BIOEQUIVALENCE STUDY OF ISOTRETINOIN CAPSULES 20 MG UNDER FASTING CONDITION

RAPTIM RESEARCH. LTD MUMBAI
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Sponsor:

Olive Healthcare
Unit-II,163/2, Athiyawad, Village
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India

1 TITLE PAGE

STUDY CODE: DAP/CHL/001

Study Title: A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in Normal, Healthy Adult, Human Subjects Under Fasting Condition.

Formulations	Dose
Test Product (T): (Isotretinoin Capsules 20 mg) of Olive Healthcare.	Capsules
Reference Product (R): Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania	Capsules

Clinical Conduction:	
Period I	05/04/2019
Period II	26/04/2019
Date of Clinical phase Completion	30/04/2019
Subject Analysis:	
Start Date	02/05/2019
End Date	26/05/2019
Statistical Analysis	28/05/2019
Report Compilation	02/06/2019
Report Status:	Final
Version:	00
Dated:	02/06/2019
Superseded Version:	NA
Dated:	NA

Principal Investigator	Sponsor's Representative
Dr. Trahar Srinivasan M. B. B. S.	Dr. Hardik Shah
Screening, Clinical Facility and Statistical Facility	**Sponsor**
RAPTIM RESEARCH LIMITED A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, INDIA Tel: + 91 22 27781889	**Olive Healthcare.** Unit-II,163/2, Athiyawad, Village Dabhel, Daman-396210 India
Bio-analytical Facility	
RAPTIM RESEARCH LIMITED A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, INDIA Tel: + 91 22 27781889	

GCP Compliance Note: This study was conducted in compliance with ICH GCP Guidelines including archiving of essential documents and current version of Declaration of Helsinki.

2 SYNOPSIS

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		
Study Title: A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in Normal, Healthy Adult, Human Subjects Under Fasting Condition.		
Investigators and other important participants in the study		
Dr. Trahar Srinivasan, Principal Investigator Dr. Manish Jadhav, Co-Investigator	Ms. Trupti Deshmukh, Biostatistician Mr. R. S. Saravanan, Bioanalytical Investigator Mr. Yashodhan Warke, Quality Assurance Head	

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Study Centre(s):

Screening, Clinical, Bio-analytical and Statistical Facility :

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Bio-analytical Facilities:

RAPTIM RESEARCH LIMITED

A-242, T.T.C. Industrial Area,

Mahape M.I.D.C., Navi Mumbai-400 701, INDIA

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Pathology Laboratory

Shree Diagnostic Centre

4 A, Basement Arwattagi, Zenith,

Opp. Arwattagi Petrol Pump,

Below ICICI Bank, Miraj

Sangli Road,Miraj - 416416

Publication (reference): Not Applicable

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Study period:

Date of Study (Clinical Phase)

Period I : 05/04/2019

Period II : 26/04/2019

Date of Clinical phase Completion : 30/04/2019

Date of Completion of Report : 02/06/2019

Objective: Pharmacokinetic objective was to assess the oral bioequivalence of (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane Isotretinoin Capsules 20 mgg) of Catalent Germany Eberbach GMBH, Alemania in Normal Healthy Adult, Human Subjects Under fasting Condition. in a randomized crossover design.

Safety Objective: was to monitor the safety and tolerability of the test product as compared to the reference product in healthy, human subjects.

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Methodology: Total of 24 normal, healthy, adult male human subjects was enrolled in the study. The subjects were confined with in the facility for at least 11 hours prior to dosing until 96.00 hours post-dose during each study period. Subjects were administered single oral dose (Isotretinoin Capsules 20 mg) of test product or single Roaccutane Capsules of reference product with about 240 mL of water at ambient temperature in sitting position. Dosing was done as per randomization schedule in each study period. A mouth check was done immediately after dosing using a tongue depressor and torch to assess the compliance of the procedure. Total of 23 blood samples (5mL per sample) were collected from the subjects during each study period from Pre-dose (collected within 1hr prior to dosing) to 96.00 hours (post-dose). Analysis of plasma conc. and was done by a validated LC-MS/MS Bioanalytical method. A non-compartmental method was use to calculate the pharmacokinetic using drug con. time profile. The anlaysis was considered for statistical analysis and for establishing bioequivalence.

