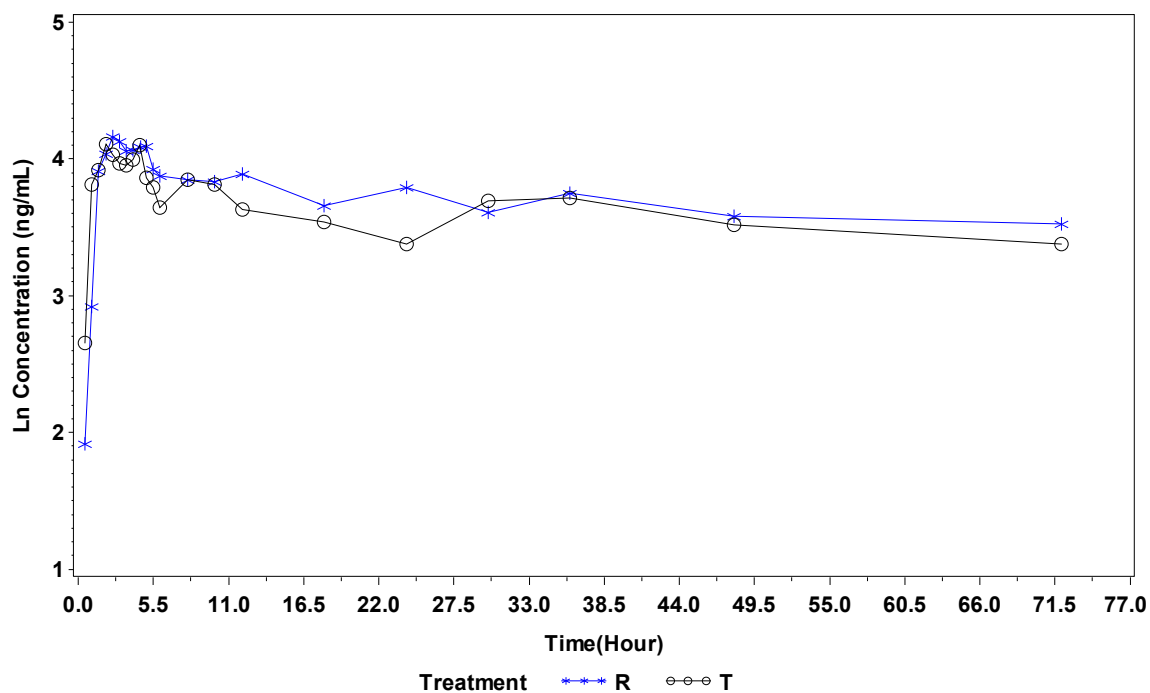


Figure 17

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=9

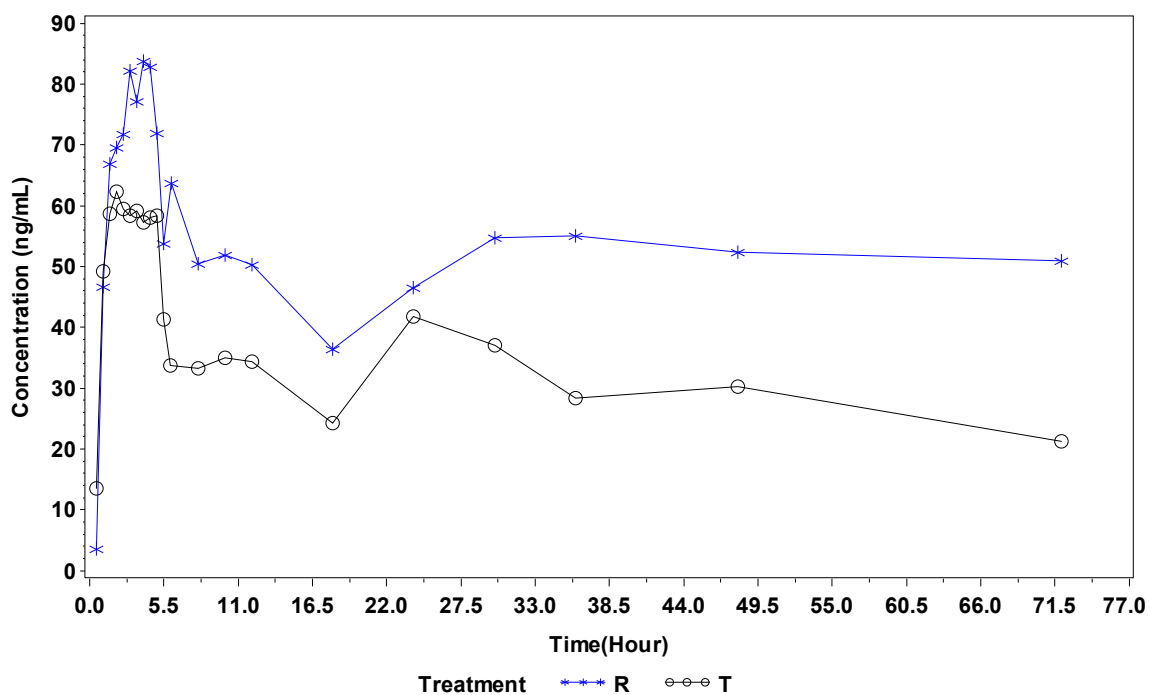


Figure 18

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=9

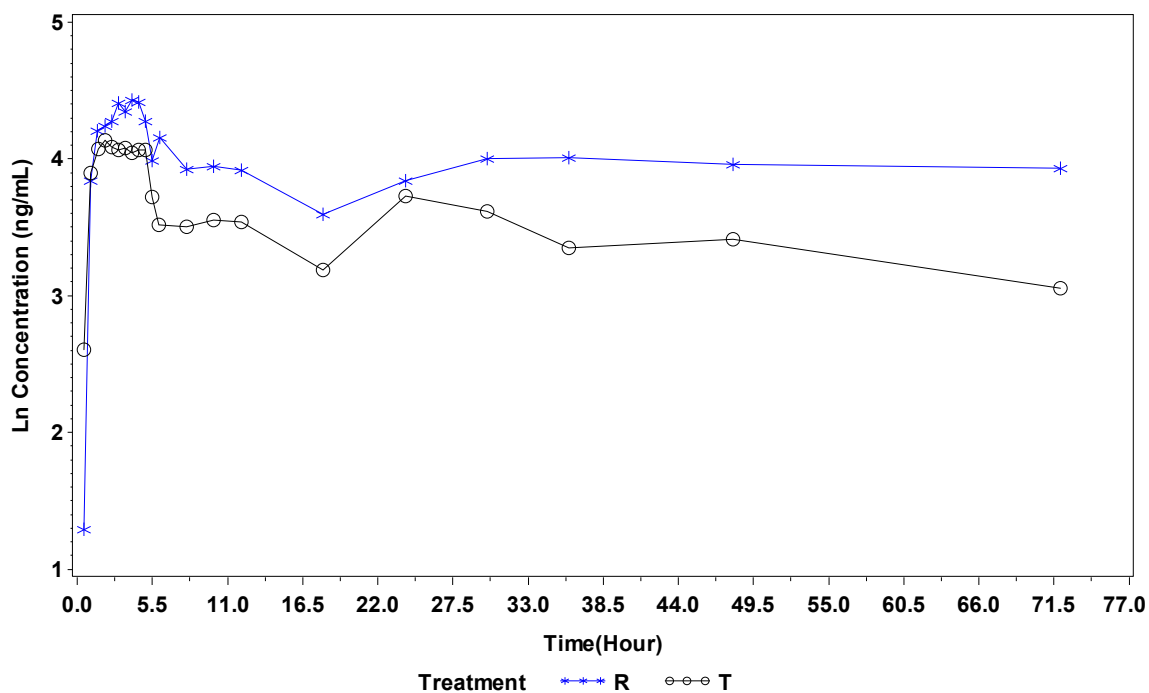


Figure 19

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=10

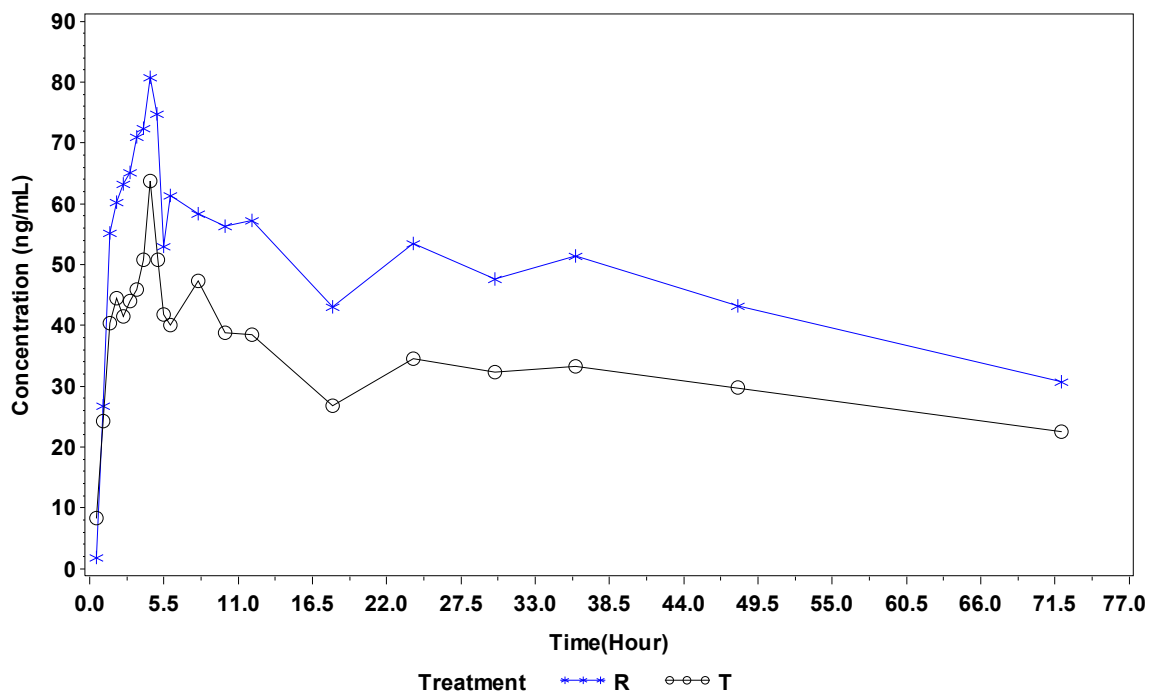


Figure 20

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=10

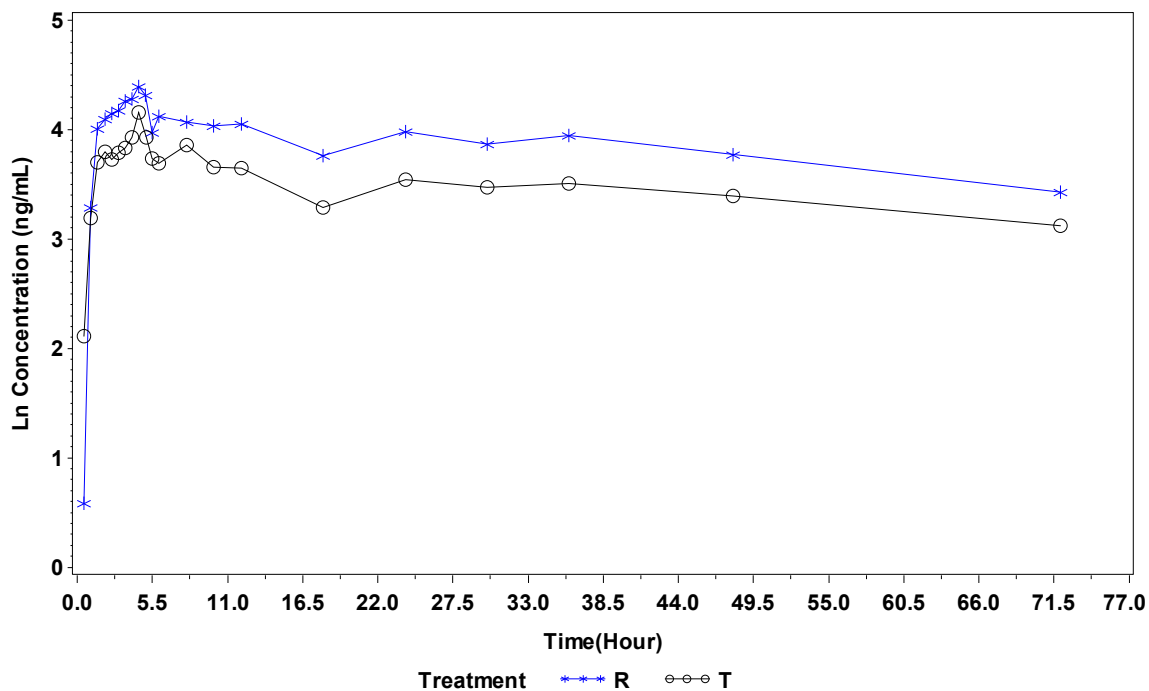


Figure 21

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=11

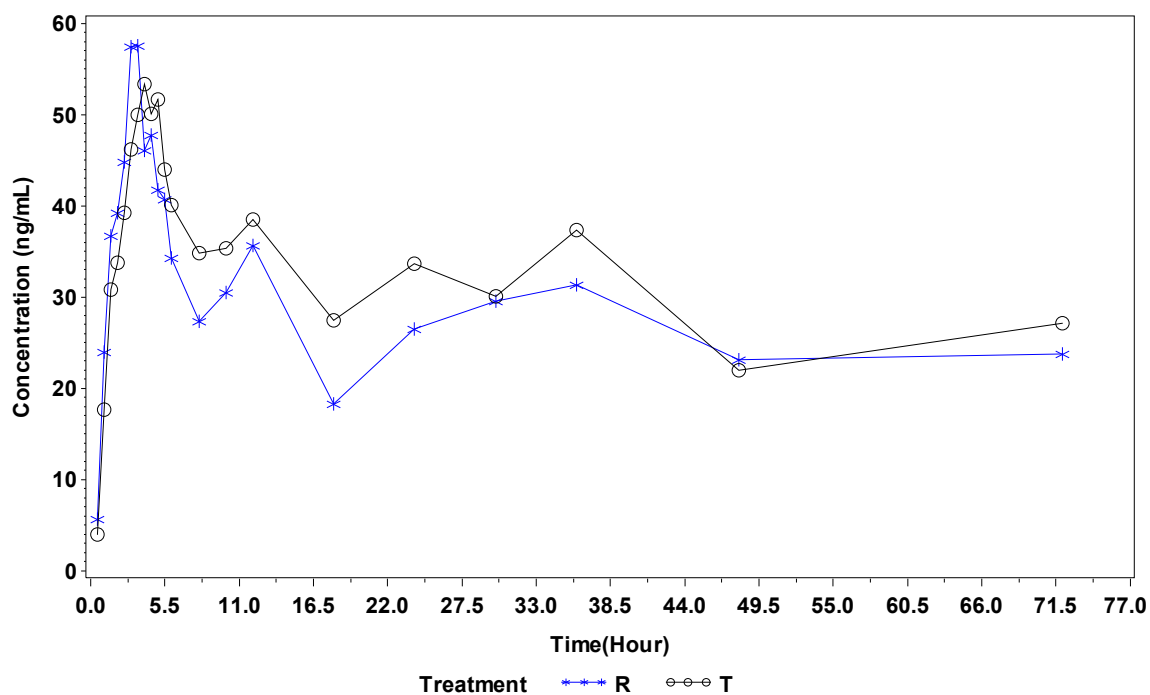


Figure 22

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=11

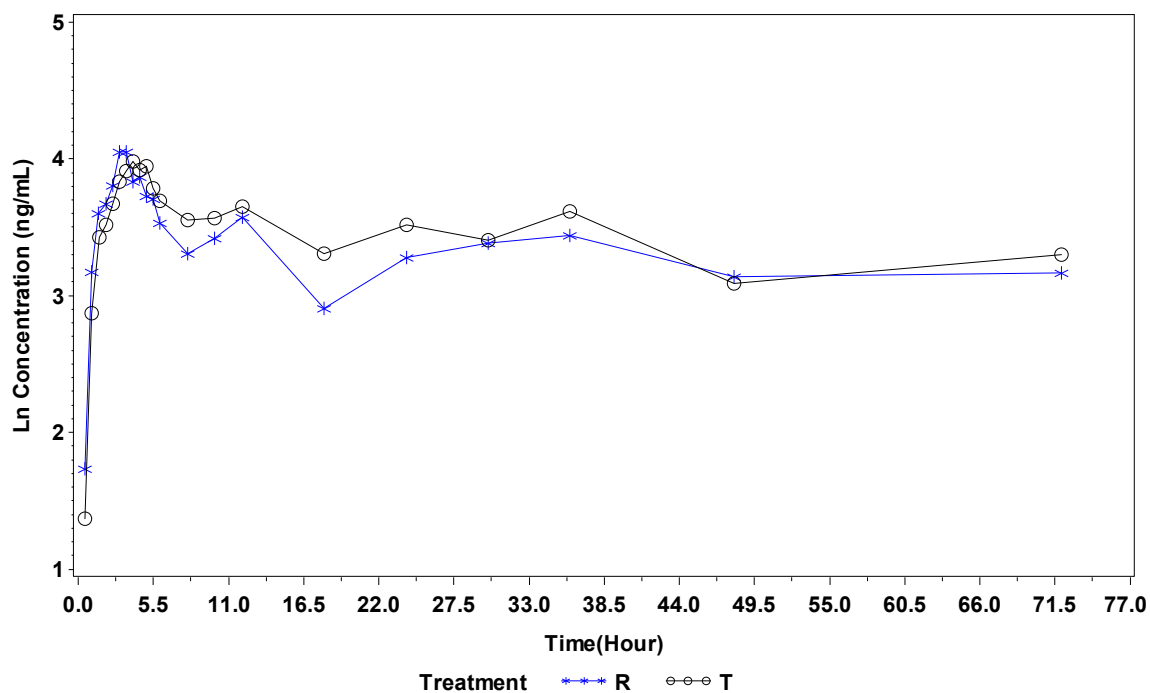


Figure 23

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=12

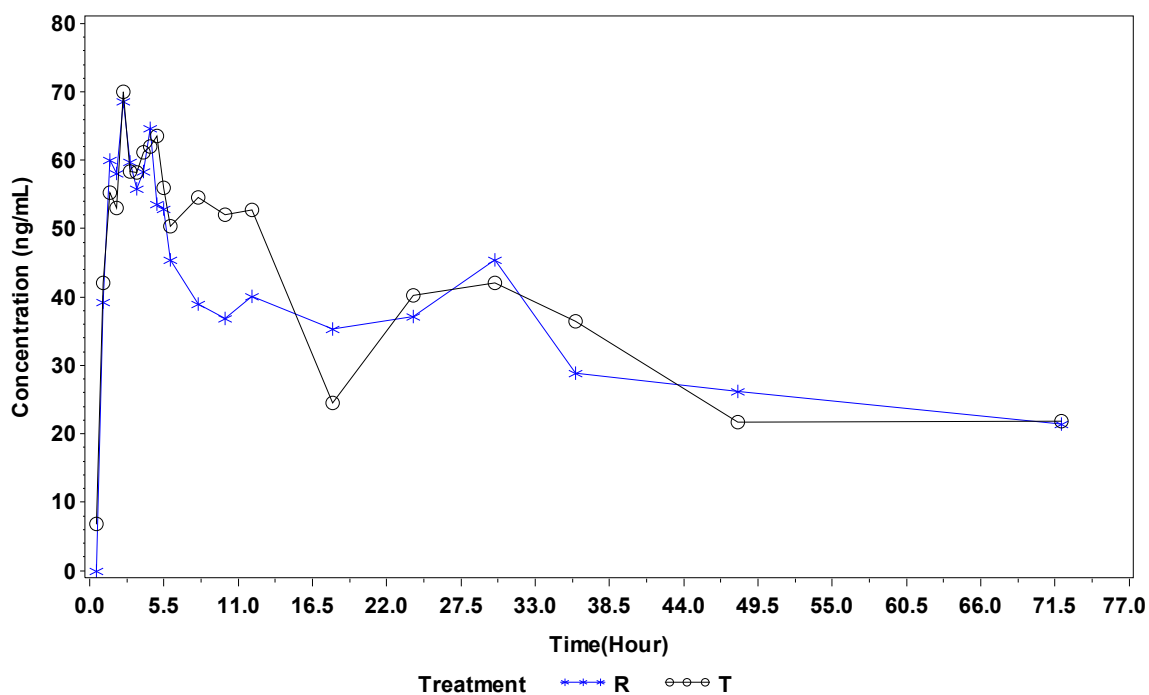


Figure 24

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=12

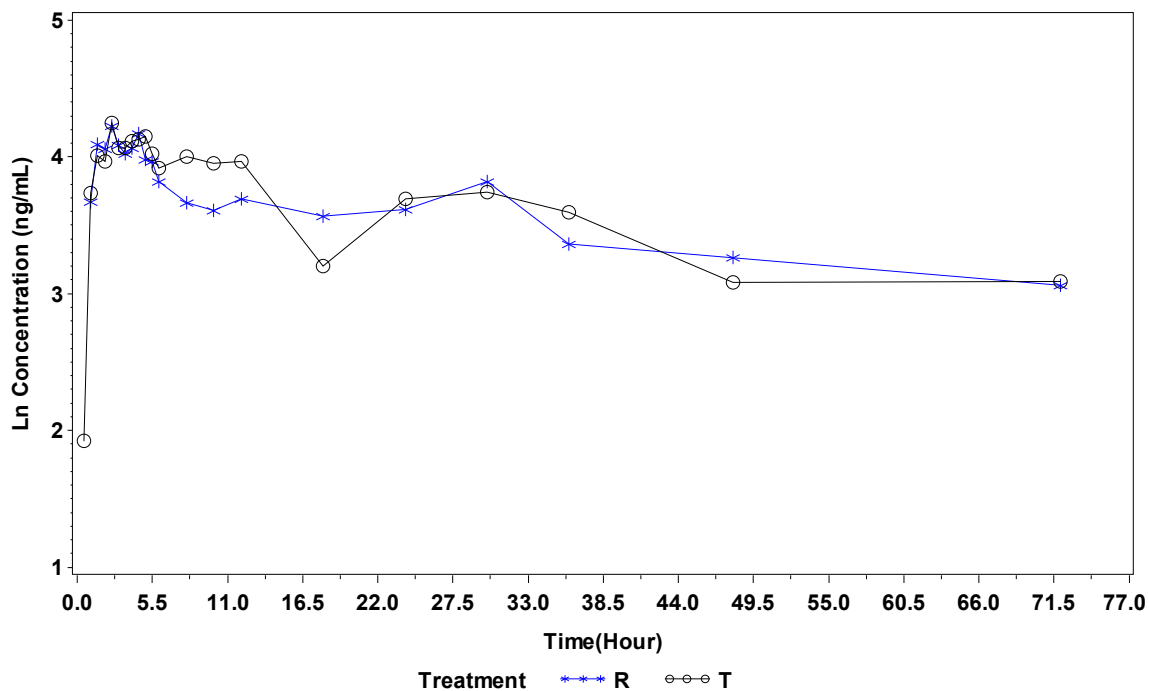


Figure 25

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=13

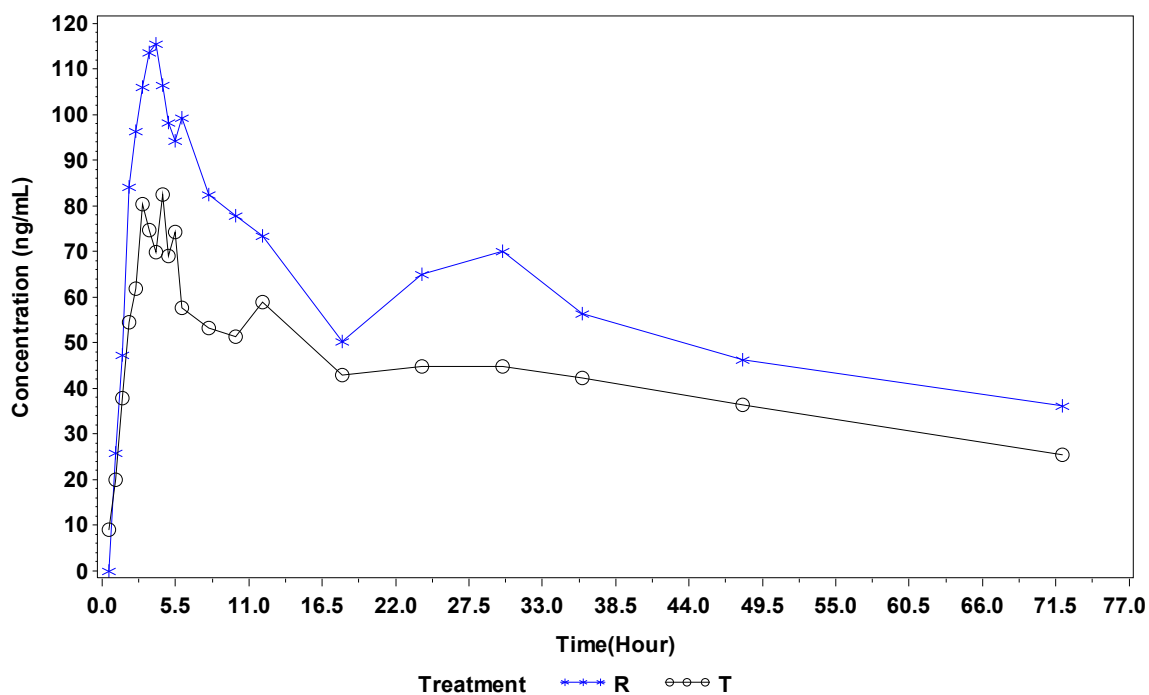


Figure 26

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=13

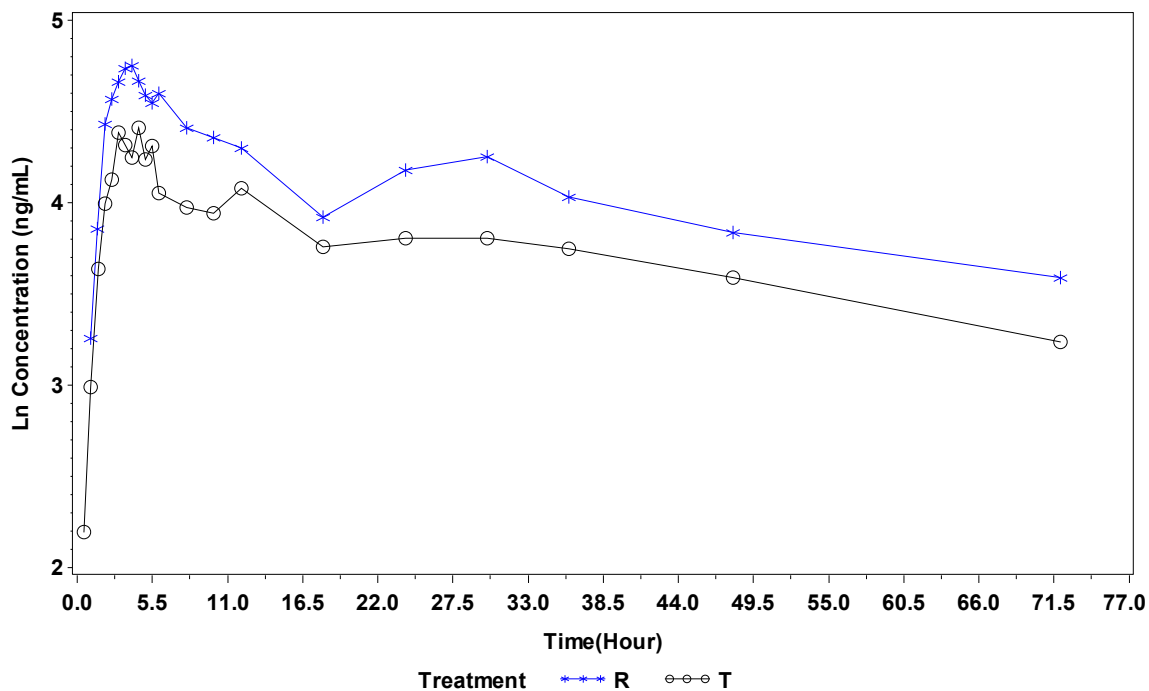


Figure 27

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=14

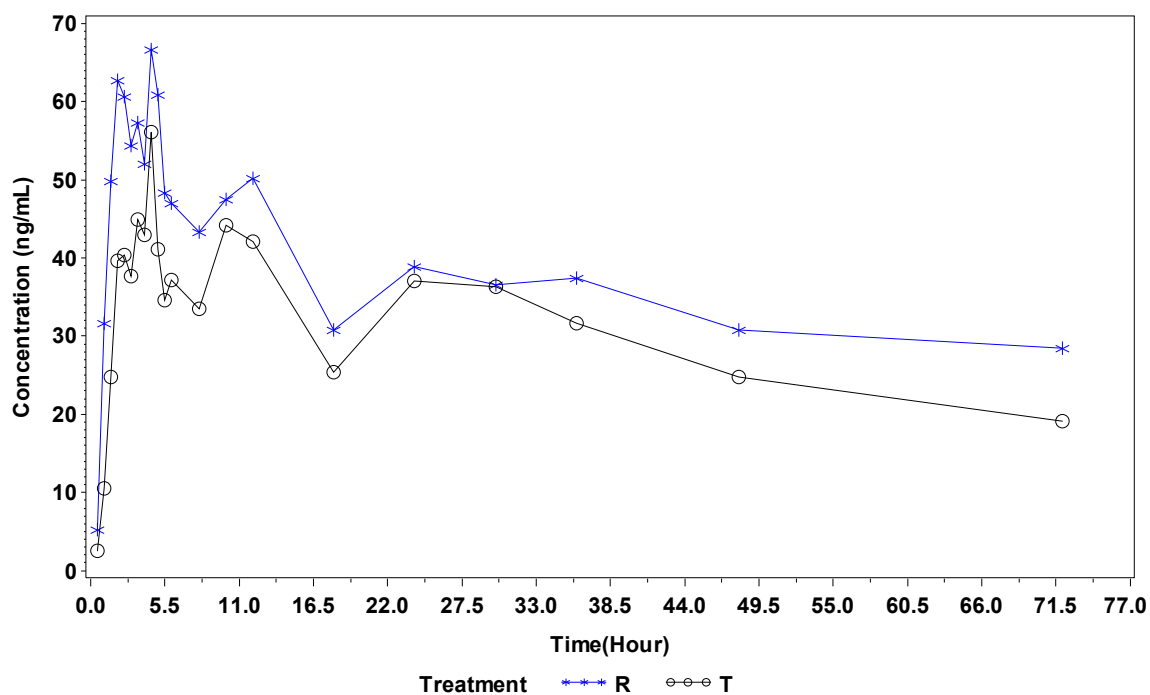


Figure 28

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=14

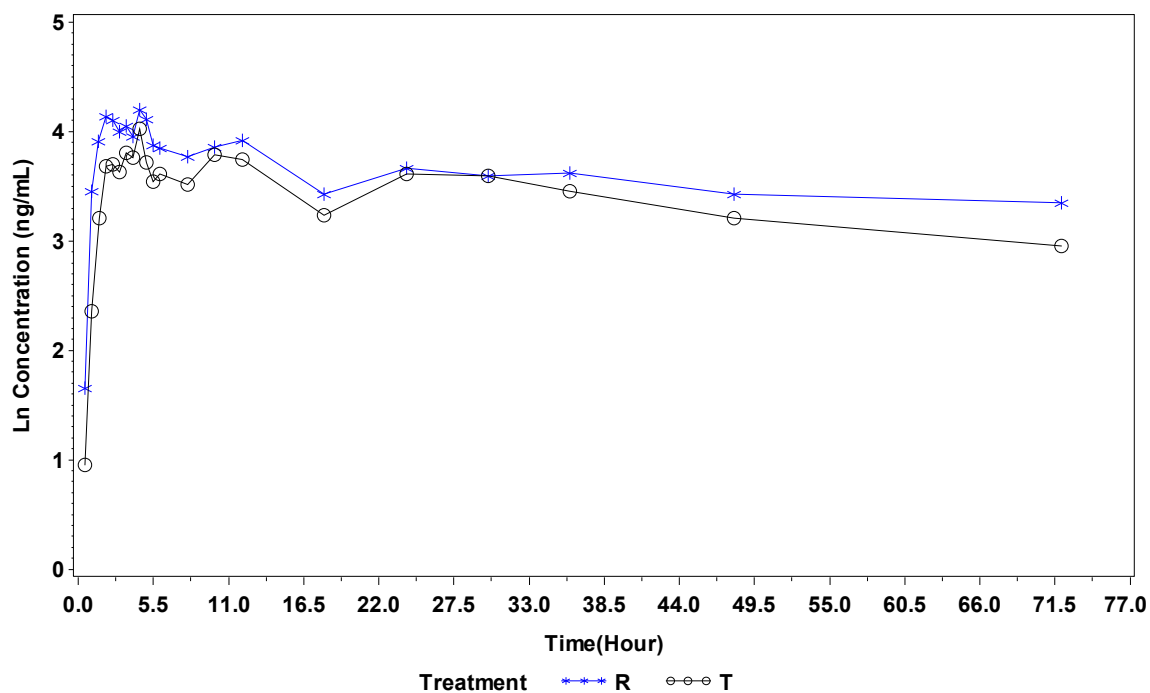


Figure 29

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=15

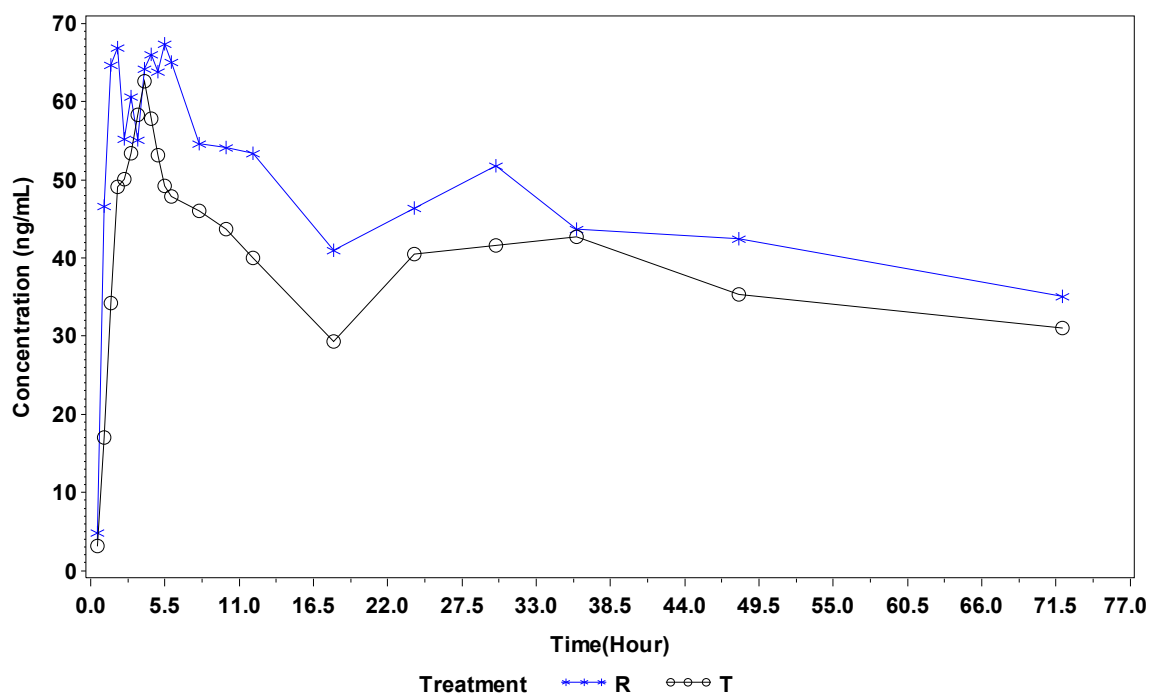


Figure 30

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=15

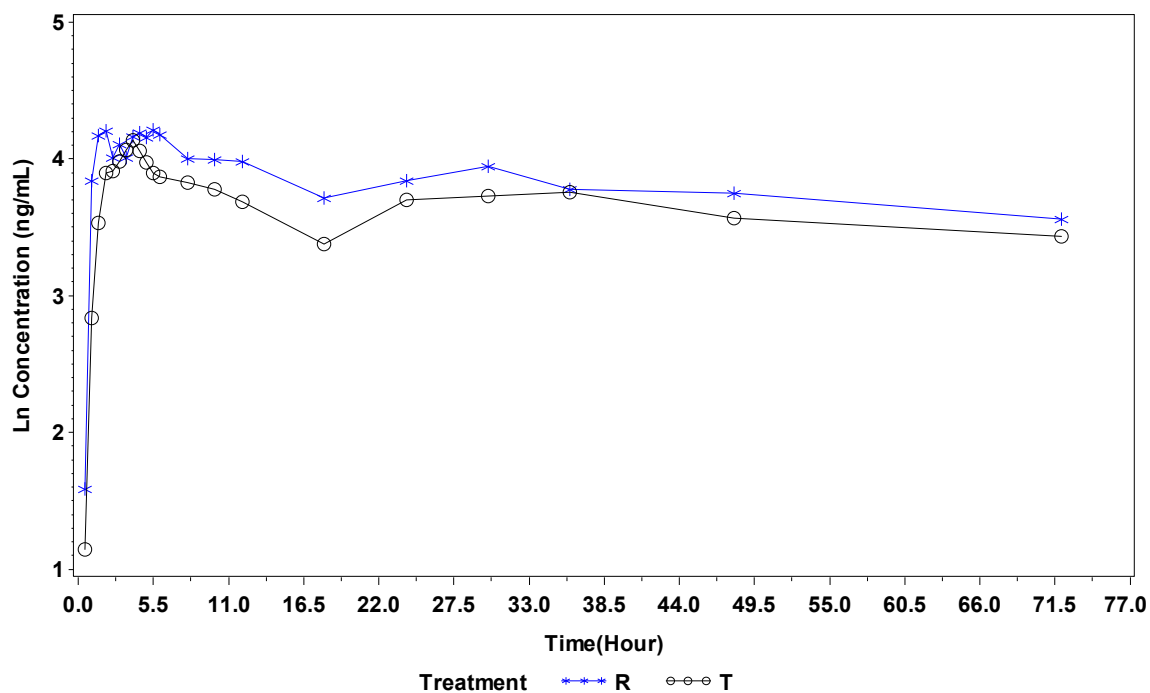


Figure 31

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=16

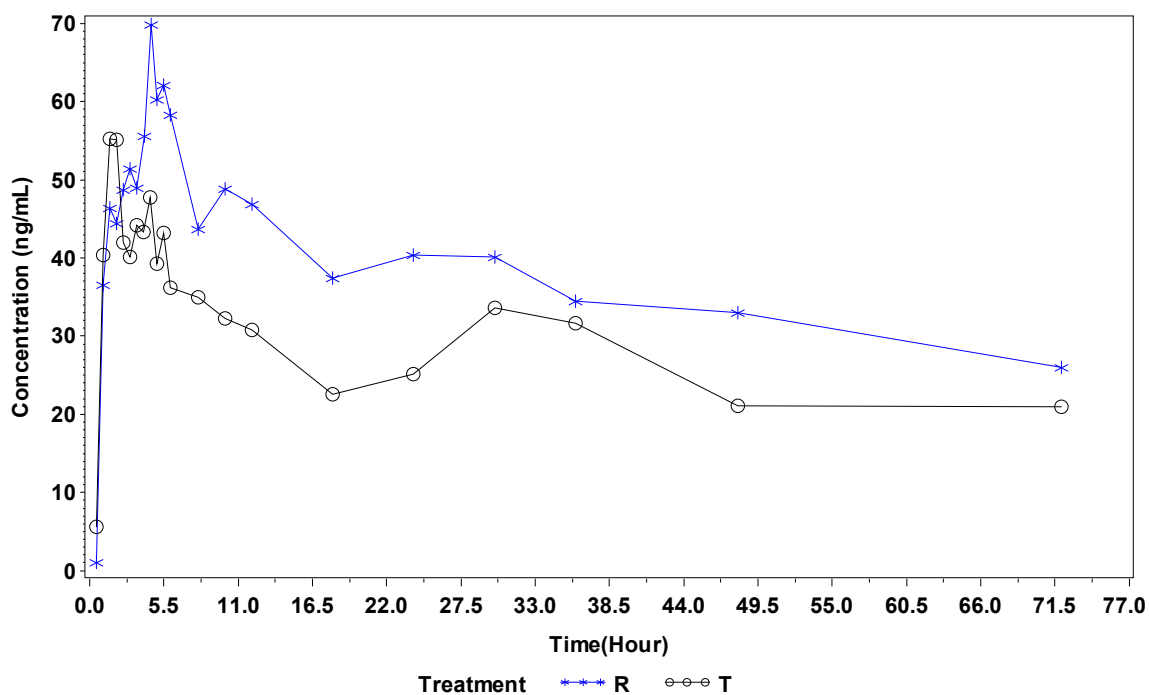


Figure 32

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=16

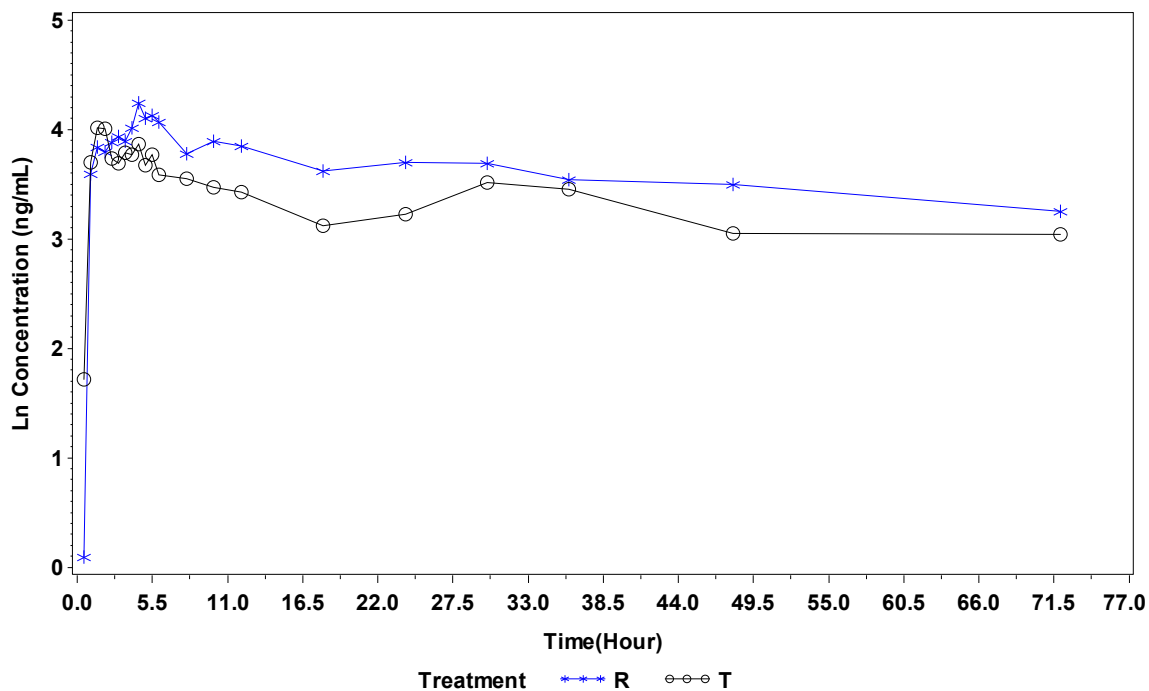


Figure 33

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=17

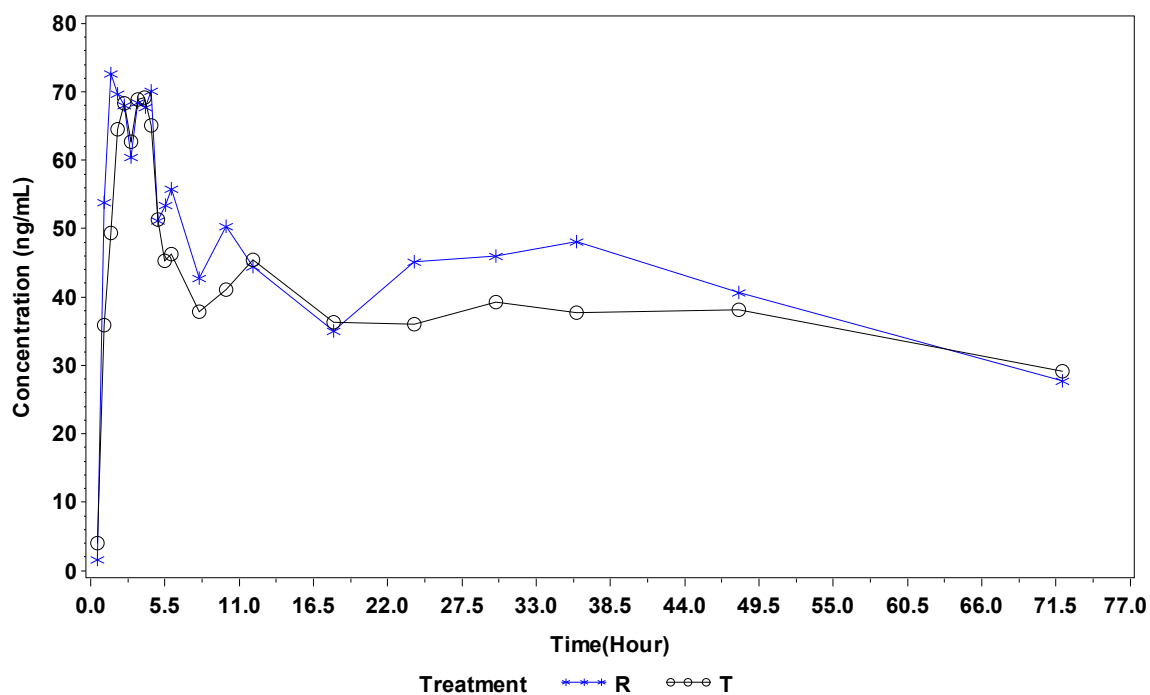


Figure 34

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=17

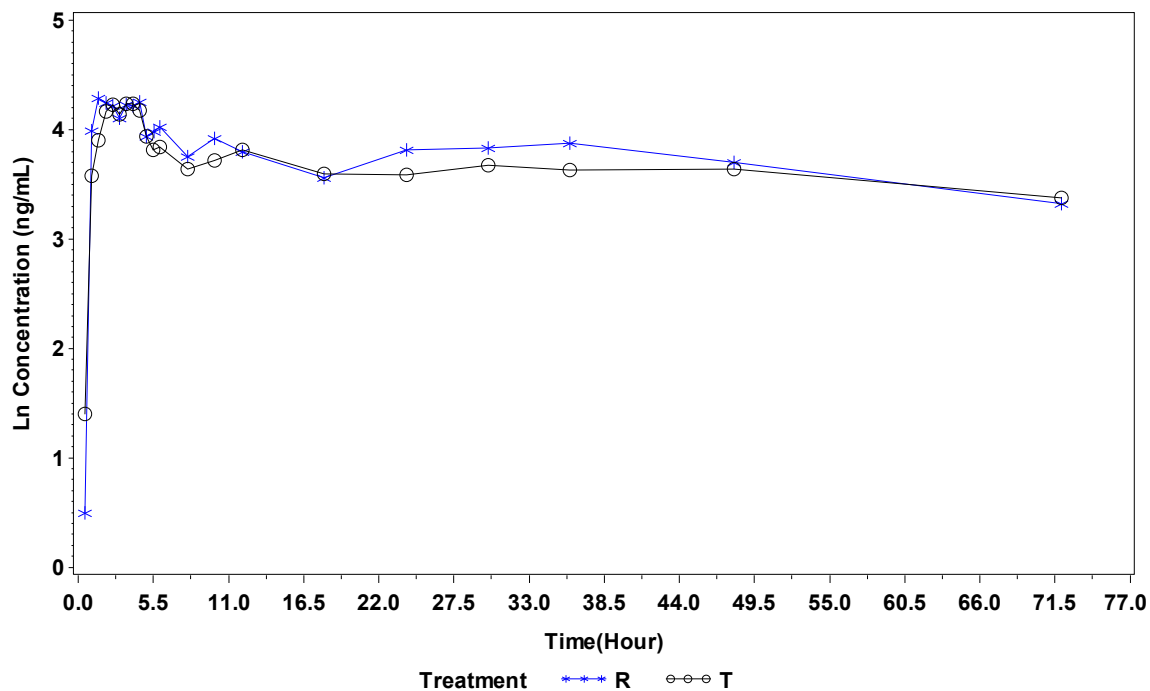


Figure 35

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=18

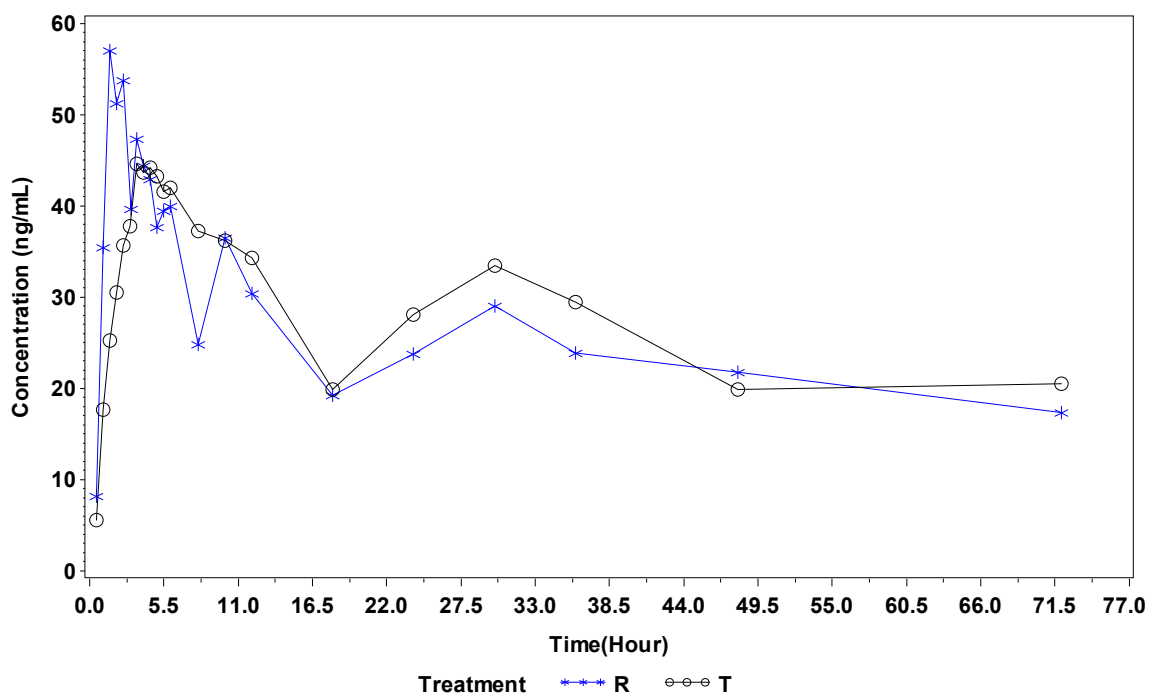


Figure 36

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=18

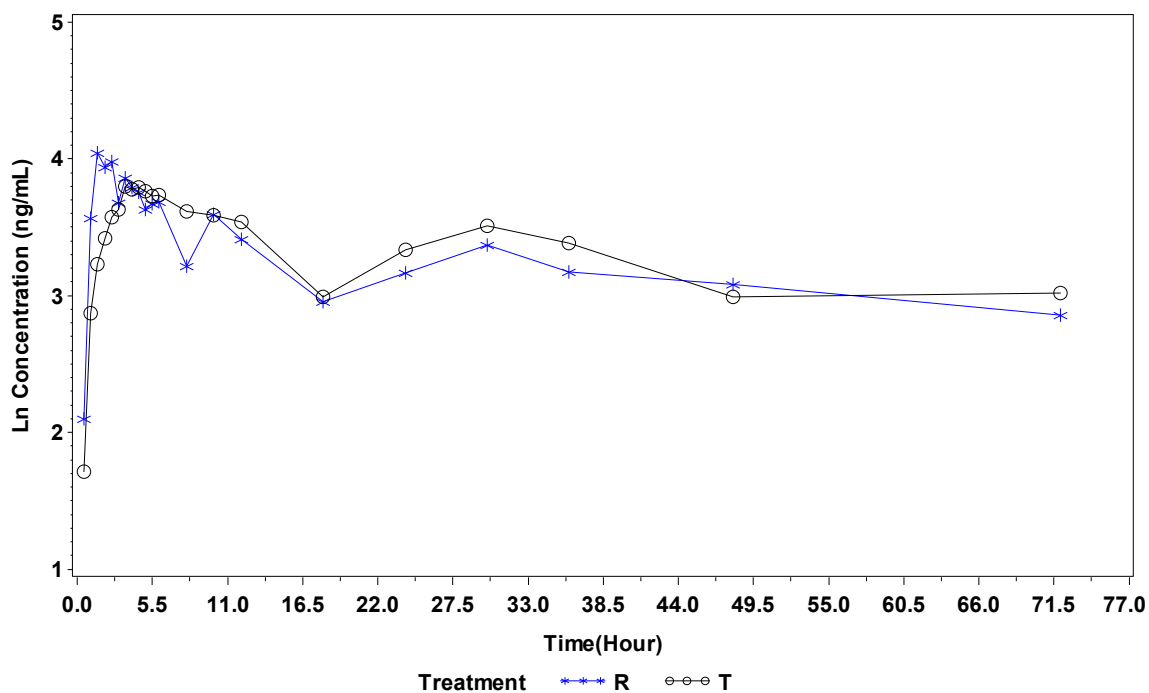


Figure 37