Number of Subjects (planned and analysed):

Total of 39 adult, male human volunteers were screened in order to recruit 32 subjects for this study. 24 fit volunteers were selected for study. No subjects were discontinued from the study. So all 24 subjects has completed the clinical phase of the study successfully. Plasma samples of these 24 subjects were analyzed and were considered to draw statistical conclusion.

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Diagnosis and Main Criteria For Inclusion: Normal, healthy, adult male human subjects, age in the range of 18 – 45 years were enrolled. The screening examination consisted of demographic data, clinical history, physical examination (including vital signs), laboratory tests including haemogram, biochemistry, serology (HIV, hepatitis B and hepatitis C), 12 lead ECG, Breath alcohol test and urinalysis. Urine screen for drug of abuse & Breath alcohol test were done before check-in for each study period. Any significant diseases or clinically significant abnormal findings were ruled out during screening by obtaining complete clinical history.

Test Product (T):	(Isotretinoin Capsules 20 mg)
Label Claim:	Each Soft Gelatin Capsule Contains: Isotretinoin USP.....20mg
Mode of administration:	Capsules was administered orally with about 240 mL water at ambient temperature in sitting position.
Batch No:	T18F001
MFG. DATE	06/2018
EXPIRY DATE:	05/2021
Manufactured by:	Olive Healthcare

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Reference Product:	Roaccutane
Label Claim:	Each Soft Gelatin Capsule Contains: Isotretinoin.....20 mg
Mode of administration:	Administered orally with about 240 mL of water at ambient temperature in sitting position.
Batch No:	B9397805
EXPIRY DATE:	02/2020
Manufactured by:	Catalent Germany Eberbach GMBH, Alemania
Duration of treatment	The duration of clinical phase was 30 days, including the washout period of 21 days.

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Criteria for evaluation Bioequivalence: Assessment of bioequivalence was done by comparing pharmacokinetic parameters of the Test Product (Isotretinoin Capsules 20 mg) and bioequivalence would be concluded if 90% Confidence Interval based on two one sided 't' tests for the test by reference ratio of geometric least square mean, lie within the range of 80-125% for Cmax.

Safety: Safety of subjects was evaluated by Physical examination, vital examination (Blood pressure, pulse rate, temperature and respiratory rate) and well being assessment done at the time of check in, check out of each study period. Sitting blood pressure and radial pulse rate were measured at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose ± 45 minutes (except for pre-dose) of scheduled time in each study period, and whenever the physician thinks it necessary throughout the stay of subjects in each period. Well being assessment was done at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose in each study period .

Statistical methods: ANOVA & 90 % confidence interval for the ratio of the population means for log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were performed using SAS® Software (Version 9.2). All pharmacokinetics and statistical analysis was performed by SAS® Software (Version 9.2).

Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

SUMMARY – CONCLUSION

BIOEQUIVALENCE RESULTS:

All pharmacokinetics and statistical analysis was performed by SAS® Software (Version 9.2).

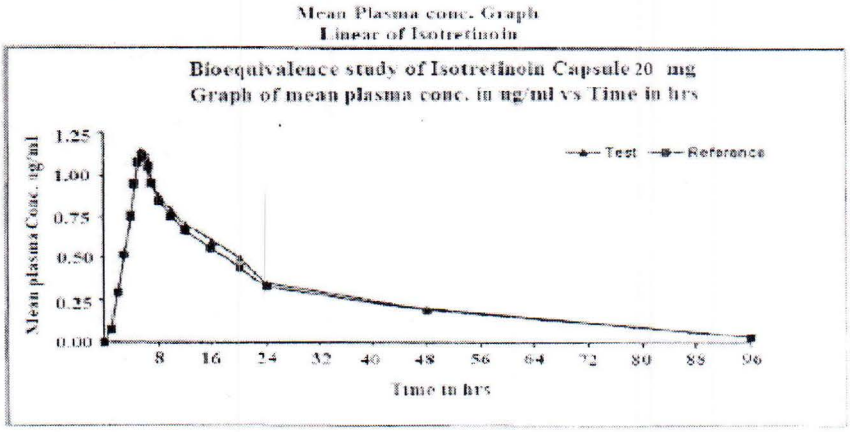
Isotretinoin was considered for statistical analysis and establishing bioequivalence.