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=19

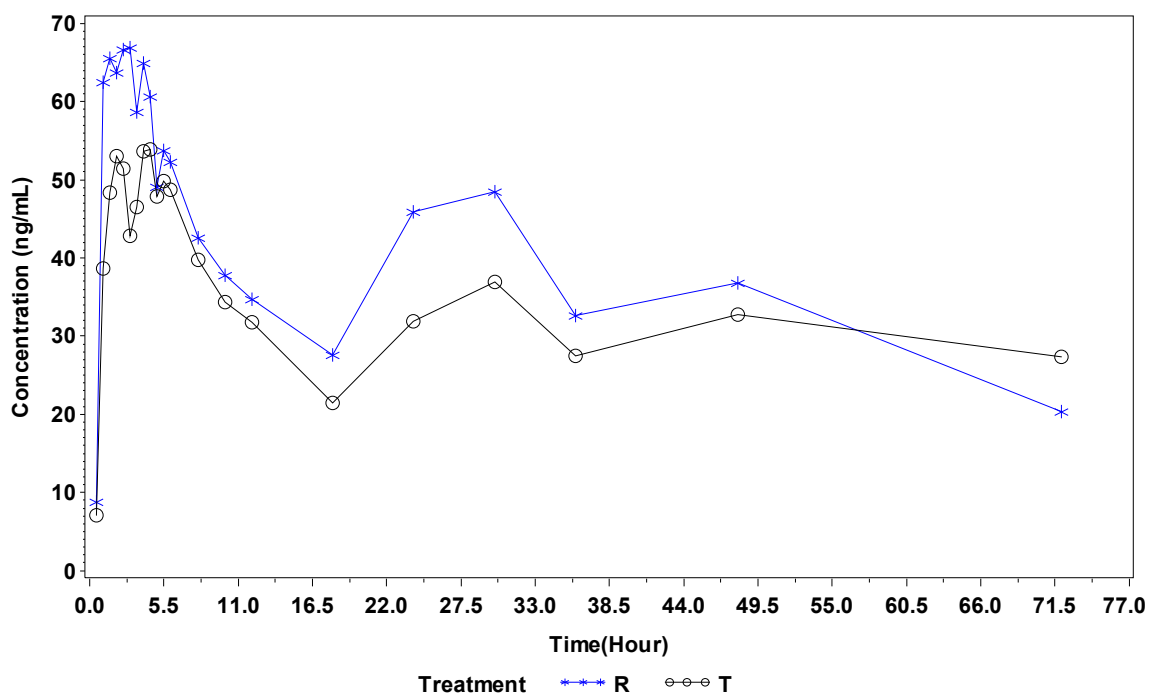


Figure 38

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=19

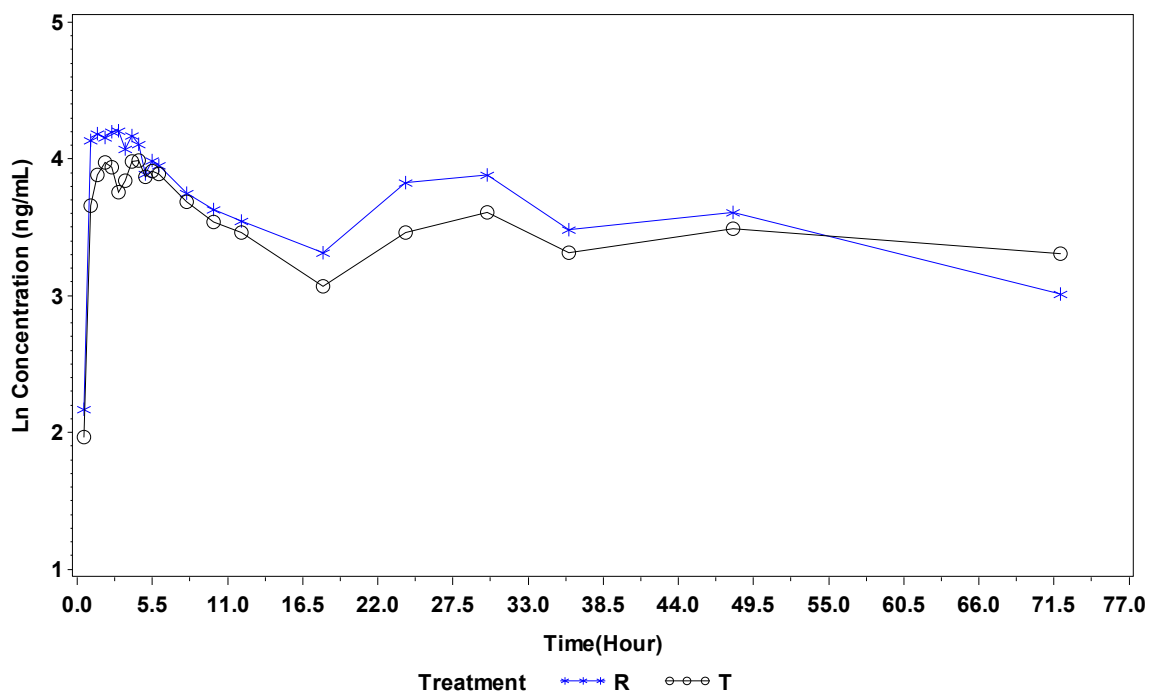


Figure 39

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=20

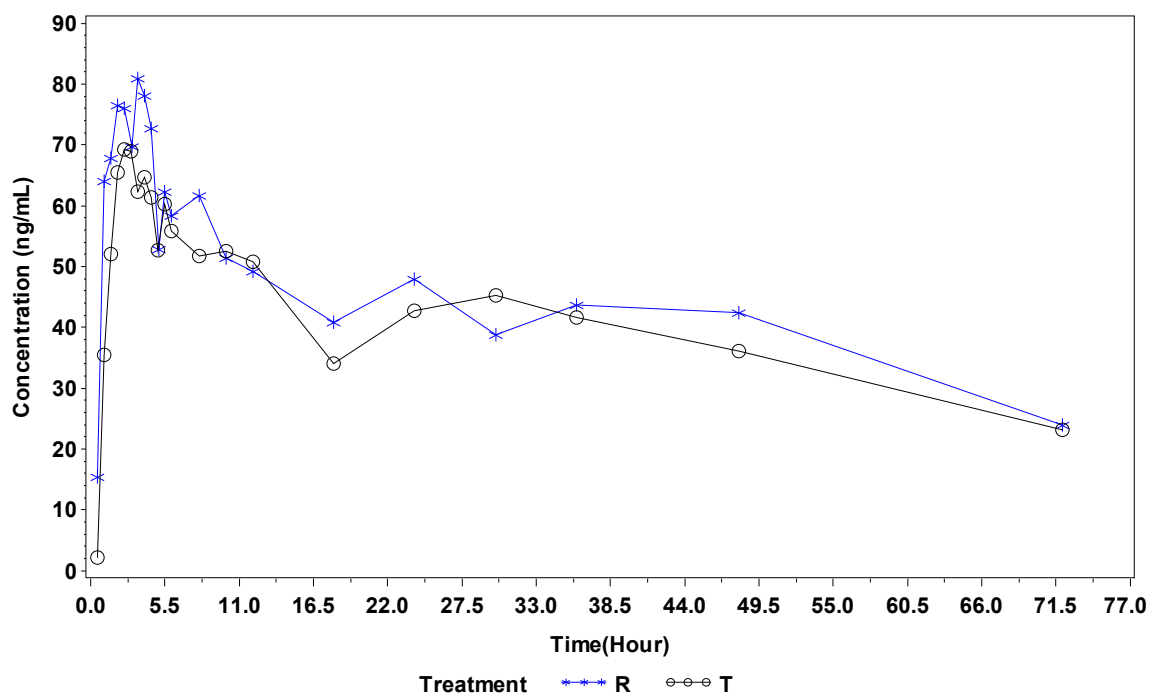


Figure 40

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=20

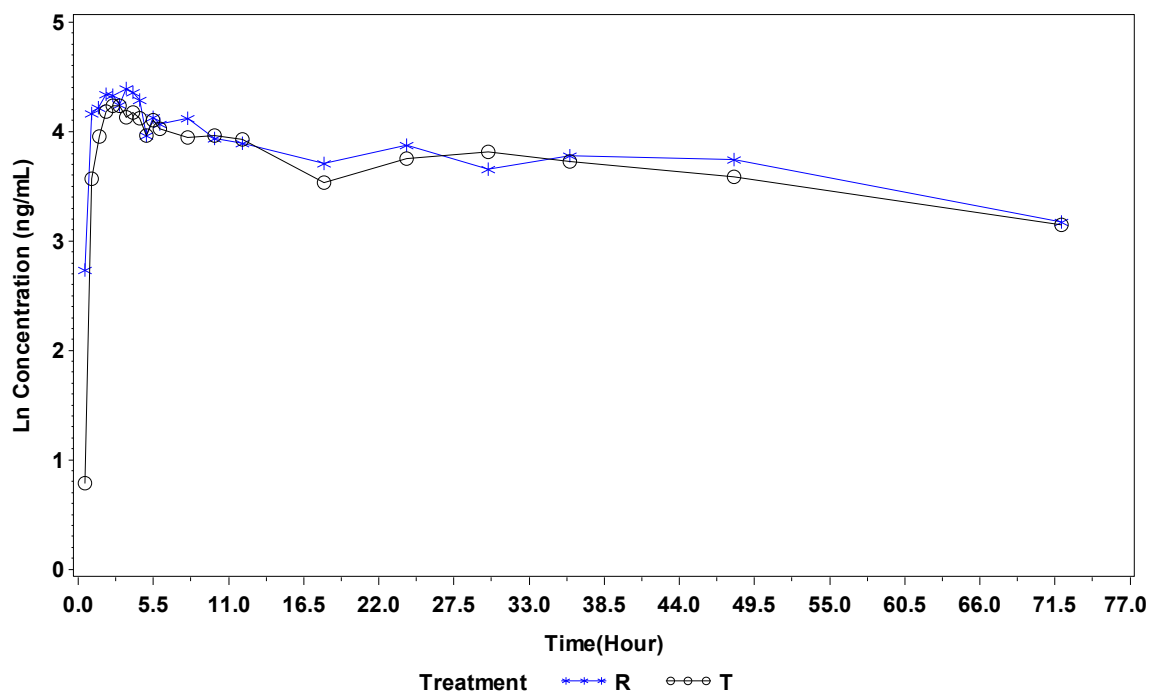


Figure 41

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=21

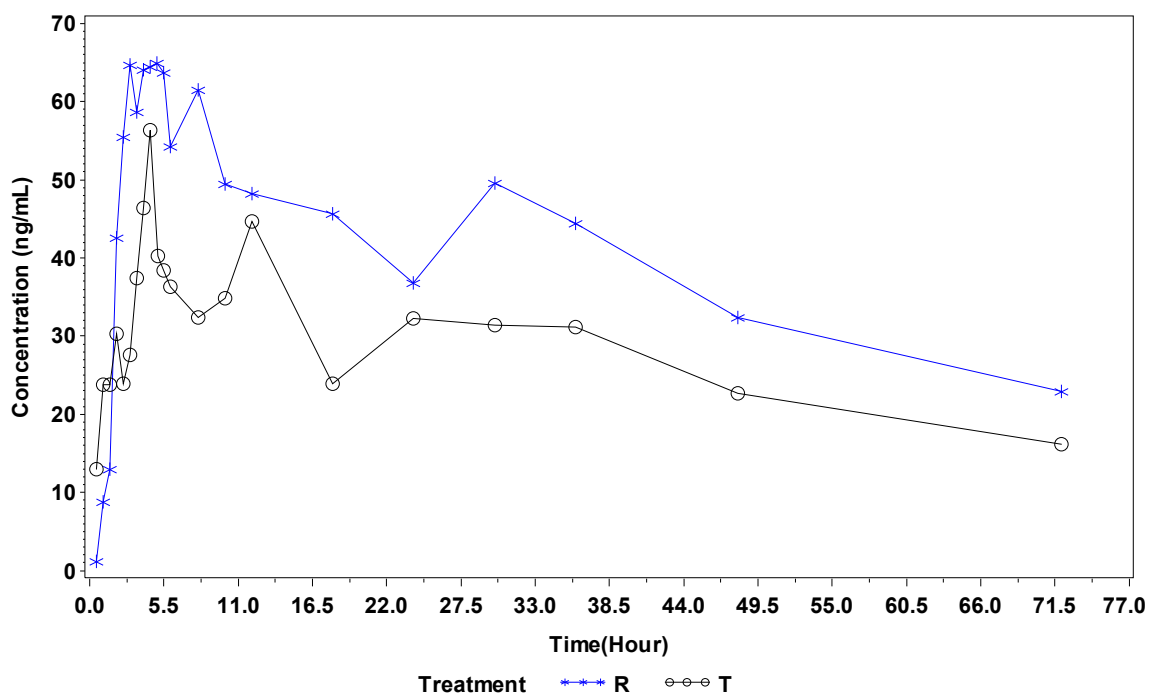


Figure 42

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=21

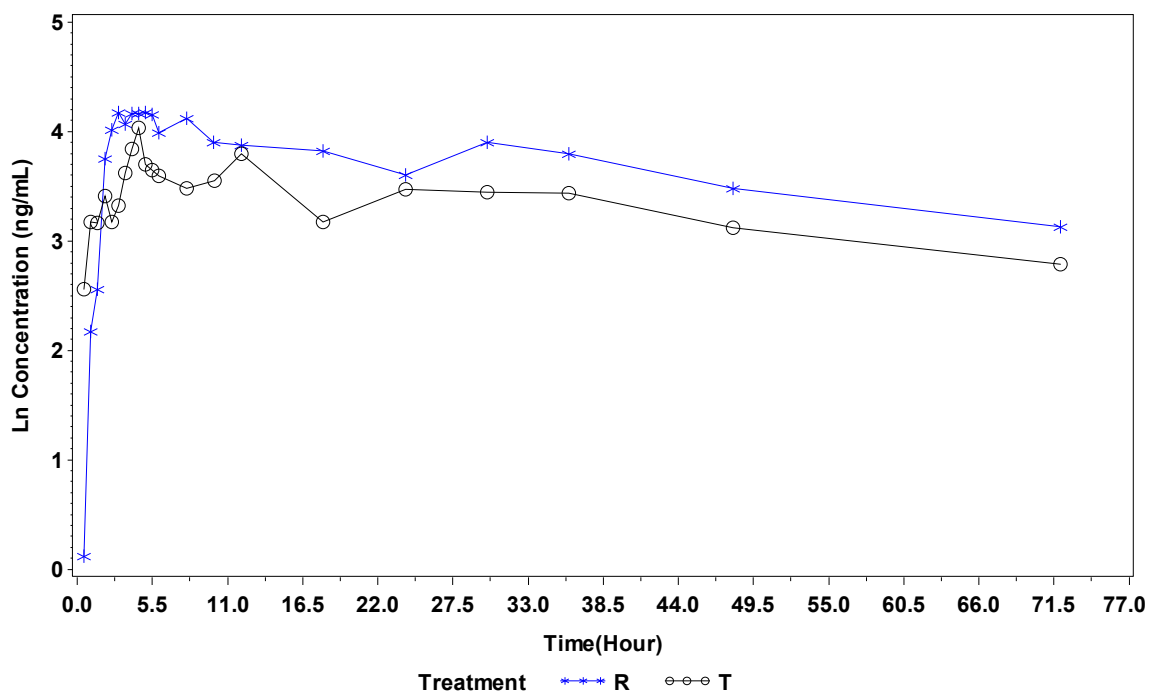


Figure 43

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=22

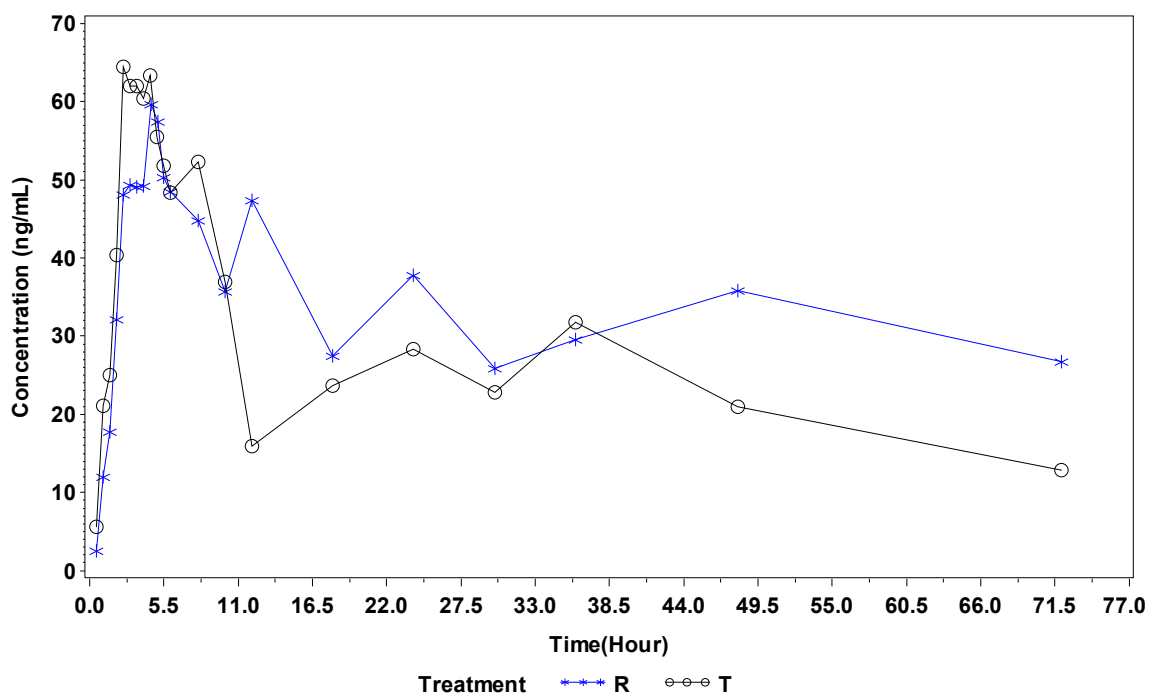


Figure 44

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=22

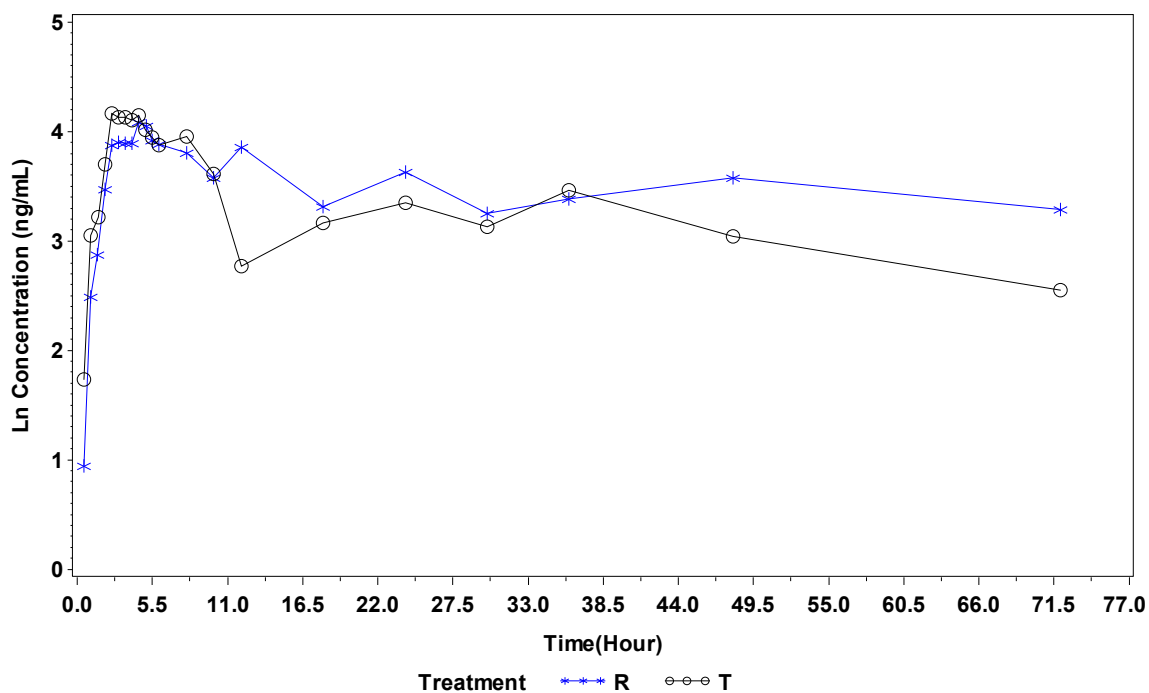


Figure 45

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=23

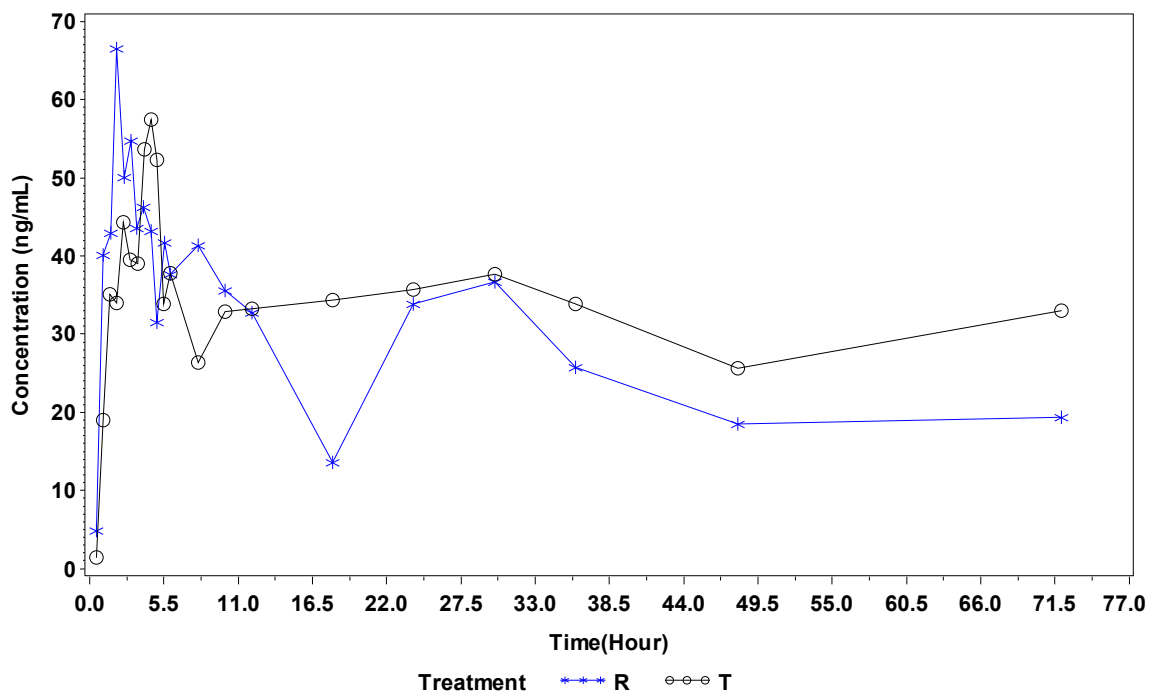


Figure 46

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=23

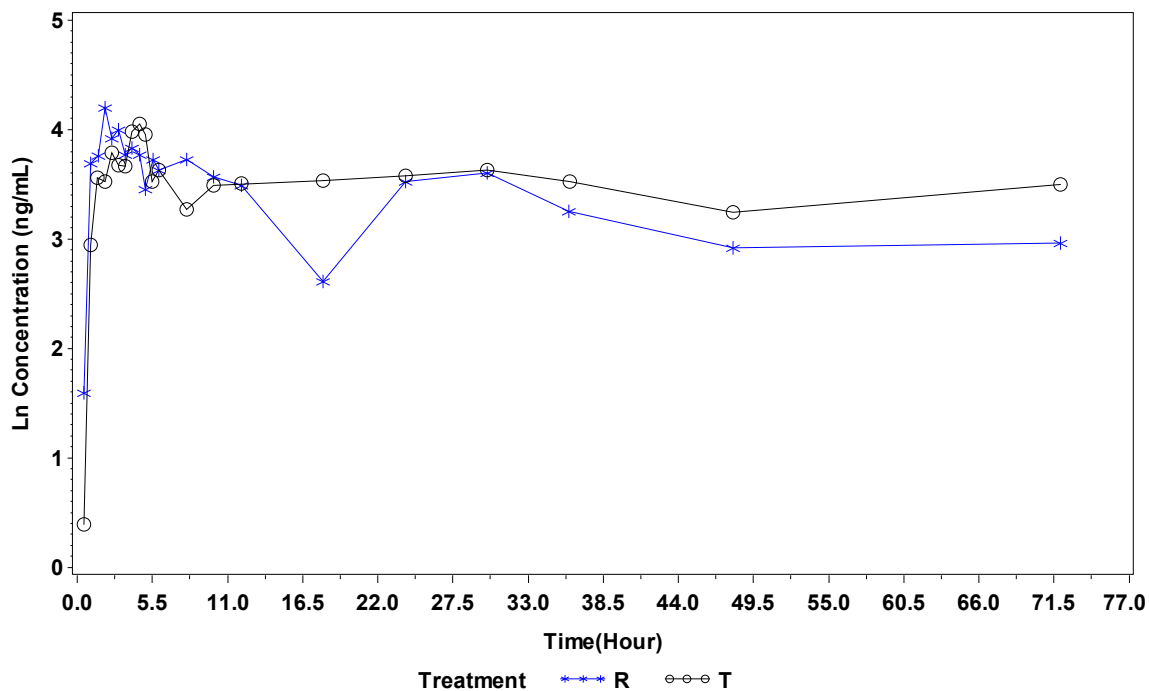


Figure 47

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=24

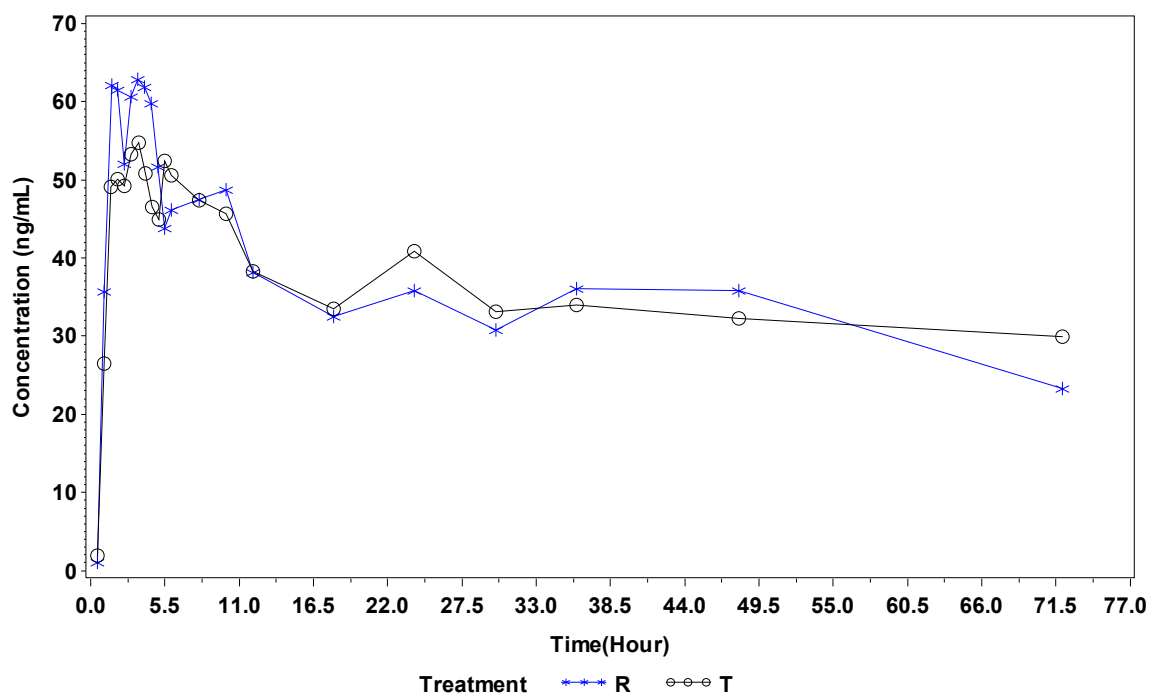


Figure 48

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=24

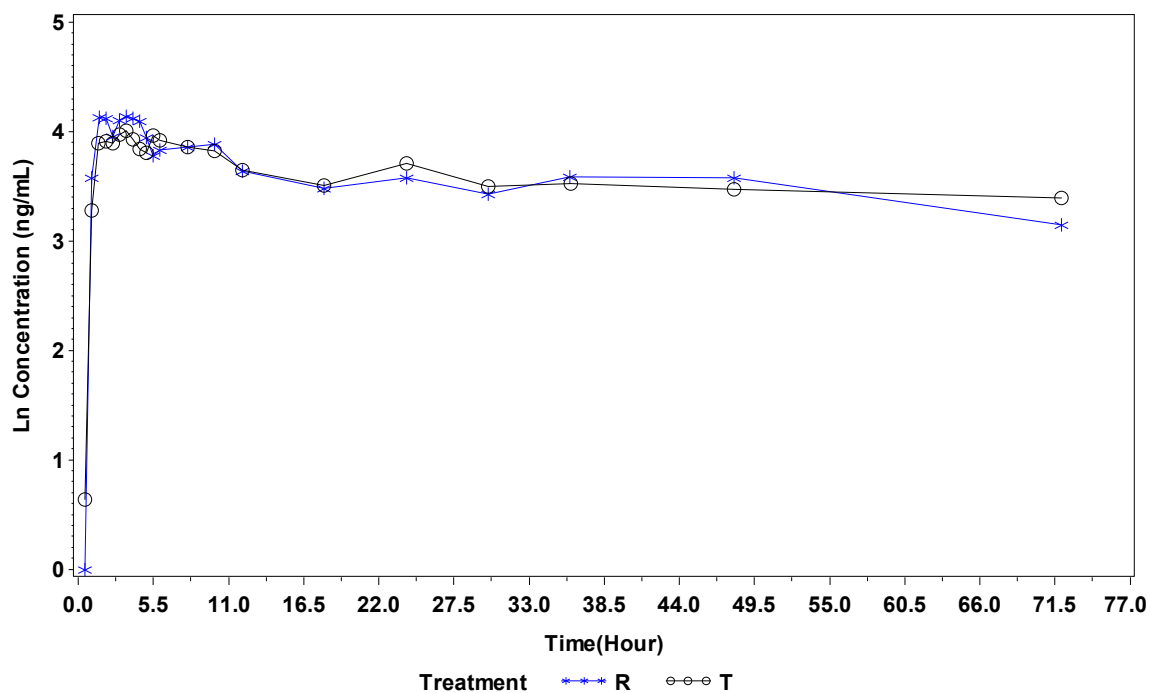


Figure 49

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=25

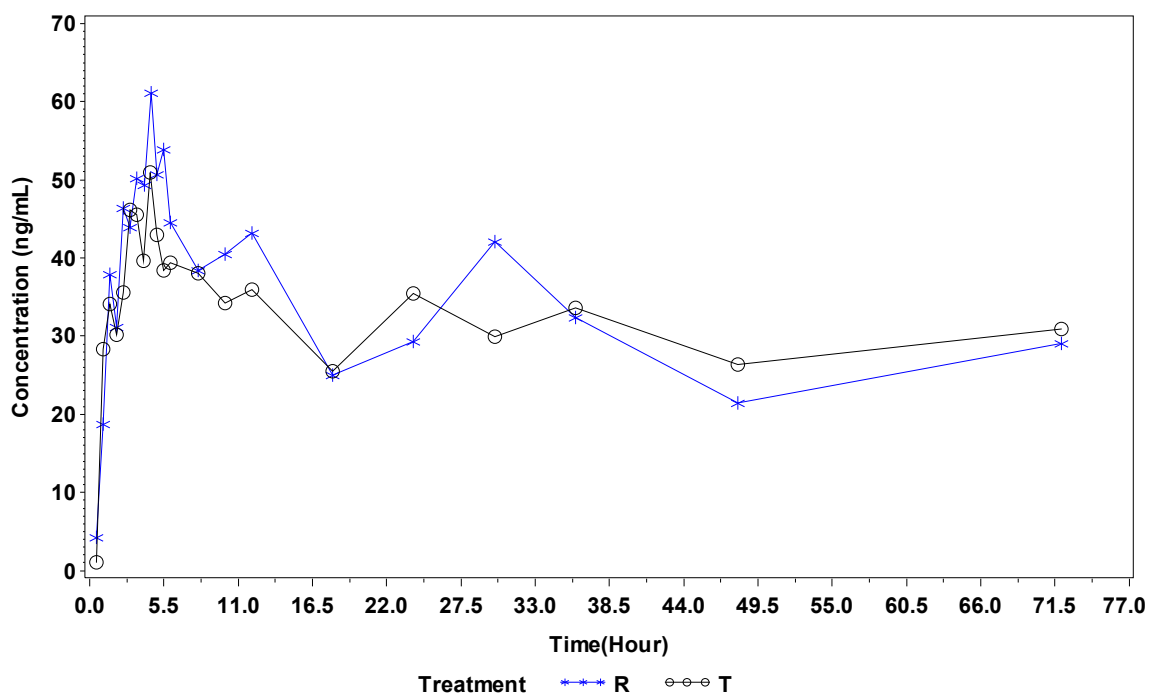


Figure 50

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=25

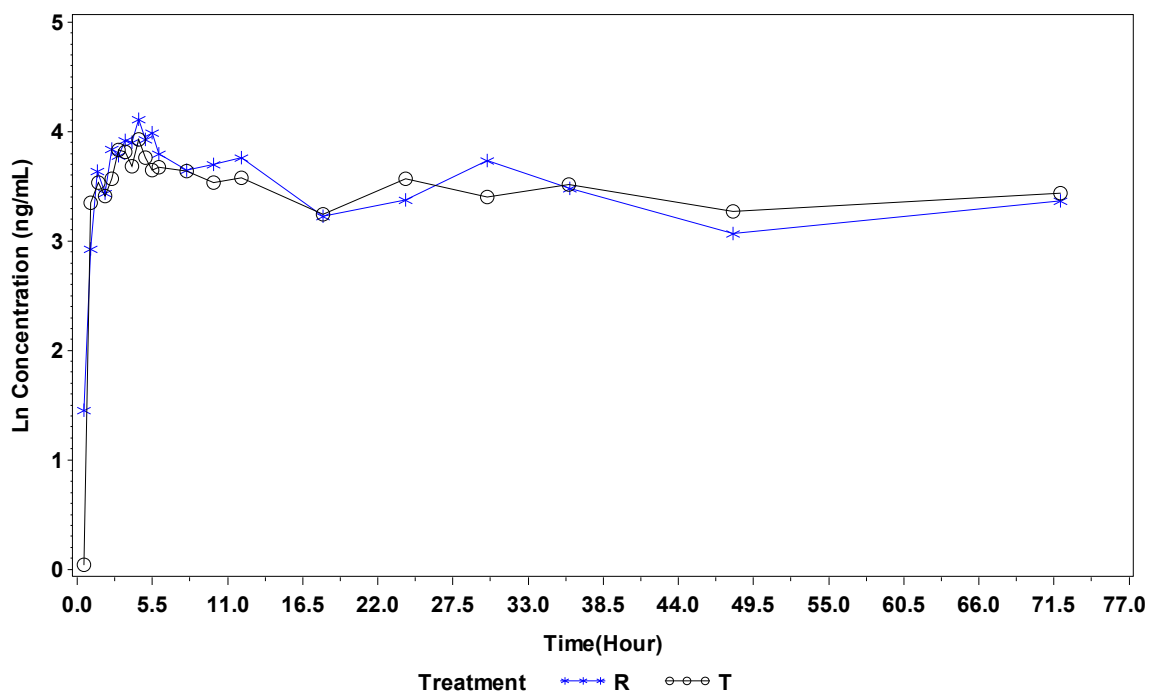


Figure 51

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=26

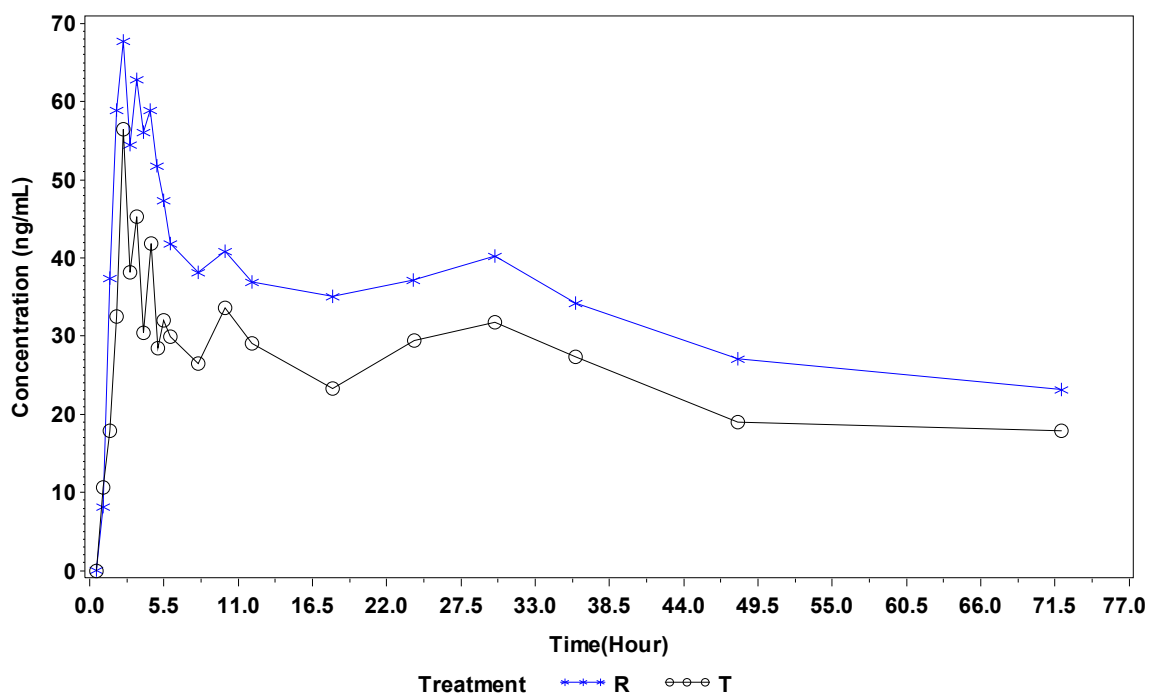


Figure 52

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=26

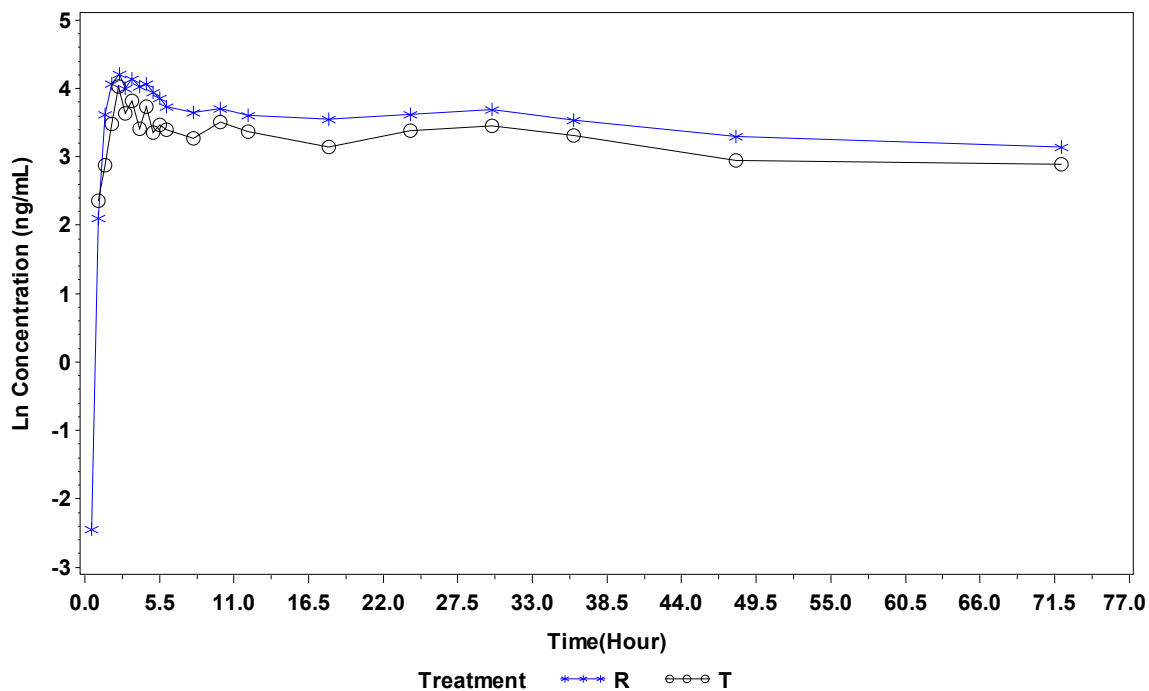


Figure 53

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=27

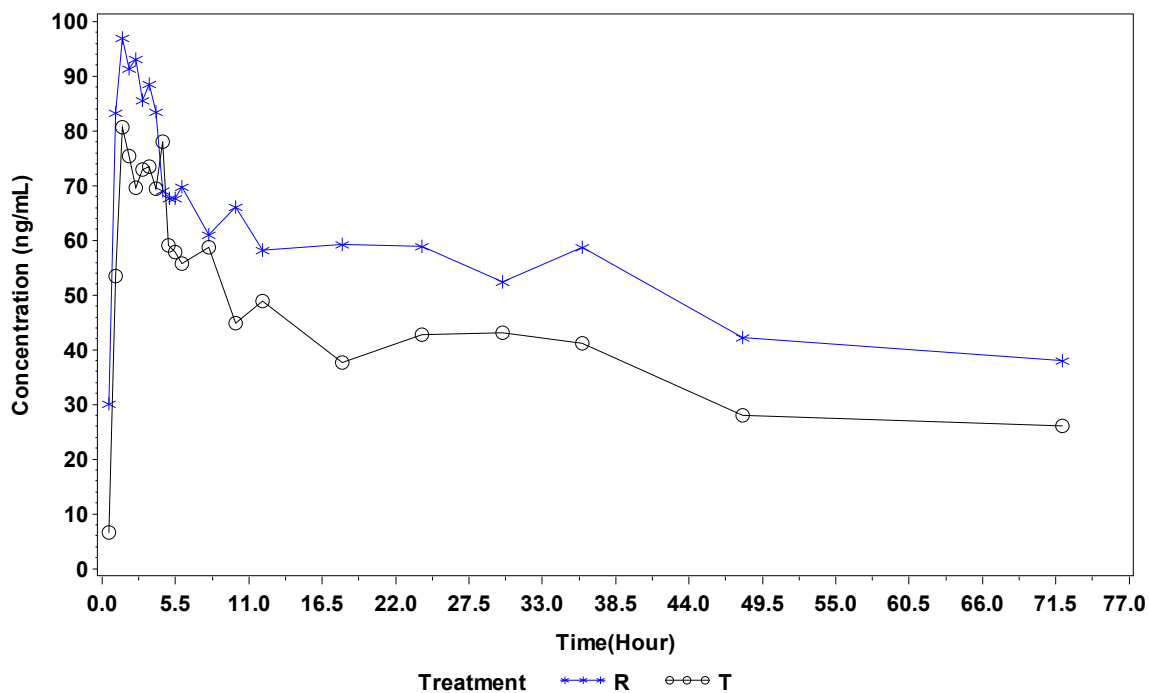


Figure 54

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=27

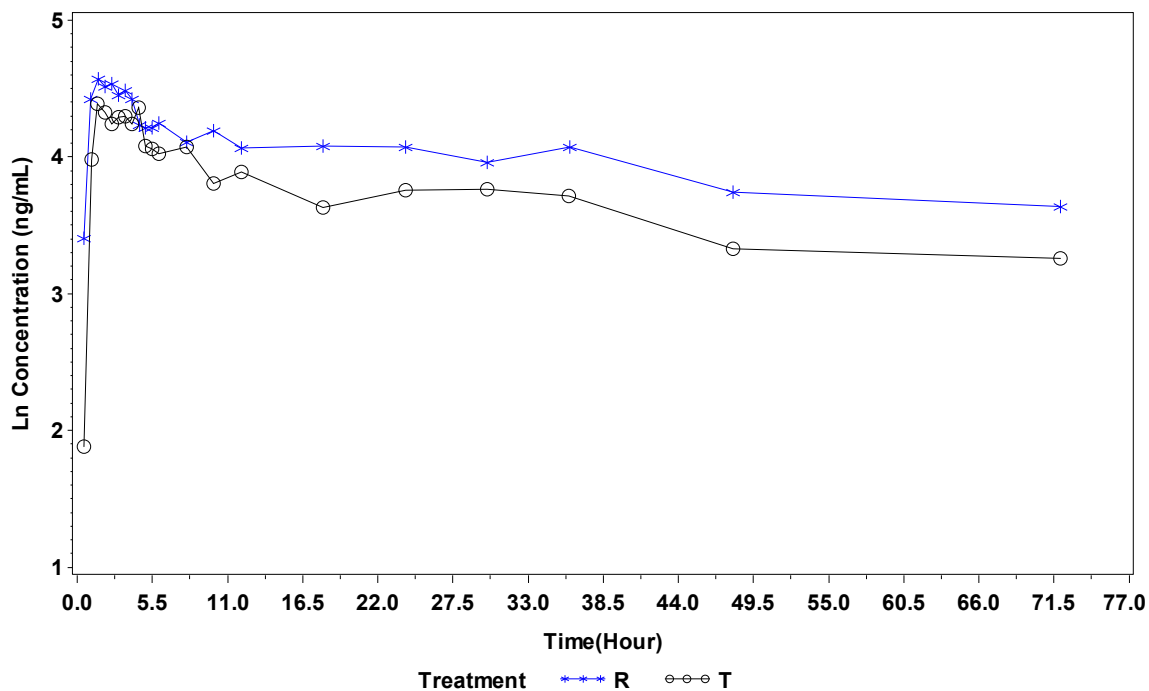


Figure 55

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=28

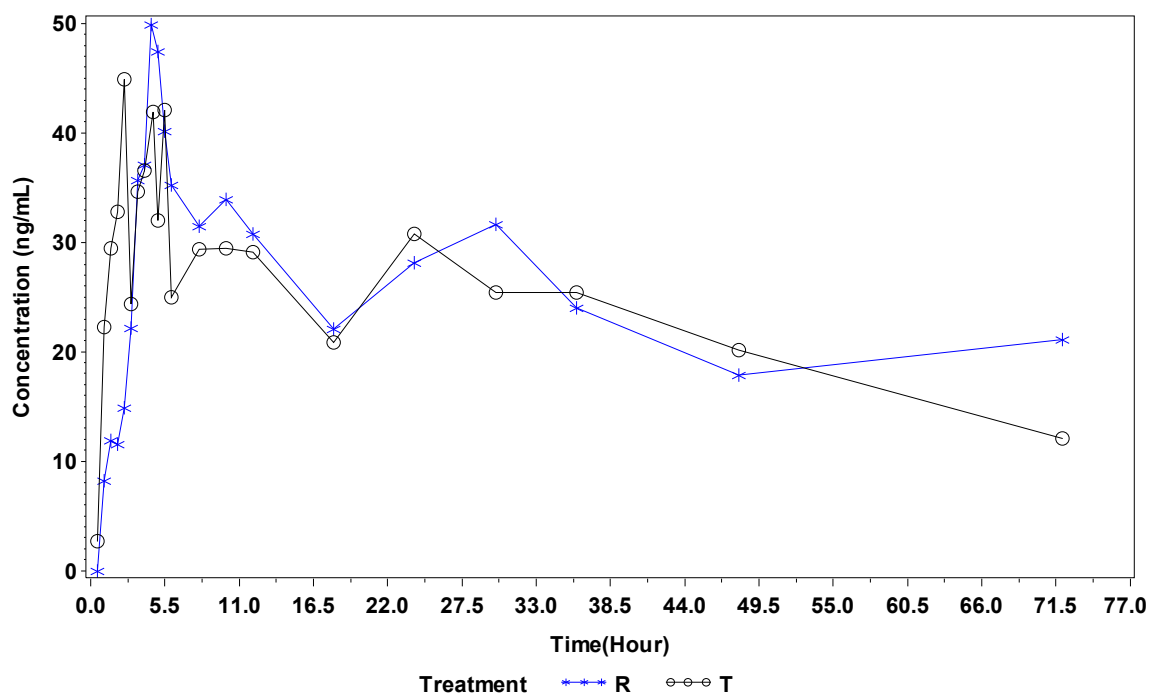


Figure 56

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=28

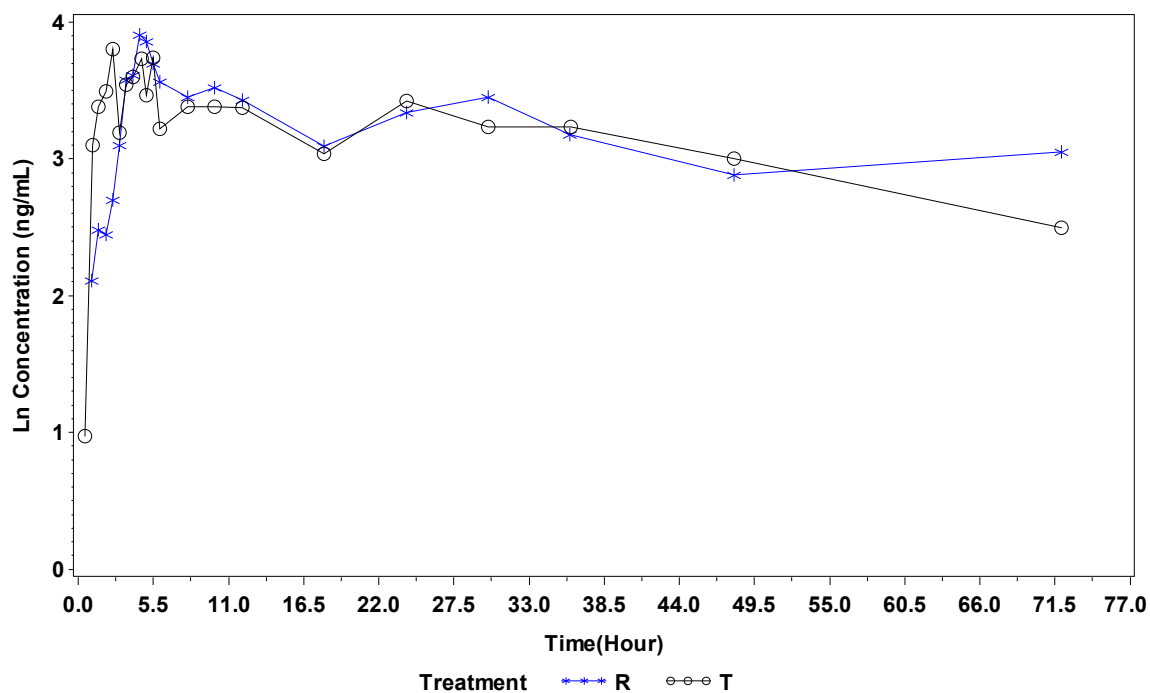


Figure 57

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=29

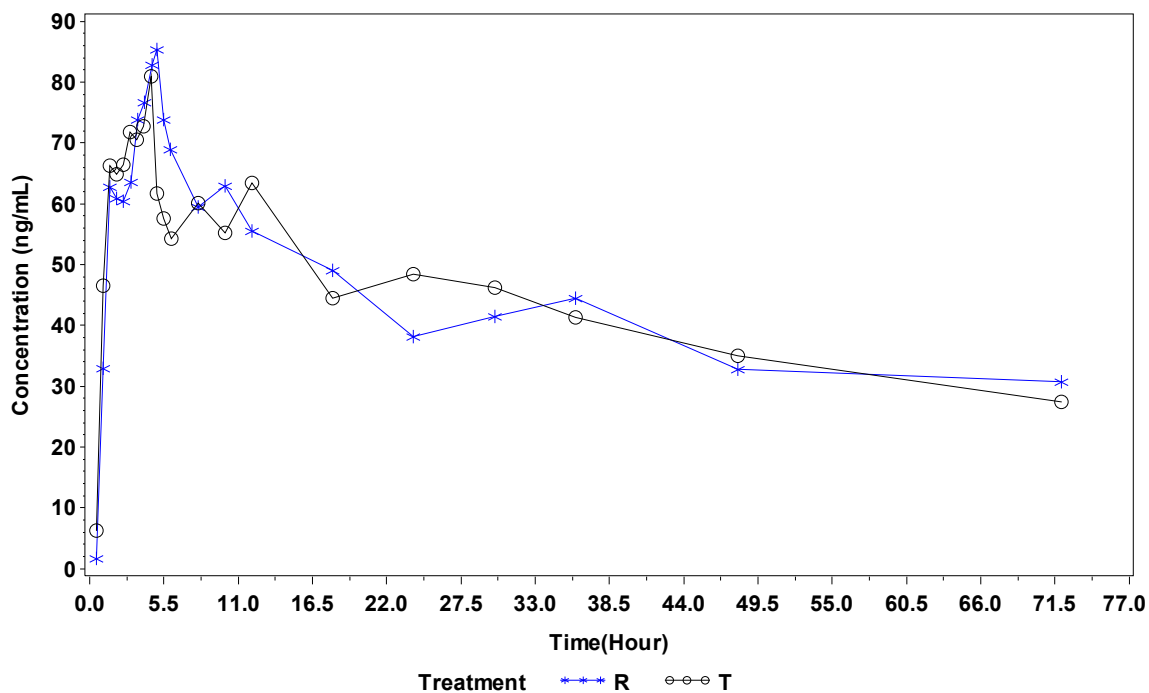


Figure 58

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=29

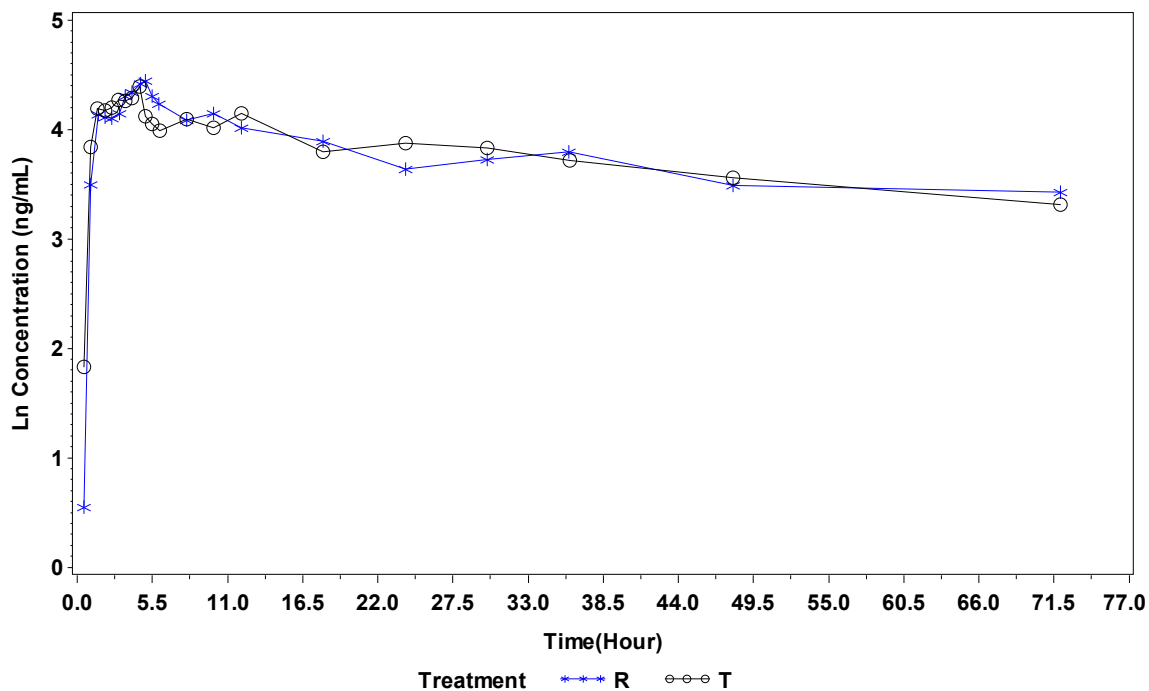


Figure 59

Comparative Linear Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=30

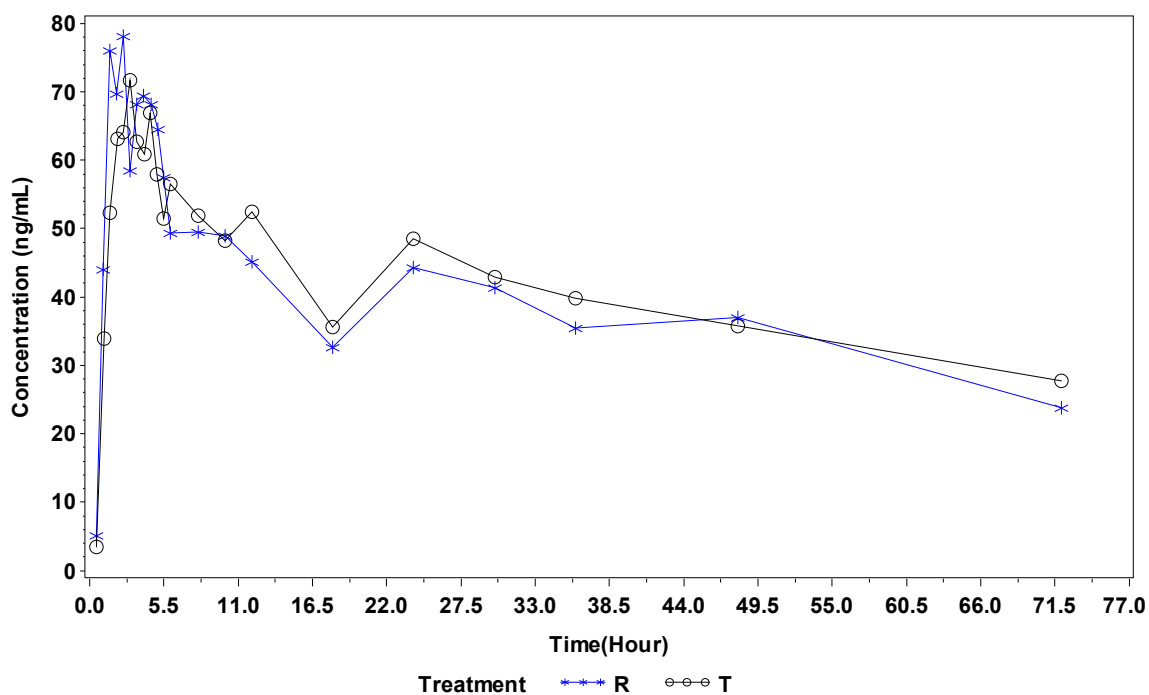


Figure 60

Comparative Semi Log Plot of Levothyroxine Serum Concentration (ng/mL) Vs Time (Hour)
Subject No.=30

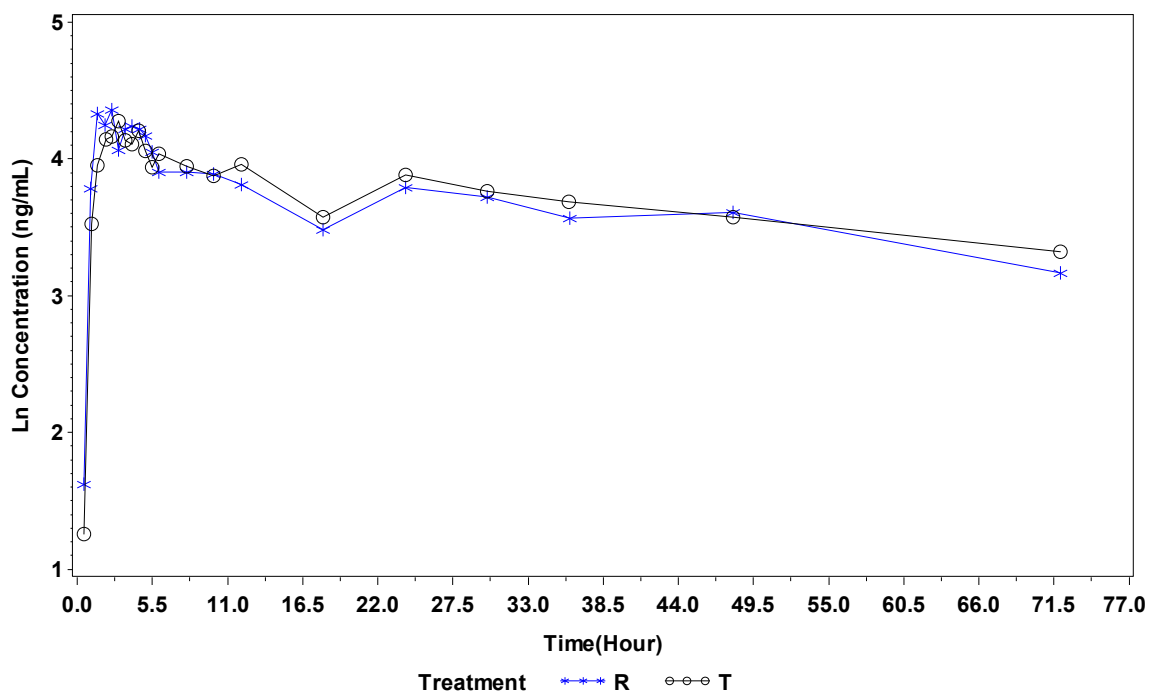


TABLE NO. 1
INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETERS (C_{max} & AUC₀₋₇₂)

Subject No.	Sequence	C _{max} (ng/mL)		Ratio C _{max} (T/R) (%)	AUC ₀₋₇₂ (ng*hrs/mL)		Ratio AUC ₀₋₇₂ (T/R) (%)
		Reference	Test		Reference	Test	
1	RT	72.64	61.78	85.05	2722.3341	2348.0069	86.25
2	RT	38.71	45.47	117.46	1909.0000	1311.9150	68.72
3	TR	59.24	47.64	80.42	2252.9100	1938.2175	86.03
4	TR	66.07	37.24	56.36	2454.6696	1482.0825	60.38
5	TR	76.76	68.76	89.58	3085.3950	2676.1801	86.74
6	RT	57.95	48.89	84.37	2460.2052	2041.4834	82.98
7	TR	72.63	60.49	83.29	2706.6762	2461.8940	90.96
8	RT	64.25	60.84	94.69	2866.9023	2598.5725	90.64
9	TR	83.76	62.35	74.44	3717.2454	2273.9212	61.17
10	RT	80.81	63.76	78.90	3323.3650	2270.3728	68.32
11	TR	57.53	53.38	92.79	1948.1900	2157.0338	110.72
12	RT	68.66	70.01	101.97	2350.5325	2403.7250	102.26
13	TR	115.49	82.37	71.32	4067.2396	2962.8033	72.85
14	TR	66.63	56.05	84.12	2586.3425	2109.5209	81.56
15	TR	67.46	62.55	92.72	3232.8475	2702.9075	83.61
16	RT	69.91	55.22	78.99	2632.0583	1933.5750	73.46
17	RT	72.67	69.12	95.11	3006.2731	2734.8985	90.97
18	RT	57.05	44.59	78.16	1768.7318	1876.5175	106.09
19	RT	66.95	53.86	80.45	2605.9075	2286.5288	87.74
20	RT	80.90	69.34	85.71	3060.2705	2813.0645	91.92
21	TR	64.91	56.31	86.75	2781.9275	1944.7120	69.91
22	RT	59.71	64.42	107.89	2403.0682	1824.1391	75.91
23	TR	66.50	57.40	86.32	1865.8722	2311.8996	123.90
24	TR	62.81	54.79	87.23	2520.8802	2531.0661	100.40
25	RT	61.19	50.94	83.25	2213.8496	2226.8556	100.59
26	TR	67.78	56.51	83.37	2359.6414	1751.5858	74.23
27	RT	96.90	80.62	83.20	3762.5491	2745.7423	72.98
28	TR	49.88	44.87	89.96	1718.7516	1634.9526	95.12
29	TR	85.46	80.90	94.66	3022.6380	3050.2654	100.91
30	RT	78.19	71.70	91.70	2749.0101	2869.3482	104.38
N		30	30	30	30	30	30
Arithmetic Mean		69.647	59.739	----	2671.84279	2275.79291	----
Median		67.21	58.95	----	2618.9829	2280.2250	----
S.D.		14.2765	11.1848	----	582.826467	445.738194	----
C.V.%		20.50	18.72	----	21.81	19.59	----
Minimum		38.71	37.24	----	1718.7516	1311.9150	----
Maximum		115.49	82.37	----	4067.2396	3050.2654	----

TABLE NO. 2
INDIVIDUAL AND MEAN PHARMACOKINETIC PARAMETER (T_{max})

Subject No.	Sequence	T _{max} (hrs)	
		Reference Te	st
1	RT	2.00	3.00
2	RT	5.50	3.00
3	TR	3.00	1.50
4	TR	4.00	3.50
5	TR	4.50	4.50
6	RT	2.50	4.52
7	TR	2.00	2.50
8	RT	2.50	2.00
9	TR	4.00	2.00
10	RT	4.50	4.50
11	TR	3.50	4.00
12	RT	2.50	2.50
13	TR	4.00	4.50
14	TR	4.50	4.50
15	TR	5.50	4.00
16	RT	4.52	1.50
17	RT	1.50	4.00
18	RT	1.50	3.50
19	RT	3.00	4.50
20	RT	3.50	2.50
21	TR	5.00	4.50
22	RT	4.52	2.50
23	TR	2.00	4.57
24	TR	3.50	3.52
25	RT	4.52	4.50
26	TR	2.52	2.50
27	RT	1.52	1.50
28	TR	4.50	2.50
29	TR	5.00	4.53
30	RT	2.50	3.00
N		30	30
Arithmetic Mean		3.470	3.338
Median		3.50	3.50
S.D.		1.2384	1.0741
C.V.%		35.69	32.18
Minimum		1.50	1.50
Maximum		5.50	4.57

ADVERSE EVENT LISTING

Listing of Adverse Events by Subjects:

- During Study:**

There was no adverse event occurred during conduct of the study.

- Post-study Evaluation:**

During post-study safety assessment adverse events were reported for twelve subjects (subject number 05, 06, 08, 09, 14, 21, 23, 24, 25, 28, 29 and 30).The detailed description of the adverse events and their handling are mentioned below:

Sub. No.	Period	Adverse Events/ Symptoms	Date and time of Occurrence	Date and time of Resolution	Date and Time of Last Dose Administration	Treatment Received (Sequence)	Expected (Y/N)	Serious (Y/N)	Action Taken	Severity	Impact of Adverse Drug Reaction on Future Health	Relationship with Study Drug
05	Post study	Potassium (5.82 mmol/ L)- Increased	12 th May 2018 09:37 hrs	N/AP	09 th May 2018 09:12 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
06	Post study	Potassium (5.76 mmol/ L)- Increased	12 th May 2018 09:44 hrs	N/AP	09 th May 2018 09:15 hrs	T (RT)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
08	Post study	SGPT (85.4 U/L) – Increased	12 th May 2018 09:53 hrs	N/AP	09 th May 2018 09:21 hrs	T (RT)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
09	Post study	Haemoglobin (11.4 g/dL) – Decreased	12 th May 2018 09:56 hrs	N/AP	09 th May 2018 09:24 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
		Potassium (5.64 mmol/ L)- Increased										
14	Post study	Eosinophils (15%)- Increased	12 th May 2018 10:12 hrs	N/AP	09 th May 2018 09:39 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely

Sub. No.	Period	Adverse Events/ Symptoms	Date and time of Occurrence	Date and time of Resolution	Date and Time of Last Dose Administration	Treatment Received (Sequence)	Expected (Y/N)	Serious (Y/N)	Action Taken	Severity	Impact of Adverse Drug Reaction on Future Health	Relationship with Study Drug
21	Post study	Alkaline Phosphatase (144.5 U/L)- Increased	12 th May 2018 09:47 hrs	N/AP	09 th May 2018 09:15 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
23	Post study	SGOT (47.7 U/L) – Increased	12 th May 2018 09:53 hrs	N/AP	09 th May 2018 09:21 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
24	Post study	Alkaline Phosphatase (152.8 U/L)- Increased	12 th May 2018 09:57 hrs	N/AP	09 th May 2018 09:24 hrs	R (TR)	N	N	N/AP (Lost for follow-up)	Mild	No consequence	Unlikely
25	Post study	Potassium (5.51 mmol/ L)- Increased	12 th May 2018 10:01 hrs	N/AP	09 th May 2018 09:27 hrs	T (RT)	N	N	N/AP (Lost for follow- up)	Mild	No consequence	Unlikely
28	Post study	Potassium (5.44 mmol/ L)- Increased	12 th May 2018 10:12 hrs	N/AP	09 th May 2018 09:36 hrs	R (TR)	N	N	N/AP (Lost for follow- up)	Mild	No consequence	Unlikely
29	Post study	SGPT (110.2 U/L) – Increased	12 th May 2018 10:15 hrs	N/AP	09 th May 2018 09:39 hrs	R (TR)	N	N	N/AP (Lost for follow- up)	Mild	No consequence	Unlikely
		SGOT (57.7 U/L) – Increased										
30	Post study	Alkaline Phosphatase (140.8 U/L)- Increased	12 th May 2018 10:18 hrs	N/AP	09 th May 2018 09:42 hrs	T (RT)	N	N	N/AP (Lost for follow- up)	Mild	No consequence	Unlikely

R: Reference Drug

T: Test Drug

N/AP: Not Applicable

Time Format: 24 Hours (hh:mm hrs)

Y: Yes

N: No

Description:

Subject No. 05:

Subject showed a clinically significant increase in Potassium 5.82 mmol/L (Reference range: 3.50 - 5.10 mmol/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 22nd June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in Potassium was unlikely related to study drug.

Subject No. 06:

Subject showed a clinically significant increase in Potassium 5.76 mmol/L (Reference range: 3.50 - 5.10 mmol/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 20th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in Potassium was unlikely related to study drug.

Subject No. 08:

Subject showed a clinically significant increase in SGPT 85.4 U/L (Reference range: 16.0 – 63.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 16th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in SGPT was unlikely related to study drug.

Subject No. 09:

Subject showed a clinically significant decrease in Haemoglobin 11.4 g/dL (Reference range: 13.0– 17.0 g/dL) and increase in Potassium 5.64 mmol/L (Reference range: 3.50 - 5.10 mmol/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 11th June 2018 subject informed that he had no health

related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Decrease in Haemoglobin and increase in Potassium were unlikely related to study drug.

Subject No. 14:

Subject showed a clinically significant increase in Eosinophils 15% (Reference range: 1 – 6 %) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 13th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in Eosinophils was unlikely related to study drug.

Subject No. 21:

Subject showed a clinically significant increase in Alkaline Phosphatase 144.5 U/L (Reference range: 46.0 -116.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 22nd June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason .Increase in Alkaline Phosphatase was unlikely related to study drug.

Subject No. 23:

Subject showed a clinically significant increase in SGOT 47.7 U/L (Reference range: 15.0 – 40.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 21st June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in SGOT was unlikely related to study drug.

Subject No. 24:

Subject showed a clinically significant increase in Alkaline Phosphatase 152.8 U/L (Reference range: 46.0 -116.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to

report to the clinical facility, however on 19th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason .Increase in Alkaline Phosphatase was unlikely related to study drug.

Subject No. 25:

Subject showed a clinically significant increase in Potassium 5.51 mmol/L (Reference range: 3.50 - 5.10 mmol/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 20th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in Potassium was unlikely related to study drug.

Subject No. 28:

Subject showed a clinically significant increase in Potassium 5.44 mmol/L (Reference range: 3.50 - 5.10 mmol/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 19th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in Potassium was unlikely related to study drug.

Subject No. 29:

Subject showed a clinically significant increase in SGPT 110.2 U/L (Reference range: 16.0 – 63.0 U/L) and SGOT 57.7 U/L (Reference range: 15.0 – 40.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 14th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason. Increase in SGPT and SGOT were unlikely related to study drug.

Subject No. 30:

Subject showed a clinically significant increase in Alkaline Phosphatase 140.8 U/L (Reference range: 46.0 -116.0 U/L) in the post-study safety assessment done on 12th May 2018. The subject was contacted over telephone and was informed to report to the clinical facility for follow-up. After repeated follow-up, subject failed to report to the clinical facility, however on 25th June 2018 subject informed that he had no health related problem and was not willing to report to the facility for follow-up. Hence the case was lost to follow-up due to personal reason .Increase in Alkaline Phosphatase was unlikely related to study drug.

APPENDIX 16.2.8

LISTING OF INDIVIDUAL LABORATORY PARAMETERS BY SUBJECT

A Baseline Laboratory Tests Report (screening)

Volunteer Reg. No.	Sub. No.	Haematology												
		Leucocyte Count (4.00 – 10.00) x 1000/ µL	Erythrocyte Count (4.5- 5.5) x million/ µL	Haemoglobin (13.0 – 17.0) g/dL	Hematocrit (40.0 – 50.0) %	Platelet Count (150 – 410) x 1000/ µL	Neutrophils (40 – 80) %	Eosinophils (1 – 6) %	Lymphocytes (20 – 40) %	Monocytes (2 – 10) %	Basophils (<1 – 2) %	E.S.R. <15mm/hr	R.B.C. Morphology	Platelets on Smear
BEQ-18872	01	8.41	4.78	12.2*	39.2*	384	70	7*	20	3	0	7	NN	AD
BEQ-4651	02	7.19	4.09*	12.1*	38.6*	310	64	4	30	2	0	7	NN	AD
BEQ-22047	03	7.76	4.89	12.6*	39.3*	412*	76	2	20	2	0	5	NN	IN
BEQ-9543	04	6.84	5.15	13.7	40.8	226	60	8*	30	2	0	5	NN	AD
BEQ-30488	05	6.40	5.36	14.7	46.0	322	66	2	30	2	0	4	NN	AD
BEQ-21341	06	5.46	5.16	12.2*	39.3*	275	56	4	36	4	0	5	NN	AD
BEQ-28073	07	4.05	5.33	14.1	42.1	168	55	2	40	3	0	6	NN	AD
BEQ-30510	08	5.31	5.04	12.8*	39.0*	234	55	5	33	7	0	9	NN	AD
BEQ-23283	09	5.79	4.26*	11.7*	37.0*	260	69	2	22	7	0	11	NN	AD
BEQ-23897	10	9.24	4.88	14.1	42.2	453*	76	2	20	2	0	5	NN	IN
BEQ-19335	11	4.39	4.98	12.6*	39.5*	292	76	2	20	2	0	3	NN	AD
BEQ-18886	12	6.85	4.68	15.4	44.8	269	68	2	27	3	0	5	NN	AD
BEQ-27715	13	9.40	5.22	12.7*	41.6	307	75	2	20	3	0	6	NN	AD
BEQ-26391	14	8.99	5.07	14.3	43.7	247	65	8*	25	2	0	3	NN	AD
BEQ-26962	15	5.76	5.26	14.5	44.2	242	58	2	37	3	0	2	NN	AD
BEQ-30496	16	6.28	4.70	15.3	44.3	285	68	2	27	3	0	3	NN	AD
BEQ-30500	17	8.15	4.47*	13.0	38.3*	245	68	2	28	2	0	5	NN	AD
BEQ-30498	18	5.26	5.68*	12.6*	40.6	249	64	4	30	2	0	2	MI+	AD
BEQ-19761	19	5.89	4.83	13.5	41.2	263	57	3	38	2	0	4	NN	AD
BEQ-22590	20	6.06	5.67*	11.8*	39.9*	215	58	2	38	2	0	5	MI+	AD

Volunteer Reg. No.	Sub. No.	Haematology												
		Leucocyte Count (4.00 – 10.00) x 1000/ µL	Erythrocyte Count (4.5- 5.5) x million/ µL	Haemoglobin (13.0 – 17.0) g/dL	Hematocrit (40.0 – 50.0) %	Platelet Count (150 – 410) x 1000/ µL	Neutrophils (40 – 80) %	Eosinophils (1 – 6) %	Lymphocytes (20 – 40) %	Monocytes (2 – 10) %	Basophils (<1 – 2) %	E.S.R. <15mm/hr	R.B.C. Morphology	Platelets on Smear
BEQ-26842	21	7.35	4.71	13.4	40.3	382	68	2	28	2	0	14	NN	AD
BEQ-30512	22	5.14	5.78*	16.7	47.4	224	51	5	38	6	0	9	NN	AD
BEQ-28272	23	9.81	4.09*	14.0	40.7	440*	65	3	30	2	0	12	NN	IN
BEQ-30523	24	5.55	4.87	14.9	43.8	223	66	2	30	2	0	3	NN	AD
BEQ-16974	25	7.17	4.79	13.7	42.3	282	66	4	28	2	0	5	NN	AD
BEQ-30520	26	9.52	5.34	13.3	43.7	384	66	2	30	2	0	6	NN	AD
BEQ-30517	27	6.88	4.95	12.3*	39.6*	340	64	4	30	2	0	12	NN	AD
BEQ-19531	28	6.95	4.96	13.8	42.0	282	55	2	40	3	0	7	NN	AD
BEQ-12307	29	5.66	4.66	14.3	42.7	252	68	2	28	2	0	4	NN	AD
BEQ-24855	30	8.76	6.10** 5.93* R	15.0	46.9	299	75	2	20	3	0	3	NN	AD

Note: Interpretation of results is based on the methods, units and ranges provided by the pathology laboratory. Value of laboratory test in bracket indicates reference ranges and out of bracket indicates unit.

*: Within Acceptable Limit

**: Outside Acceptable Limit

+: Positive

AD: Adequate

IN: Increased

MI : Microcytosis

NN: Normocytic Normochromic

R: Repeat

Volunteer Reg. No.	Sub. No.	Clinical Biochemistry																Serology		
		Random Blood Sugar (70.0 – 150.0) mg/dL	Total Cholesterol Less than 200.0 mg/dL	Triglycerides Less than 150.0 mg/dL	Blood Urea Nitrogen (7.00 - 18.00) mg/dL	Creatinine (0.70 – 1.30) mg /dL	Alkaline Phosphatase (46.0 – 116.0) U/L	SGPT (16.0 – 63.0) U/L	SGOT (15.0 – 40.0) U/L	Calcium (8.50 – 10.10) mg/dL	GGT (15.0 – 85.0) U/L	Bilirubin Total (0.10 – 1.20) mg/dL	Bilirubin Direct (Less than 0.30) mg/ dL	Bilirubin Indirect (0.10 – 1.00) mg/ dL	Sodium (136.0 – 145.0) mmol/L	Potassium (3.50 – 5.10) mmol/L	Chloride (98.0 – 107.0) mmol/L	HBsAg	HIV 1 & HIV 2	HCV
BEQ-18872	01	96.1	143.7	53.3	8.40	0.82	65.4	21.3	17.2	9.38	26.0	0.33	0.09	0.24	141.5	4.17	104.6	ND	NR	NR
BEQ-4651	02	98.3	140.2	119.5	4.70	0.95	69.4	24.6	20.3	8.97	23.4	0.32	0.08	0.24	140.0	4.63	105.3	ND	NR	NR
BEQ-22047	03	86.7	180.5	88.9	7.30	0.93	91.4	33.8	23.4	9.57	41.5	0.53	0.12	0.41	137.7	4.35	101.6	ND	NR	NR
BEQ-9543	04	89.2	158.0	75.5	12.70	0.89	75.2	42.1	31.3	9.29	45.9	0.57	0.13	0.44	140.7	4.50	104.2	ND	NR	NR
BEQ-30488	05	99.5	178.4	80.0	4.60*	0.80	72.9	32.7	18.5	10.01	35.2	0.87	0.14	0.73	142.0	4.47	103.7	ND	NR	NR
BEQ-21341	06	86.5	169.1	53.8	8.50	0.94	80.0	23.3	18.6	9.34	33.6	0.37	0.09	0.28	139.9	4.39	102.5	ND	NR	NR
BEQ-28073	07	88.7	137.2	73.2	6.00*	0.76	73.2	19.9	16.9	9.20	29.9	0.39	0.10	0.29	139.3	4.73	102.5	ND	NR	NR
BEQ-30510	08	96.9	176.8	88.1	3.40*	0.96	63.1	25.9	15.4	9.39	46.3	0.75	0.15	0.60	141.2	5.04	103.6	ND	NR	NR
BEQ-23283	09	101.5	118.9	56.7	4.80*	0.75	63.3	19.8	20.2	9.20	33.3	0.41	0.10	0.31	137.8	4.73	101.4	ND	NR	NR
BEQ-23897	10	94.2	84.5	77.3	4.10*	0.79	54.0	11.9*	11.0*	9.26	27.7	0.43	0.11	0.32	139.4	4.05	101.3	ND	NR	NR
BEQ-19335	11	146.9	125.2	139.5	10.90	0.95	46.3	17.9	19.7	8.97	34.4	0.82	0.14	0.68	137.5	4.03	102.5	ND	NR	NR
BEQ-18886	12	87.8	141.2	53.7	9.60	0.79	37.2*	12.4*	13.9*	9.00	22.6	0.99	0.15	0.84	142.0	4.31	104.3	ND	NR	NR
BEQ-27715	13	146.5	159.4	95.6	4.10*	0.93	72.4	19.0	16.5	9.09	28.1	0.75	0.13	0.62	139.5	4.34	101.6	ND	NR	NR
BEQ-26391	14	95.0	102.8	36.1	11.40	0.93	91.9	16.5	12.8*	9.16	17.6	0.80	0.16	0.64	143.6	4.16	105.9	ND	NR	NR
BEQ-26962	15	89.2	143.2	82.4	12.60	0.86	60.4	23.9	21.1	9.66	25.0	0.43	0.09	0.34	141.5	4.21	106.8	ND	NR	NR
BEQ-30496	16	107.6	126.4	53.1	10.30	0.73	71.0	33.0	22.1	9.25	27.2	1.14	0.20	0.94	141.6	3.49*	105.2	ND	NR	NR
BEQ-30500	17	116.2	112.3	96.2	8.30	0.86	52.1	25.5	19.1	9.05	17.5	0.53	0.11	0.42	141.1	3.72	105.0	ND	NR	NR
BEQ-30498	18	93.4	144.4	100.9	8.90	1.02	84.4	26.7	15.7	9.03	27.7	1.05	0.17	0.88	139.2	4.28	102.7	ND	NR	NR
BEQ-19761	19	91.6	173.1	104.9	7.20	0.70	80.1	28.4	28.6	9.34	28.6	0.49	0.12	0.37	136.9	4.27	99.7	ND	NR	NR
BEQ-22590	20	92.0	168.0	69.0	10.20	1.08	87.6	21.1	24.7	9.67	21.7	0.34	0.09	0.25	138.3	4.63	101.0	ND	NR	NR
BEQ-26842	21	133.3	160.6	78.0	5.40*	0.65*	112.4	37.1	24.1	9.26	51.1	0.60	0.10	0.50	141.6	4.46	106.6	ND	NR	NR
BEQ-30512	22	93.5	138.1	126.7	10.20	1.01	73.0	30.0	25.3	9.58	28.8	1.21*	0.21	1.00	140.3	4.48	101.7	ND	NR	NR

Appendix 16.2.8

Volunteer Reg. No.	Sub. No.	Clinical Biochemistry																Serology		
		Random Blood Sugar (70.0 – 150.0) mg/dL	Total Cholesterol Less than 200.0 mg/dL	Triglycerides Less than 150.0 mg/dL	Blood Urea Nitrogen (7.00 - 18.00) mg/dL	Creatinine (0.70 – 1.30) mg/dL	Alkaline Phosphatase (46.0 – 116.0) U/L	SGPT (16.0 – 63.0) U/L	SGOT (15.0 – 40.0) U/L	Calcium (8.50 – 10.10) mg/dL	GGT (15.0 – 85.0) U/L	Bilirubin Total (0.10 – 1.20) mg/dL	Bilirubin Direct (Less than 0.30) mg/dL	Bilirubin Indirect (0.10 – 1.00) mg/ dL	Sodium (136.0 – 145.0) mmol/L	Potassium (3.50 – 5.10) mmol/L	Chloride (98.0 – 107.0) mmol/L	HBsAg	HIV 1 & HIV 2	HCV
BEQ-28272	23	87.3	150.6	218.8** 139.6 R	8.80	0.89	85.2	22.2	16.1	8.94	21.4	0.72	0.11	0.61	140.9	4.41	103.4	ND	NR	NR
BEQ-30523	24	88.3	165.5	88.2	6.90*	0.90	121.0*	32.3	25.2	8.79	36.4	0.67	0.12	0.55	138.7	4.32	102.0	ND	NR	NR
BEQ-16974	25	85.4	145.3	81.8	9.60	1.01	78.7	26.8	23.2	8.89	26.2	0.64	0.13	0.51	137.9	4.18	99.5	ND	NR	NR
BEQ-30520	26	102.5	189.3	138.0	3.50*	0.95	88.2	37.5	31.6	9.71	41.4	0.28	0.06	0.22	139.6	5.11*	102.0	ND	NR	NR
BEQ-30517	27	91.7	190.7	135.5	15.80	0.93	88.2	24.7	26.4	8.94	22.8	0.59	0.11	0.48	140.9	4.92	105.0	ND	NR	NR
BEQ-19531	28	94.4	168.7	122.0	14.90	1.12	96.5	30.7	24.8	9.48	23.9	0.46	0.11	0.35	137.3	5.17*	101.0	ND	NR	NR
BEQ-12307	29	104.7	185.3	137.5	4.30*	0.75	78.6	66.0*	35.8	9.11	22.0	0.47	0.09	0.38	139.7	4.70	102.9	ND	NR	NR
BEQ-24855	30	72.8	122.6	31.1	10.20	0.76	123.3*	65.2*	28.8	9.04	21.3	0.56	0.12	0.44	139.1	4.30	104.1	ND	NR	NR

Note: Interpretation of results is based on the methods, units and ranges provided by the pathology laboratory. Value of laboratory test in bracket indicates reference ranges and out of bracket indicates unit.

*: Within Acceptable Limit

**: Outside Acceptable Limit

NR: Non Reactive

ND: Not Detected

R: Repeat

Volunteer Reg. No.	Sub. No.	Routine Examination of Urine																				
		Physical Examination						Chemical Examination							Microscopic Examination							
		Quantity (15 – 100 ml)	Colour (Colourless to yellow)	Appearance (Clear)	Deposits (Absent)	pH (5.0 – 9.0)	Specific Gravity (1.001 – 1.035)	Protein (Negative)	Glucose (Negative)	Ketones (Negative)	Occult Blood (Negative)	Bile Pigments (Negative)	Bile Salts (Absent)	Urobilinogen (Normal)	Red Blood Cells /hpf (0 – 2)	Leucocytes or Pus Cells (/hpf) (2 – 3)	Epithelial Cells /hpf (2 – 5)	Casts /hpf (Absent)	Crystals/hpf (Absent)	Amorphous Material (Absent)	Trichomonas Vaginalis (Absent)	Bacteria /hpf (Absent)
BEQ-18872	01	40	PY	CL	A	6.0	1.025	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	0-1	A	A	A	A	A
BEQ-4651	02	40	PY	CL	A	7.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	0-1	A	A	A	A	A
BEQ-22047	03	30	PY	CL	A	5.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	2-3	A	A	A	A	A
BEQ-9543	04	40	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	1-2	A	A	A	A	A
BEQ-30488	05	40	PY	CL	A	6.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-21341	06	30	PY	CL	A	6.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	2-3	A	A	A	A	A
BEQ-28073	07	45	PY	CL	A	6.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	0-1	A	A	A	A	A
BEQ-30510	08	50	PY	CL	A	6.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-23283	09	40	PY	CL	A	7.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	2-3	1-2	A	A	A	A	A
BEQ-23897	10	50	PY	CL	A	6.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	1-2	A	A	A	A	A
BEQ-19335	11	40	PY	CL	A	6.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-18886	12	50	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	2-3	A	A	A	A	A
BEQ-27715	13	50	PY	CL	A	7.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	OC	2-3	A	A	A	A	A
BEQ-26391	14	45	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	0-1	A	A	A	A	A
BEQ-26962	15	25	PY	CL	A	6.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	1-2	A	A	A	A	A
BEQ-30496	16	45	PY	CL	A	7.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	1-2	A	A	A	A	A
BEQ-30500	17	45	PY	CL	A	7.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	OC	1-2	A	A	A	A	A
BEQ-30498	18	45	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-19761	19	40	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A

Volunteer Reg. No.	Sub. No.	Routine Examination of Urine																				
		Physical Examination						Chemical Examination							Microscopic Examination							
		Quantity (15 – 100 ml)	Colour (Colourless to yellow)	Appearance (Clear)	Deposits (Absent)	pH (5.0 – 9.0)	Specific Gravity (1.001 – 1.035)	Protein (Negative)	Glucose (Negative)	Ketones (Negative)	Occult Blood (Negative)	Bile Pigments (Negative)	Bile Salts (Absent)	Urobilinogen (Normal)	Red Blood Cells /hpf (0 – 2)	Leucocytes or Pus Cells (/hpf) (2 – 3)	Epithelial Cells /hpf (2 – 5)	Casts /hpf (Absent)	Crystals/hpf (Absent)	Amorphous Material (Absent)	Trichomonas Vaginalis (Absent)	Bacteria /hpf (Absent)
BEQ-22590	20	45	PY	CL	A	5.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	OC	A	A	A	A	A
BEQ-26842	21	35	PY	CL	A	7.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	OC	2-3	A	A	A	A	A
BEQ-30512	22	45	PY	CL	A	7.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	1-2	A	A	A	A	A
BEQ-28272	23	40	PY	CL	A	6.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-30523	24	30	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	0-1	A	A	A	A	A
BEQ-16974	25	40	PY	CL	A	7.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	OC	2-3	A	A	A	A	A
BEQ-30520	26	40	PY	CL	A	7.0	1.010	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	1-2	A	A	A	A	A
BEQ-30517	27	50	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	2-3	A	A	A	A	A
BEQ-19531	28	30	PY	CL	A	6.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	0-1	0-1	A	A	A	A	A
BEQ-12307	29	30	PY	CL	A	7.0	1.020	-ve	-ve	-ve	-ve	-ve	A	N	0	2-3	1-2	A	A	A	A	A
BEQ-24855	30	40	PY	CL	A	7.0	1.015	-ve	-ve	-ve	-ve	-ve	A	N	0	1-2	0-1	A	A	A	A	A

Note: Interpretation of results is based on the methods, units and ranges provided by the pathology laboratory. Value of laboratory test in bracket indicates reference ranges and out of bracket indicates unit.

PY: Pale Yellow, CL: Clear, hpf: high power field, N : Normal, -ve: Negative, A: Absent, OC: Occasional

Volunteer Reg. No.	Sub. No.	Thyroid [Serum T ₃ (total), Serum T ₄ (total), Serum Thyroid-Stimulating Hormone (TSH)]		
		Serum T ₃ (Total) (70 -200 ng/dl)	Serum T ₄ (Total) (5 -13 µg/dl)	Serum thyroid-stimulating hormone (TSH) (0.2 - 6.0 µIU/ml)
BEQ-18872	01	88.9	7.73	3.78
BEQ-4651	02	96.2	6.43	1.45
BEQ-22047	03	100.0	8.81	1.95
BEQ-9543	04	91.7	7.89	1.01
BEQ-30488	05	96.5	7.63	0.72
BEQ-21341	06	89.0	6.09	1.99
BEQ-28073	07	87.9	7.99	1.02
BEQ-30510	08	90.7	7.23	5.57
BEQ-23283	09	94.6	8.03	4.13
BEQ-23897	10	100.0	6.83	1.24
BEQ-19335	11	89.2	6.10	1.15
BEQ-18886	12	93.5	6.88	1.34
BEQ-27715	13	105.2	9.20	0.60
BEQ-26391	14	112.0	10.0	0.57
BEQ-26962	15	99.4	6.53	1.53
BEQ-30496	16	87.3	6.77	2.26
BEQ-30500	17	111.0	7.37	2.27
BEQ-30498	18	88.2	6.30	2.17
BEQ-19761	19	130.3	7.46	2.38
BEQ-22590	20	139.3	8.67	1.89
BEQ-26842	21	110.0	6.67	2.82
BEQ-30512	22	92.4	7.80	1.56
BEQ-28272	23	96.2	8.37	1.29
BEQ-30523	24	87.9	7.52	5.18
BEQ-16974	25	100.5	8.72	3.50
BEQ-30520	26	92.5	8.04	4.07
BEQ-30517	27	105.3	9.1	1.17
BEQ-19531	28	89.6	7.98	1.62
BEQ-12307	29	87.2	7.53	3.69
BEQ-24855	30	117.2	10.4	1.50

B Laboratory Tests Report (Post Study Safety Assessment)

Volunteer Reg. No.	Sub. No.	Haematology												
		Leucocyte Count (4.00 – 10.00) x 1000/ µL	Erythrocyte Count (4.5- 5.5) x million/µL	Haemoglobin (13.0 – 17.0) g/dL	Hematocrit (40.0 – 50.0) %	Platelet Count (150 – 410) x 1000 /µL	Neutrophils (40 – 80) %	Eosinophils (1 –6) %	Lymphocytes (20 – 40) %	Monocytes (2 – 10) %	Basophils (<1 –2) %	ESR <15 mm / hr	R.B.C. Morphology	Platelets on Smear
BEQ-18872	01	7.09	5.04	12.6*	41.5	416*	61	7*	26	6	0	6	NN	IN
BEQ-4651	02	7.10	4.40*	13.2	41.7	259	49	6	38	7	0	5	NN	AD
BEQ-22047	03	7.31	5.14	13.5	41.9	384	60	6	27	7	0	4	NN	AD
BEQ-9543	04	7.35	5.48	15.0	44.6	251	48	7*	39	6	0	3	NN	AD
BEQ-30488	05	6.30	5.14	14.6	45.3	335	54	3	37	6	0	7	NN	AD
BEQ-21341	06	4.90	4.65	11.7*	37.6*	268	57	5	35	3	0	6	NN	AD
BEQ-28073	07	4.61	5.25	14.6	44.6	187	53	5	38	4	0	3	NN	AD
BEQ-30510	08	4.62	4.82	12.8*	38.5*	224	58	3	36	3	0	9	NN	AD
BEQ-23283	09	4.57	4.17*	11.4**	36.3*	279	66	2	29	3	0	8	NN	AD
BEQ-23897	10	8.29	4.71	14.1	41.9	379	72	2	23	3	0	7	NN	AD
BEQ-19335	11	4.31	5.08	13.1	41.5	250	60	2	34	4	0	9	NN	AD
BEQ-18886	12	7.45	4.46*	15.1	42.8	262	71	2	23	4	0	5	NN	AD
BEQ-27715	13	7.13	5.13	12.5*	41.3	290	57	4	34	5	0	6	NN	AD
BEQ-26391	14	9.60	4.65	13.4	41.2	276	53	15**	29	3	0	3	NN	AD
BEQ-26962	15	5.87	5.33	15.2	46.7	240	61	2	32	5	0	8	NN	AD
BEQ-30496	16	6.82	4.79	15.6	45.4	284	59	4	34	3	0	9	NN	AD
BEQ-30500	17	6.52	4.43*	13.2	39.3*	254	58	2	36	4	0	12	NN	AD
BEQ-30498	18	5.23	5.88*	13.3	43.2	252	59	4	32	5	0	8	MI+	AD
BEQ-19761	19	7.46	4.84	13.1	41.2	308	60	4	32	4	0	9	NN	AD
BEQ-22590	20	5.28	5.71*	12.2*	40.8	223	54	3	38	5	0	5	MI+	AD
BEQ-26842	21	7.73	4.92	13.7	42.2	406	58	2	36	4	0	7	NN	AD

Appendix 16.2.8

Volunteer Reg. No.	Sub. No.	Haematology												
		Leucocyte Count (4.00 – 10.00) x 1000/ µL	Erythrocyte Count (4.5- 5.5) x million/µL	Haemoglobin (13.0 – 17.0) g/dL	Hematocrit (40.0 – 50.0) %	Platelet Count (150 – 410) x 1000 /µL	Neutrophils (40 – 80) %	Eosinophils (1 –6) %	Lymphocytes (20 – 40) %	Monocytes (2 – 10) %	Basophils (<1 –2) %	ESR <15 mm / hr	R.B.C. Morphology	Platelets on Smear
BEQ-30512	22	6.57	5.49	16.4	47.5	265	64	3	29	4	0	5	NN	AD
BEQ-28272	23	10.03*	4.40*	15.4	45.4	404	65	3	29	3	0	6	MA+	AD
BEQ-30523	24	5.70	4.99	15.0	44.4	177	61	3	33	3	0	6	NN	AD
BEQ-16974	25	5.67	4.70	14.3	44.1	279	60	3	33	4	0	5	NN	AD
BEQ-30520	26	8.04	5.04	12.9*	41.7	352	57	3	37	3	0	3	NN	AD
BEQ-30517	27	5.63	5.02	12.5*	40.0	302	53	5	37	5	0	6	NN	AD
BEQ-19531	28	5.71	4.65	12.9*	39.9*	310	55	2	40	3	0	3	NN	AD
BEQ-12307	29	5.90	4.53	14.2	42.5	260	63	3	30	4	0	9	NN	AD
BEQ-24855	30	8.22	5.71*	14.0	43.9	320	64	3	29	4	0	10	NN	AD

Note: Interpretation of results is based on the methods, units and ranges provided by the pathology laboratory. Value of laboratory test in bracket indicates reference ranges and out of bracket indicates unit.

*: Within Acceptable Limit

**: Outside Acceptable Limit

+: Positive

AD: Adequate

IN: Increased

MI : Microcytosis

NN: Normocytic Normochromic

MA : Macrocytosis

Volunteer Reg. No.	Sub. No.	Clinical Biochemistry															
		Fasting Blood Sugar (70.0 – 110.0) mg/dL	Total Cholesterol Less than 200.0 mg/dL	Triglycerides Less than 150.0 mg/dL	Blood Urea Nitrogen (7.00 to 18.00) mg/dL	Creatinine (0.70 – 1.30) mg /dL	Alkaline Phosphatase (46.0 – 116.0) U/L	SGPT (16.0 – 63.0) U/L	SGOT (15.0 – 40.0) U/L	Calcium (8.50 – 10.10) mg/dL	GGT (15.0 – 85.0) U/L	Bilirubin Total (0.10 – 1.20) mg/dL	Bilirubin Direct Less than 0.30 mg/dL	Bilirubin Indirect (0.10 – 1.00) mg/dL	Sodium (136.0 – 145.0) mmol/L	Potassium (3.50 – 5.10) mmol/L	Chloride (98.0 – 107.0) mmol/L
BEQ-18872	01	108.7	147.0	49.3	8.20	0.78	76.3	22.8	19.1	9.31	30.0	0.29	0.07	0.22	139.8	5.30*	103.6
BEQ-4651	02	103.3	205.9*	123.7	6.20*	0.88	82.7	25.5	28.0	9.46	27.8	0.40	0.08	0.32	142.3	4.77	104.2
BEQ-22047	03	100.8	144.3	89.5	6.20*	0.78	87.9	32.4	24.7	9.34	41.1	0.27	0.07	0.20	140.3	4.84	103.4
BEQ-9543	04	95.7	176.5	58.1	7.90	0.78	92.5	55.9	35.4	9.41	71.9	0.47	0.11	0.36	142.0	5.22*	103.9
BEQ-30488	05	96.9	167.4	95.6	9.40	0.74	84.2	67.4*	35.5	9.61	52.4	0.87	0.14	0.73	141.6	5.82**	103.8
BEQ-21341	06	102.9	159.2	67.9	6.40*	0.86	73.3	21.7	17.9	9.15	36.1	0.32	0.07	0.25	141.4	5.76**	105.2
BEQ-28073	07	103.0	125.8	51.2	6.90*	0.72	89.3	21.2	20.2	9.24	26.2	0.34	0.08	0.26	139.8	5.02	101.8
BEQ-30510	08	98.1	155.0	94.0	6.80*	0.80	75.7	85.4**	43.2*	8.97	64.9	0.54	0.12	0.42	139.6	4.95	102.4
BEQ-23283	09	103.9	104.1	44.1	6.70*	0.68*	63.4	42.9	41.0*	9.31	43.0	0.32	0.09	0.23	138.9	5.64**	100.6
BEQ-23897	10	93.9	74.1	76.5	7.00	0.76	57.1	19.9	18.7	8.90	27.0	0.60	0.14	0.46	142.9	4.99	105.6
BEQ-19335	11	98.3	107.5	66.4	5.60*	0.84	44.3*	22.4	19.9	9.25	31.5	0.69	0.16	0.53	140.0	4.65	101.6
BEQ-18886	12	92.8	145.6	74.6	6.00*	0.75	44.7*	17.4	13.5*	8.93	23.4	0.88	0.16	0.72	143.1	4.21	104.1
BEQ-27715	13	100.5	143.6	82.1	5.70*	0.72	72.5	23.2	18.9	9.13	26.0	0.60	0.12	0.48	139.9	4.90	100.8
BEQ-26391	14	97.6	104.1	45.1	7.50	0.77	90.1	19.1	13.7*	9.19	18.5	0.89	0.18	0.71	143.5	4.21	106.2
BEQ-26962	15	94.5	166.2	85.1	8.10	0.80	73.9	26.4	21.0	9.62	25.5	0.50	0.09	0.41	143.9	4.41	105.3
BEQ-30496	16	95.3	128.2	73.0	6.60*	0.65*	83.1	36.4	21.7	9.47	32.4	0.54	0.14	0.40	141.9	5.17*	103.5
BEQ-30500	17	84.0	115.6	50.8	7.40	0.77	58.6	22.5	19.3	8.90	16.4	0.43	0.11	0.32	142.2	4.19	103.5
BEQ-30498	18	94.3	166.0	54.5	7.20	0.96	81.9	22.0	14.0*	9.54	32.1	0.59	0.11	0.48	143.2	4.98	104.0
BEQ-19761	19	96.9	158.9	100.6	5.70*	0.67*	81.7	29.6	28.2	9.03	26.4	0.32	0.07	0.25	143.5	5.06	104.4
BEQ-22590	20	97.1	174.1	104.8	6.30*	0.94	91.4	20.7	19.5	9.45	23.8	0.31	0.06	0.25	141.5	4.63	102.5
BEQ-26842	21	112.1*	165.2	55.2	5.20*	0.57*	144.5**	46.0	31.7	9.16	47.1	0.34	0.07	0.27	142.6	5.16*	106.6
BEQ-30512	22	98.2	143.8	106.4	6.60*	0.91	83.3	41.9	22.5	9.36	28.8	0.80	0.15	0.65	143.1	5.27*	104.3

Appendix 16.2.8

Volunteer Reg. No.	Sub. No.	Clinical Biochemistry															
		Fasting Blood Sugar (70.0 – 110.0) mg/dL	Total Cholesterol Less than 200.0 mg/dL	Triglycerides Less than 150.0 mg/dL	Blood Urea Nitrogen (7.00 to 18.00) mg/dL	Creatinine (0.70 – 1.30) mg /dL	Alkaline Phosphatase (46.0 – 116.0) U/L	SGPT (16.0 – 63.0) U/L	SGOT (15.0 – 40.0) U/L	Calcium (8.50 – 10.10) mg/dL	GGT (15.0 – 85.0) U/L	Bilirubin Total (0.10 – 1.20) mg/dL	Bilirubin Direct Less than 0.30 mg/dL	Bilirubin Indirect (0.10 – 1.00) mg/dL	Sodium (136.0 – 145.0) mmol/L	Potassium (3.50 – 5.10) mmol/L	Chloride (98.0 – 107.0) mmol/L
BEQ-28272	23	101.6	155.8	181.8**	9.40	0.84	95.1	49.3	47.7**	9.40	26.8	0.66	0.12	0.54	140.5	5.31*	101.7
BEQ-30523	24	102.4	129.5	62.0	5.50*	0.76	152.8**	59.4	34.4	8.94	39.6	0.45	0.10	0.35	142.6	4.45	105.3
BEQ-16974	25	94.6	164.0	37.3	7.00	0.82	97.1	43.7	35.0	9.38	30.5	0.50	0.10	0.40	143.5	5.51**	104.4
BEQ-30520	26	116.7*	172.5	102.4	4.90*	0.88	80.5	42.5	28.7	9.39	37.9	0.27	0.06	0.21	142.0	5.12*	104.5
BEQ-30517	27	95.7	179.0	83.6	11.30	0.83	83.5	31.1	28.3	8.76	27.2	0.43	0.09	0.34	139.7	5.35*	104.1
BEQ-19531	28	106.1	144.0	103.4	6.40*	1.20	103.6	23.8	19.5	8.99	24.2	0.38	0.08	0.30	140.7	5.44**	104.4
BEQ-12307	29	111.3*	173.1	142.1	5.40*	0.76	86.5	110.2**	57.7**	9.30	28.6	0.71	0.13	0.58	140.1	5.09	102.3
BEQ-24855	30	93.2	111.9	74.9	8.50	0.69*	140.8**	56.8	25.1	9.41	23.9	0.37	0.09	0.28	142.5	5.05	105.3

Note: Interpretation of results is based on the methods, units and ranges provided by the pathology laboratory. Value of laboratory test in bracket indicates reference ranges and out of bracket indicates unit.

*: Within Acceptable Limit

**: Outside Acceptable Limit

C ECG AND X-RAY CHEST (PA VIEW)

Volunteer Reg. No.	Subject No.	ECG (Screening)	Chest X-ray (PA view) (Screening)	ECG (Post Study Assessment)
		Clinical Impression	Clinical Impression	Clinical Impression
BEQ-18872	01	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-4651	02	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-22047	03	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-9543	04	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30488	05	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-21341	06	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-28073	07	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30510	08	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-23283	09	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-23897	10	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-19335	11	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-18886	12	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-27715	13	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-26391	14	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-26962	15	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30496	16	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30500	17	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30498	18	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-19761	19	Clinically acceptable	Clinically acceptable	Clinically acceptable

Volunteer Reg. No.	Subject No.	ECG (Screening)	Chest X-ray (PA view) (Screening)	ECG (Post Study Assessment)
		Clinical Impression	Clinical Impression	Clinical Impression
BEQ-22590	20	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-26842	21	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30512	22	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-28272	23	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30523	24	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-16974	25	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30520	26	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-30517	27	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-19531	28	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-12307	29	Clinically acceptable	Clinically acceptable	Clinically acceptable
BEQ-24855	30	Clinically acceptable	Clinically acceptable	Clinically acceptable

D VITAL PARAMETERS LISTING

LIST OF TABLES

Table No.	Content Page	number
1.	Baseline Vitals (Screening)	16 of 36
2.	Vitals (Study Period – 1)	17 of 36 to 26 of 36
3.	Vitals (Study Period – 2)	27 of 36 to 36 of 36

TABLE 1

Baseline – Vitals (Screening)

Vol. Reg. No.	Subject No.	Supine			
		Respiration (Rate/Min)	Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
BEQ-18872	01	18	72	97.5	118/70
BEQ-4651	02	18	76	98.2	122/80
BEQ-22047	03	17	68	98.0	120/70
BEQ-9543	04	16	70	98.0	126/72
BEQ-30488	05	17	70	96.0	124/70
BEQ-21341	06	18	76	97.3	122/80
BEQ-28073	07	17	60	96.5	112/64
BEQ-30510	08	20	66	97.7	110/80
BEQ-23283	09	20	74	97.9	110/70
BEQ-23897	10	18	68	97.1	110/68
BEQ-19335	11	17	72	97.4	116/72
BEQ-18886	12	17	66	96.7	120/66
BEQ-27715	13	17	62	96.2	124/68
BEQ-26391	14	18	76	96.8	110/70
BEQ-26962	15	18	64	97.9	102/66
BEQ-30496	16	17	62	96.0	106/80
BEQ-30500	17	16	72	98.0	124/72
BEQ-30498	18	16	66	96.2	132/80
BEQ-19761	19	18	60	97.1	104/60
BEQ-22590	20	18	60	97.3	134/86
BEQ-26842	21	17	82	98.3	122/66
BEQ-30512	22	18	74	98.0	116/82
BEQ-28272	23	17	80	97.2	124/80
BEQ-30523	24	18	62	97.3	130/84
BEQ-16974	25	20	70	96.4	120/80
BEQ-30520	26	18	64	97.5	116/80
BEQ-30517	27	17	62	97.1	112/80
BEQ-19531	28	18	68	97.2	110/80
BEQ-12307	29	18	62	96.8	110/70
BEQ-24855	30	17	66	97.6	110/70

TABLE- 2
Vitals (Study Period – 1)

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
01	03/04/2018	Check-in	76	97.0	118/84
	04/04/2018	PD	70	97.4	120/80
	04/04/2018	1.00	68	97.4	120/78
	04/04/2018	3.00	64	96.6	114/74
	04/04/2018	6.00	72	97.7	120/74
	04/04/2018	9.00	74	97.6	120/80
	05/04/2018	23.00	68	97.3	116/80
	05/04/2018	29.00	72	97.6	114/70
	05/04/2018	35.00	74	97.2	118/76
	06/04/2018	48.00	66	96.7	108/72
	07/04/2018	72.00	70	97.2	110/76
02	03/04/2018	Check-in	80	97.5	120/82
	04/04/2018	PD	76	98.1	116/76
	04/04/2018	1.00	68	96.3	110/72
	04/04/2018	3.00	62	96.7	108/64
	04/04/2018	6.00	74	97.6	114/70
	04/04/2018	9.00	66	98.0	122/78
	05/04/2018	23.00	78	97.1	110/68
	05/04/2018	29.00	70	97.6	112/70
	05/04/2018	35.00	68	97.2	114/76
	06/04/2018	48.00	68	97.2	114/70
	07/04/2018	72.00	72	97.4	116/78
03	03/04/2018	Check-in	64	97.3	108/68
	04/04/2018	PD	70	97.5	110/70
	04/04/2018	1.00	64	97.0	118/74
	04/04/2018	3.00	64	97.1	120/80
	04/04/2018	6.00	68	97.7	124/80
	04/04/2018	9.00	70	97.4	114/76
	05/04/2018	23.00	66	97.1	110/70
	05/04/2018	29.00	68	97.4	108/66
	05/04/2018	35.00	72	97.7	110/72
	06/04/2018	48.00	62	96.8	112/70
	07/04/2018	72.00	74	98.6	124/80

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
04	03/04/2018	Check-in	82	97.6	112/76
	04/04/2018	PD	78	98.2	114/70
	04/04/2018	1.00	72	96.5	108/70
	04/04/2018	3.00	64	97.3	104/62
	04/04/2018	6.00	78	98.0	118/70
	04/04/2018	9.00	76	97.9	114/72
	05/04/2018	23.00	76	96.7	110/70
	05/04/2018	29.00	70	97.2	106/66
	05/04/2018	35.00	74	97.6	108/74
	06/04/2018	48.00	72	97.2	110/68
	07/04/2018	72.00	70	96.7	112/68
05	03/04/2018	Check-in	72	97.3	110/66
	04/04/2018	PD	74	97.8	118/74
	04/04/2018	1.00	64	96.7	110/68
	04/04/2018	3.00	60	97.1	108/70
	04/04/2018	6.00	72	96.5	110/70
	04/04/2018	9.00	68	96.8	110/74
	05/04/2018	23.00	68	96.6	108/66
	05/04/2018	29.00	74	97.9	110/72
	05/04/2018	35.00	78	98.2	122/78
	06/04/2018	48.00	68	97.4	102/64
	07/04/2018	72.00	76	96.6	108/66
06	03/04/2018	Check-in	86	97.9	118/82
	04/04/2018	PD	74	97.5	124/76
	04/04/2018	1.00	68	97.3	110/80
	04/04/2018	3.00	72	97.0	120/80
	04/04/2018	6.00	88	97.8	118/74
	04/04/2018	9.00	82	97.1	124/82
	05/04/2018	23.00	74	97.6	120/80
	05/04/2018	29.00	70	97.2	118/72
	05/04/2018	35.00	68	97.1	114/78
	06/04/2018	48.00	80	97.2	120/80
	07/04/2018	72.00	76	97.5	118/70

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
07	03/04/2018	Check-in	72	97.2	112/68
	04/04/2018	PD	68	97.1	110/66
	04/04/2018	1.00	64	96.8	104/64
	04/04/2018	3.00	68	97.3	112/70
	04/04/2018	6.00	72	97.9	110/68
	04/04/2018	9.00	70	97.3	112/74
	05/04/2018	23.00	68	96.5	110/72
	05/04/2018	29.00	66	97.1	106/68
	05/04/2018	35.00	64	97.3	110/70
	06/04/2018	48.00	68	97.2	110/70
	07/04/2018	72.00	64	97.4	112/76
08	03/04/2018	Check-in	84	97.6	114/72
	04/04/2018	PD	76	97.9	120/80
	04/04/2018	1.00	76	96.8	110/74
	04/04/2018	3.00	68	97.1	114/80
	04/04/2018	6.00	74	97.5	120/80
	04/04/2018	9.00	76	97.7	114/78
	05/04/2018	23.00	68	97.5	110/76
	05/04/2018	29.00	66	97.1	116/68
	05/04/2018	35.00	68	97.3	114/72
	06/04/2018	48.00	66	97.0	110/74
	07/04/2018	72.00	70	97.8	108/66
09	03/04/2018	Check-in	80	98.0	106/74
	04/04/2018	PD	72	97.7	112/70
	04/04/2018	1.00	72	97.1	108/66
	04/04/2018	3.00	76	97.8	104/60
	04/04/2018	6.00	76	97.2	112/68
	04/04/2018	9.00	74	97.7	108/72
	05/04/2018	23.00	68	96.9	108/64
	05/04/2018	29.00	70	97.4	110/70
	05/04/2018	35.00	72	97.7	124/76
	06/04/2018	48.00	66	96.8	106/64
	07/04/2018	72.00	66	96.9	104/68

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
10	03/04/2018	Check-in	76	96.9	110/64
	04/04/2018	PD	74	97.2	116/68
	04/04/2018	1.00	64	96.8	104/70
	04/04/2018	3.00	60	97.1	100/64
	04/04/2018	6.00	72	97.6	108/72
	04/04/2018	9.00	66	96.9	110/70
	05/04/2018	23.00	68	96.8	106/68
	05/04/2018	29.00	72	97.1	104/66
	05/04/2018	35.00	66	97.3	110/70
	06/04/2018	48.00	64	97.3	102/64
	07/04/2018	72.00	70	97.6	106/64
11	03/04/2018	Check-in	68	96.8	110/64
	04/04/2018	PD	70	97.4	116/80
	04/04/2018	1.00	68	96.6	120/80
	04/04/2018	3.00	64	97.1	110/72
	04/04/2018	6.00	64	97.5	118/74
	04/04/2018	9.00	68	97.9	122/78
	05/04/2018	23.00	66	97.1	120/70
	05/04/2018	29.00	68	97.6	116/68
	05/04/2018	35.00	64	98.2	124/78
	06/04/2018	48.00	66	97.2	116/70
	07/04/2018	72.00	76	98.0	110/74
12	03/04/2018	Check-in	64	97.0	104/66
	04/04/2018	PD	68	97.3	108/74
	04/04/2018	1.00	72	97.1	104/64
	04/04/2018	3.00	64	96.3	100/60
	04/04/2018	6.00	74	97.9	114/80
	04/04/2018	9.00	72	98.2	116/78
	05/04/2018	23.00	68	96.6	108/74
	05/04/2018	29.00	70	97.0	110/72
	05/04/2018	35.00	78	97.8	116/78
	06/04/2018	48.00	68	97.0	110/64
	07/04/2018	72.00	64	96.8	108/70

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
13	03/04/2018	Check-in	76	97.9	122/74
	04/04/2018	PD	72	97.7	116/76
	04/04/2018	1.00	72	97.0	120/70
	04/04/2018	3.00	62	97.7	114/68
	04/04/2018	6.00	68	98.1	124/76
	04/04/2018	9.00	64	97.8	116/74
	05/04/2018	23.00	66	96.9	112/76
	05/04/2018	29.00	64	97.0	110/70
	05/04/2018	35.00	66	97.2	114/76
	06/04/2018	48.00	72	97.0	102/64
	07/04/2018	72.00	66	97.8	106/66
	14	03/04/2018	Check-in	68	96.9
04/04/2018		PD	66	97.2	110/74
04/04/2018		1.00	60	96.4	104/68
04/04/2018		3.00	62	96.8	104/60
04/04/2018		6.00	76	97.3	118/72
04/04/2018		9.00	72	97.0	124/82
05/04/2018		23.00	66	96.8	110/70
05/04/2018		29.00	74	97.1	120/80
05/04/2018		35.00	76	97.3	118/72
06/04/2018		48.00	72	97.4	104/70
07/04/2018		72.00	68	97.8	106/70
15		03/04/2018	Check-in	72	97.6
	04/04/2018	PD	70	97.9	120/80
	04/04/2018	1.00	64	96.5	114/72
	04/04/2018	3.00	60	97.1	108/64
	04/04/2018	6.00	68	97.6	120/70
	04/04/2018	9.00	70	97.0	124/76
	05/04/2018	23.00	76	97.5	120/70
	05/04/2018	29.00	68	97.1	116/68
	05/04/2018	35.00	70	96.8	114/74
	06/04/2018	48.00	68	97.2	110/68
	07/04/2018	72.00	70	97.7	108/66

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
16	03/04/2018	Check-in	82	97.9	124/82
	04/04/2018	PD	74	97.5	116/80
	04/04/2018	1.00	70	97.4	114/76
	04/04/2018	3.00	68	97.6	110/70
	04/04/2018	6.00	66	97.2	112/74
	04/04/2018	9.00	70	97.1	108/72
	05/04/2018	23.00	72	97.4	112/68
	05/04/2018	29.00	84	97.9	118/74
	05/04/2018	35.00	76	97.3	108/72
	06/04/2018	48.00	72	97.6	110/70
	07/04/2018	72.00	72	96.7	108/70
17	03/04/2018	Check-in	68	97.1	104/66
	04/04/2018	PD	64	97.0	108/64
	04/04/2018	1.00	66	96.8	110/70
	04/04/2018	3.00	70	97.2	114/76
	04/04/2018	6.00	68	96.9	112/70
	04/04/2018	9.00	72	97.3	108/72
	05/04/2018	23.00	76	96.9	104/64
	05/04/2018	29.00	76	97.0	110/70
	05/04/2018	35.00	74	97.3	120/68
	06/04/2018	48.00	68	97.1	116/74
	07/04/2018	72.00	76	96.6	110/68
18	03/04/2018	Check-in	70	96.6	108/72
	04/04/2018	PD	68	97.2	110/70
	04/04/2018	1.00	72	97.1	114/76
	04/04/2018	3.00	74	96.9	110/74
	04/04/2018	6.00	70	97.6	112/70
	04/04/2018	9.00	68	97.1	108/72
	05/04/2018	23.00	64	97.4	112/68
	05/04/2018	29.00	64	96.8	108/70
	05/04/2018	35.00	66	97.3	112/72
	06/04/2018	48.00	72	97.5	106/68
	07/04/2018	72.00	64	97.5	104/70

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
19	03/04/2018	Check-in	68	96.7	106/68
	04/04/2018	PD	76	97.3	110/72
	04/04/2018	1.00	70	97.5	116/74
	04/04/2018	3.00	68	97.3	114/70
	04/04/2018	6.00	66	97.4	108/72
	04/04/2018	9.00	70	97.3	112/68
	05/04/2018	23.00	64	96.8	110/70
	05/04/2018	29.00	64	97.7	114/72
	05/04/2018	35.00	66	97.4	112/70
	06/04/2018	48.00	70	97.6	116/72
	07/04/2018	72.00	76	96.4	110/64
20	03/04/2018	Check-in	66	96.4	110/62
	04/04/2018	PD	70	96.9	116/80
	04/04/2018	1.00	68	97.1	112/70
	04/04/2018	3.00	72	97.4	120/76
	04/04/2018	6.00	64	97.1	114/70
	04/04/2018	9.00	66	97.0	108/66
	05/04/2018	23.00	68	96.6	104/60
	05/04/2018	29.00	64	97.3	124/80
	05/04/2018	35.00	66	97.2	120/78
	06/04/2018	48.00	64	97.1	112/70
	07/04/2018	72.00	64	97.5	118/76
21	03/04/2018	Check-in	72	98.1	116/66
	04/04/2018	PD	68	96.9	110/64
	04/04/2018	1.00	70	97.4	110/70
	04/04/2018	3.00	66	97.1	114/74
	04/04/2018	6.00	66	97.7	116/68
	04/04/2018	9.00	74	97.3	112/72
	05/04/2018	23.00	80	96.8	110/78
	05/04/2018	29.00	84	98.2	120/70
	05/04/2018	35.00	76	97.3	114/68
	06/04/2018	48.00	70	97.7	110/70
	07/04/2018	72.00	66	97.4	116/74

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
22	03/04/2018	Check-in	82	97.6	120/78
	04/04/2018	PD	70	97.1	114/70
	04/04/2018	1.00	62	97.1	106/64
	04/04/2018	3.00	64	97.3	110/70
	04/04/2018	6.00	68	97.0	114/66
	04/04/2018	9.00	74	96.9	112/68
	05/04/2018	23.00	64	96.4	108/64
	05/04/2018	29.00	68	97.2	114/70
	05/04/2018	35.00	66	97.0	108/68
	06/04/2018	48.00	64	96.9	110/64
	07/04/2018	72.00	68	97.2	114/70
23	03/04/2018	Check-in	76	98.0	110/70
	04/04/2018	PD	68	96.8	108/64
	04/04/2018	1.00	70	97.0	104/62
	04/04/2018	3.00	66	97.2	110/68
	04/04/2018	6.00	64	97.4	110/66
	04/04/2018	9.00	74	97.3	108/72
	05/04/2018	23.00	68	96.9	112/76
	05/04/2018	29.00	80	98.2	118/70
	05/04/2018	35.00	76	97.3	120/64
	06/04/2018	48.00	72	97.8	116/76
	07/04/2018	72.00	74	98.0	120/80
24	03/04/2018	Check-in	66	97.8	124/80
	04/04/2018	PD	64	96.6	118/76
	04/04/2018	1.00	68	97.2	114/70
	04/04/2018	3.00	70	97.6	116/74
	04/04/2018	6.00	68	97.7	118/70
	04/04/2018	9.00	76	97.5	116/80
	05/04/2018	23.00	64	97.1	120/74
	05/04/2018	29.00	84	97.8	124/80
	05/04/2018	35.00	78	97.5	114/68
	06/04/2018	48.00	72	97.9	110/70
	07/04/2018	72.00	70	97.7	116/72

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
25	03/04/2018	Check-in	70	98.4	108/76
	04/04/2018	PD	68	97.1	114/70
	04/04/2018	1.00	64	96.9	116/74
	04/04/2018	3.00	66	97.2	110/70
	04/04/2018	6.00	70	97.9	114/68
	04/04/2018	9.00	68	97.2	112/74
	05/04/2018	23.00	60	96.3	104/62
	05/04/2018	29.00	64	97.0	114/64
	05/04/2018	35.00	66	96.8	110/70
	06/04/2018	48.00	70	97.2	108/66
	07/04/2018	72.00	64	97.0	112/68
26	03/04/2018	Check-in	66	98.3	130/80
	04/04/2018	PD	64	96.7	124/80
	04/04/2018	1.00	70	97.2	120/70
	04/04/2018	3.00	74	97.6	116/80
	04/04/2018	6.00	72	97.6	114/70
	04/04/2018	9.00	74	97.2	108/76
	05/04/2018	23.00	68	97.0	114/68
	05/04/2018	29.00	80	97.6	120/80
	05/04/2018	35.00	78	97.2	120/68
	06/04/2018	48.00	74	98.0	116/80
	07/04/2018	72.00	64	97.6	120/76
27	03/04/2018	Check-in	82	98.7	104/76
	04/04/2018	PD	74	97.0	122/80
	04/04/2018	1.00	66	97.3	120/76
	04/04/2018	3.00	72	97.0	114/70
	04/04/2018	6.00	70	97.4	110/68
	04/04/2018	9.00	68	96.9	114/74
	05/04/2018	23.00	74	97.4	120/70
	05/04/2018	29.00	84	98.0	124/78
	05/04/2018	35.00	76	97.6	120/72
	06/04/2018	48.00	68	97.3	116/76
	07/04/2018	72.00	74	98.0	124/84

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
28	03/04/2018	Check-in	80	97.6	122/84
	04/04/2018	PD	74	97.4	116/70
	04/04/2018	1.00	76	97.5	110/68
	04/04/2018	3.00	70	97.3	116/72
	04/04/2018	6.00	68	97.2	114/70
	04/04/2018	9.00	72	97.1	108/68
	05/04/2018	23.00	68	97.3	114/70
	05/04/2018	29.00	72	97.0	110/70
	05/04/2018	35.00	70	97.3	112/68
	06/04/2018	48.00	68	97.5	116/70
	07/04/2018	72.00	76	97.8	110/74
	29	03/04/2018	Check-in	66	96.9
04/04/2018		PD	70	97.2	116/80
04/04/2018		1.00	64	97.0	120/80
04/04/2018		3.00	66	97.4	110/66
04/04/2018		6.00	70	97.1	114/70
04/04/2018		9.00	68	97.0	110/68
05/04/2018		23.00	64	96.6	108/72
05/04/2018		29.00	64	97.2	120/80
05/04/2018		35.00	68	97.0	114/68
06/04/2018		48.00	70	97.7	110/70
07/04/2018		72.00	72	97.2	116/80
30		03/04/2018	Check-in	68	98.0
	04/04/2018	PD	72	97.6	110/70
	04/04/2018	1.00	70	97.9	116/72
	04/04/2018	3.00	76	97.7	120/80
	04/04/2018	6.00	68	97.2	116/68
	04/04/2018	9.00	76	97.4	118/74
	05/04/2018	23.00	64	96.3	110/68
	05/04/2018	29.00	78	97.7	114/80
	05/04/2018	35.00	74	97.4	110/72
	06/04/2018	48.00	66	97.1	118/80
	07/04/2018	72.00	70	97.6	112/74

TABLE- 3
Vitals (Study Period – 2)

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
01	08/05/2018	Check-in	68	97.3	112/80
	09/05/2018	PD	64	97.3	110/68
	09/05/2018	1.00	68	97.1	108/64
	09/05/2018	3.00	68	97.4	110/64
	09/05/2018	6.00	78	97.5	118/72
	09/05/2018	9.00	72	97.3	120/78
	10/05/2018	23.00	72	96.4	120/70
	10/05/2018	29.00	84	97.9	114/70
	10/05/2018	35.00	78	96.8	110/68
	11/05/2018	48.00	68	96.5	108/70
	12/05/2018	72.00	70	97.2	116/68
02	08/05/2018	Check-in	68	97.4	118/64
	09/05/2018	PD	66	96.0	110/68
	09/05/2018	1.00	68	96.9	110/64
	09/05/2018	3.00	64	96.4	114/70
	09/05/2018	6.00	74	97.3	108/66
	09/05/2018	9.00	72	97.0	110/70
	10/05/2018	23.00	68	96.8	108/70
	10/05/2018	29.00	74	97.2	110/74
	10/05/2018	35.00	72	97.4	114/70
	11/05/2018	48.00	64	96.6	110/70
	12/05/2018	72.00	76	97.7	112/76
03	08/05/2018	Check-in	70	97.1	124/76
	09/05/2018	PD	66	96.8	104/62
	09/05/2018	1.00	68	97.0	108/66
	09/05/2018	3.00	64	97.4	110/68
	09/05/2018	6.00	68	97.1	116/70
	09/05/2018	9.00	64	96.9	112/74
	10/05/2018	23.00	64	97.0	124/80
	10/05/2018	29.00	76	97.7	130/80
	10/05/2018	35.00	70	97.0	124/80
	11/05/2018	48.00	64	96.8	114/70
	12/05/2018	72.00	72	96.9	122/82

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
04	08/05/2018	Check-in	74	98.1	122/70
	09/05/2018	PD	68	96.6	118/70
	09/05/2018	1.00	64	96.4	110/68
	09/05/2018	3.00	68	97.0	108/64
	09/05/2018	6.00	66	97.3	108/66
	09/05/2018	9.00	64	98.0	112/72
	10/05/2018	23.00	68	96.6	110/70
	10/05/2018	29.00	76	97.4	108/70
	10/05/2018	35.00	78	96.6	108/68
	11/05/2018	48.00	68	97.1	104/60
	12/05/2018	72.00	68	97.4	110/62
05	08/05/2018	Check-in	72	97.9	110/66
	09/05/2018	PD	68	97.4	108/64
	09/05/2018	1.00	62	96.9	104/60
	09/05/2018	3.00	66	97.2	108/70
	09/05/2018	6.00	74	96.8	110/68
	09/05/2018	9.00	68	97.5	114/72
	10/05/2018	23.00	64	96.8	104/68
	10/05/2018	29.00	80	97.9	110/70
	10/05/2018	35.00	78	96.9	114/68
	11/05/2018	48.00	68	96.7	108/70
	12/05/2018	72.00	72	97.6	112/70
06	08/05/2018	Check-in	72	97.5	118/76
	09/05/2018	PD	68	97.4	110/68
	09/05/2018	1.00	64	96.9	116/70
	09/05/2018	3.00	68	97.1	114/70
	09/05/2018	6.00	74	96.8	110/66
	09/05/2018	9.00	72	97.1	114/72
	10/05/2018	23.00	72	96.5	110/70
	10/05/2018	29.00	88	98.2	120/70
	10/05/2018	35.00	80	97.4	118/78
	11/05/2018	48.00	76	96.6	124/80
	12/05/2018	72.00	80	97.4	120/82

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
07	08/05/2018	Check-in	72	97.5	114/70
	09/05/2018	PD	68	97.4	110/68
	09/05/2018	1.00	64	96.6	108/68
	09/05/2018	3.00	64	97.0	112/70
	09/05/2018	6.00	66	97.5	110/70
	09/05/2018	9.00	64	97.8	112/72
	10/05/2018	23.00	68	97.0	108/70
	10/05/2018	29.00	68	97.4	118/76
	10/05/2018	35.00	72	96.8	112/72
	11/05/2018	48.00	64	97.1	108/70
	12/05/2018	72.00	66	97.3	110/74
08	08/05/2018	Check-in	74	97.3	112/68
	09/05/2018	PD	68	97.4	110/68
	09/05/2018	1.00	64	97.1	112/70
	09/05/2018	3.00	68	97.6	110/64
	09/05/2018	6.00	66	97.3	112/68
	09/05/2018	9.00	62	97.6	116/76
	10/05/2018	23.00	68	96.4	110/64
	10/05/2018	29.00	74	97.0	108/70
	10/05/2018	35.00	76	97.8	110/68
	11/05/2018	48.00	72	96.4	110/70
	12/05/2018	72.00	68	96.9	108/68
09	08/05/2018	Check-in	68	97.5	114/70
	09/05/2018	PD	64	97.6	110/68
	09/05/2018	1.00	68	97.1	114/70
	09/05/2018	3.00	64	96.8	108/64
	09/05/2018	6.00	68	96.6	104/68
	09/05/2018	9.00	64	97.7	110/70
	10/05/2018	23.00	64	96.9	104/60
	10/05/2018	29.00	78	97.6	110/80
	10/05/2018	35.00	74	96.9	114/74
	11/05/2018	48.00	68	96.3	104/64
	12/05/2018	72.00	66	97.3	108/66

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
10	08/05/2018	Check-in	66	97.2	118/70
	09/05/2018	PD	64	97.1	110/64
	09/05/2018	1.00	68	96.8	106/60
	09/05/2018	3.00	64	97.0	110/64
	09/05/2018	6.00	68	97.6	112/68
	09/05/2018	9.00	74	98.0	116/64
	10/05/2018	23.00	64	96.4	104/70
	10/05/2018	29.00	78	97.3	112/70
	10/05/2018	35.00	70	96.6	110/70
	11/05/2018	48.00	68	96.6	108/66
	12/05/2018	72.00	70	97.4	106/64
11	08/05/2018	Check-in	72	97.4	114/76
	09/05/2018	PD	68	97.2	110/64
	09/05/2018	1.00	64	97.1	108/68
	09/05/2018	3.00	64	97.4	112/70
	09/05/2018	6.00	72	97.3	114/72
	09/05/2018	9.00	86	97.1	110/70
	10/05/2018	23.00	72	96.9	108/66
	10/05/2018	29.00	84	98.1	120/70
	10/05/2018	35.00	78	97.8	118/78
	11/05/2018	48.00	80	96.7	108/70
	12/05/2018	72.00	78	97.4	112/68
12	08/05/2018	Check-in	68	97.0	108/74
	09/05/2018	PD	64	96.6	110/68
	09/05/2018	1.00	66	96.9	108/64
	09/05/2018	3.00	68	97.4	114/70
	09/05/2018	6.00	66	97.1	108/72
	09/05/2018	9.00	72	98.7	122/68
	10/05/2018	23.00	64	96.6	104/60
	10/05/2018	29.00	78	97.5	108/70
	10/05/2018	35.00	80	96.9	114/74
	11/05/2018	48.00	64	96.8	110/68
	12/05/2018	72.00	66	97.8	106/66

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
13	08/05/2018	Check-in	66	97.4	110/66
	09/05/2018	PD	68	97.4	108/64
	09/05/2018	1.00	64	96.9	118/74
	09/05/2018	3.00	64	96.7	106/70
	09/05/2018	6.00	76	98.3	110/68
	09/05/2018	9.00	70	96.9	120/76
	10/05/2018	23.00	68	96.4	104/70
	10/05/2018	29.00	88	98.0	110/70
	10/05/2018	35.00	84	97.2	110/70
	11/05/2018	48.00	68	96.9	114/68
	12/05/2018	72.00	72	97.4	112/72
14	08/05/2018	Check-in	72	97.3	122/74
	09/05/2018	PD	68	97.9	106/64
	09/05/2018	1.00	64	96.8	104/60
	09/05/2018	3.00	66	96.9	108/66
	09/05/2018	6.00	68	97.1	110/64
	09/05/2018	9.00	64	97.5	108/66
	10/05/2018	23.00	64	96.7	104/60
	10/05/2018	29.00	72	97.3	114/68
	10/05/2018	35.00	70	96.9	110/74
	11/05/2018	48.00	68	96.4	112/70
	12/05/2018	72.00	74	97.8	114/74
15	08/05/2018	Check-in	66	96.8	112/72
	09/05/2018	PD	64	96.6	108/64
	09/05/2018	1.00	68	96.4	108/68
	09/05/2018	3.00	64	97.0	116/70
	09/05/2018	6.00	70	96.8	112/76
	09/05/2018	9.00	78	98.0	120/70
	10/05/2018	23.00	68	97.1	110/70
	10/05/2018	29.00	80	97.8	110/70
	10/05/2018	35.00	68	96.6	118/70
	11/05/2018	48.00	64	96.4	110/64
	12/05/2018	72.00	66	97.6	114/68

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
16	08/05/2018	Check-in	66	97.0	108/70
	09/05/2018	PD	68	97.5	110/72
	09/05/2018	1.00	70	97.2	110/70
	09/05/2018	3.00	68	97.0	108/70
	09/05/2018	6.00	74	98.4	118/74
	09/05/2018	9.00	70	98.1	112/68
	10/05/2018	23.00	68	97.3	108/70
	10/05/2018	29.00	76	97.8	114/74
	10/05/2018	35.00	72	97.6	110/72
	11/05/2018	48.00	70	97.2	116/70
	12/05/2018	72.00	74	97.0	112/66
17	08/05/2018	Check-in	70	97.3	106/68
	09/05/2018	PD	68	97.6	110/72
	09/05/2018	1.00	64	97.2	116/70
	09/05/2018	3.00	68	96.8	112/68
	09/05/2018	6.00	72	97.1	106/64
	09/05/2018	9.00	82	97.3	108/66
	10/05/2018	23.00	64	96.8	104/66
	10/05/2018	29.00	66	97.3	112/74
	10/05/2018	35.00	68	97.4	110/76
	11/05/2018	48.00	68	97.6	108/72
	12/05/2018	72.00	66	96.9	106/64
18	08/05/2018	Check-in	66	97.5	106/72
	09/05/2018	PD	64	97.0	114/70
	09/05/2018	1.00	68	97.2	116/72
	09/05/2018	3.00	64	97.0	118/74
	09/05/2018	6.00	74	97.1	114/74
	09/05/2018	9.00	66	98.1	104/68
	10/05/2018	23.00	64	97.2	118/72
	10/05/2018	29.00	72	97.5	118/68
	10/05/2018	35.00	70	97.6	116/78
	11/05/2018	48.00	72	97.8	118/72
	12/05/2018	72.00	64	97.1	108/66

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
19	08/05/2018	Check-in	64	97.1	108/66
	09/05/2018	PD	68	97.5	114/72
	09/05/2018	1.00	68	97.6	110/72
	09/05/2018	3.00	62	96.8	108/70
	09/05/2018	6.00	68	97.4	112/70
	09/05/2018	9.00	80	97.1	128/84
	10/05/2018	23.00	68	96.8	110/66
	10/05/2018	29.00	72	97.6	112/64
	10/05/2018	35.00	70	97.2	110/70
	11/05/2018	48.00	74	97.8	112/74
	12/05/2018	72.00	66	96.8	108/76
	20	08/05/2018	Check-in	68	96.6
09/05/2018		PD	70	97.3	116/72
09/05/2018		1.00	68	97.2	112/70
09/05/2018		3.00	64	97.0	110/68
09/05/2018		6.00	66	96.9	112/70
09/05/2018		9.00	72	96.6	128/70
10/05/2018		23.00	70	97.3	106/74
10/05/2018		29.00	70	97.4	122/78
10/05/2018		35.00	72	97.8	118/76
11/05/2018		48.00	70	97.6	116/72
12/05/2018		72.00	76	97.5	118/74
21		08/05/2018	Check-in	68	96.4
	09/05/2018	PD	66	97.5	110/70
	09/05/2018	1.00	70	96.8	116/72
	09/05/2018	3.00	64	97.0	110/68
	09/05/2018	6.00	84	96.8	124/72
	09/05/2018	9.00	78	98.3	110/64
	10/05/2018	23.00	66	97.0	104/64
	10/05/2018	29.00	92	98.1	136/84
	10/05/2018	35.00	78	97.6	128/82
	11/05/2018	48.00	76	96.9	120/74
	12/05/2018	72.00	74	97.5	120/72

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
22	08/05/2018	Check-in	74	98.2	122/70
	09/05/2018	PD	70	97.6	116/74
	09/05/2018	1.00	72	97.5	116/78
	09/05/2018	3.00	68	97.2	112/64
	09/05/2018	6.00	78	97.6	106/72
	09/05/2018	9.00	80	97.9	114/68
	10/05/2018	23.00	74	97.3	112/70
	10/05/2018	29.00	70	97.1	114/74
	10/05/2018	35.00	68	97.2	112/70
	11/05/2018	48.00	76	97.0	120/80
	12/05/2018	72.00	66	97.6	120/72
23	08/05/2018	Check-in	74	97.2	112/80
	09/05/2018	PD	68	96.9	110/72
	09/05/2018	1.00	64	96.4	112/70
	09/05/2018	3.00	64	97.0	108/64
	09/05/2018	6.00	72	97.4	106/64
	09/05/2018	9.00	76	98.3	120/80
	10/05/2018	23.00	74	97.1	108/66
	10/05/2018	29.00	68	97.7	106/62
	10/05/2018	35.00	72	97.8	108/68
	11/05/2018	48.00	70	98.0	110/70
	12/05/2018	72.00	66	97.5	108/66
24	08/05/2018	Check-in	72	97.5	118/70
	09/05/2018	PD	70	97.8	120/76
	09/05/2018	1.00	68	96.8	118/72
	09/05/2018	3.00	66	97.0	112/70
	09/05/2018	6.00	70	97.5	122/76
	09/05/2018	9.00	82	97.9	116/74
	10/05/2018	23.00	72	97.2	110/66
	10/05/2018	29.00	78	97.9	132/74
	10/05/2018	35.00	76	97.6	128/78
	11/05/2018	48.00	68	97.3	118/74
	12/05/2018	72.00	72	97.5	114/70

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
25	08/05/2018	Check-in	72	97.7	116/68
	09/05/2018	PD	68	97.4	118/76
	09/05/2018	1.00	70	96.8	116/72
	09/05/2018	3.00	64	97.2	110/68
	09/05/2018	6.00	62	96.6	118/66
	09/05/2018	9.00	68	97.3	110/70
	10/05/2018	23.00	70	97.5	108/66
	10/05/2018	29.00	68	97.3	116/68
	10/05/2018	35.00	70	97.6	118/70
	11/05/2018	48.00	74	97.8	122/72
	12/05/2018	72.00	66	97.6	120/72
26	08/05/2018	Check-in	64	96.9	108/66
	09/05/2018	PD	68	97.3	114/70
	09/05/2018	1.00	68	97.6	110/72
	09/05/2018	3.00	66	97.2	116/70
	09/05/2018	6.00	68	97.5	116/72
	09/05/2018	9.00	80	97.7	122/76
	10/05/2018	23.00	66	96.9	106/72
	10/05/2018	29.00	74	98.1	112/74
	10/05/2018	35.00	72	97.8	110/72
	11/05/2018	48.00	76	97.0	114/78
	12/05/2018	72.00	74	97.3	118/72
27	08/05/2018	Check-in	64	97.3	106/74
	09/05/2018	PD	66	97.6	110/70
	09/05/2018	1.00	64	97.5	116/72
	09/05/2018	3.00	68	97.4	112/68
	09/05/2018	6.00	84	97.8	128/78
	09/05/2018	9.00	70	96.9	130/80
	10/05/2018	23.00	82	97.6	122/82
	10/05/2018	29.00	86	97.9	128/80
	10/05/2018	35.00	80	97.8	126/78
	11/05/2018	48.00	84	97.3	110/72
	12/05/2018	72.00	76	97.5	120/74

Subject No.	Date (DD/MM/YYYY)	Time Point (Hours)	Supine		
			Pulse (Beats/Min)	Temperature (°F)	Blood Pressure (mmHg)
28	08/05/2018	Check-in	66	97.4	114/70
	09/05/2018	PD	64	97.2	108/66
	09/05/2018	1.00	68	97.0	110/68
	09/05/2018	3.00	64	97.6	108/64
	09/05/2018	6.00	76	97.6	116/74
	09/05/2018	9.00	72	96.9	112/76
	10/05/2018	23.00	66	97.0	114/80
	10/05/2018	29.00	74	97.7	114/72
	10/05/2018	35.00	76	97.8	118/76
	11/05/2018	48.00	70	96.9	112/80
	12/05/2018	72.00	66	97.6	110/72
29	08/05/2018	Check-in	66	96.8	118/82
	09/05/2018	PD	72	97.3	122/76
	09/05/2018	1.00	68	97.4	118/72
	09/05/2018	3.00	64	97.2	110/68
	09/05/2018	6.00	62	97.6	108/64
	09/05/2018	9.00	70	96.6	114/68
	10/05/2018	23.00	64	96.4	106/64
	10/05/2018	29.00	72	97.4	134/76
	10/05/2018	35.00	70	97.8	126/78
	11/05/2018	48.00	66	98.2	118/74
	12/05/2018	72.00	68	97.8	124/80
30	08/05/2018	Check-in	70	97.0	112/66
	09/05/2018	PD	68	97.2	116/72
	09/05/2018	1.00	64	96.9	118/76
	09/05/2018	3.00	66	96.8	112/72
	09/05/2018	6.00	68	97.0	108/64
	09/05/2018	9.00	78	98.1	120/70
	10/05/2018	23.00	70	97.3	116/68
	10/05/2018	29.00	66	97.0	102/74
	10/05/2018	35.00	70	97.8	110/72
	11/05/2018	48.00	72	96.7	120/70
	12/05/2018	72.00	68	97.1	112/70

APPENDIX 16.3.1

CRF'S FOR DEATHS, OTHER SERIOUS ADVERSE EVENTS AND WITHDRAWALS FOR ADVERSE EVENTS

(There was no death or serious adverse event reported in the study. No subject withdrawn from the study due to adverse event).

APPENDIX 16.4
INDIVIDUAL SUBJECT DATA LISTINGS
(Not Applicable)