Average of PK parameters of two periods of Test and Reference Formulation

Pharmacokinetic Parameters Isotretinoin	Test Product (B) N=24	Reference Product(A) N=24
C_{max} (ug/mL)	0.93	0.94
AUC_{0-t} (ug *hrs/mL)	3.14	3.11
$AUC_{0-\infty}$(ug *hrs/mL)	4.41	4.47
90 % Confidence Interval from Log transformed data from Sennoside B		
Ln C_{max} (ug /mL)	80-125 %	92.100- 108.388
Ln AUC_{0-t} (ug *hrs/mL)	80-125 %	90.789- 113.434
Ln $AUC_{0-\infty}$(ug *hrs/mL)	80-125 %	91.659- 106.900

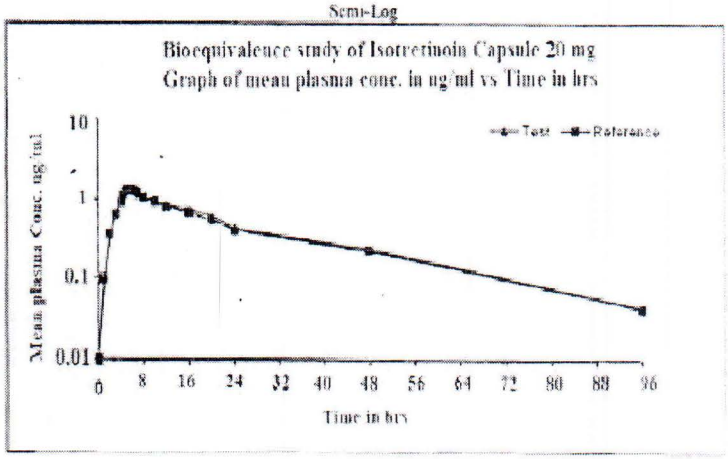
Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Isotretinoin Mean Concentration Time Profile–Un transformed



Name of the Sponsor: **Olive Healthcare**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

Isotretinoin Mean Concentration Time Profile–Log transformed



Name of the Sponsor: **Olive Healthcare.**	Individual Study Table Referring to part of the Dossier Appendix 16.2.5	(For National Authority Use only)
Name of the Finished Product: **(Isotretinoin Capsules 20 mg)**		
Name of Active Ingredient: **Isotretinoin**		

SAFETY RESULTS: Isotretinoin Capsules was well tolerated and adverse event was mild in severity. A total of two (02) adverse events were reported during the clinical phase of the study. Events were related to the study medication and were resolved. No serious adverse event was observed during any of the periods of the study.During post study assessment the laboratory values were evaluated on the basis of clinical correlation and no clinically significant abnormality was observed.

CONCLUSION:

Based on the statistical analysis results of Test Product (Isotretinoin Capsules 20 mg) of Olive Healthcare. is bioequivalent with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in Normal, Healthy Adult, Human Subjects Under FastingCondition.

Date of the report: 02/06/2019

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
AUC_{0-t}	Area Under The Concentration Versus Time Curve Calculated Using The Trapezoidal Rule Up To The Last Measurable Time Point
$AUC_{0-\infty}$	Area Under The Concentration Versus Time Curve From Time 0 To Infinity
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
BE	Bioequivalence
BLQ	Below the Limit of Quantification
BP	Blood Pressure
ß-hCG	Beta human chorionic gonadotropin
BUN	Blood Urea Nitrogen
Cal	Calorie
CHO	Carbohydrate
CDSCO	Central Drug Standard Control Organization
CI	Confidence Interval
Cm	Centimeter (s)
c.mm	Cubic Millimeter
C_{max}	Maximum Observed Drug Concentration In Plasma
COA	Certificate of Analysis
CPU	Clinical Pharmacological Unit
CRF	Case Report Form
CTMS	Clinical Trial Management Software
°C	Degree Celsius
dL	Deciliter
ECG	Electrocardiogram
fL	Femtolitre
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
hr(s)	Hour(s)
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IP	Investigational Product
IU	International Unit
i.v.	Intravenous
K_{el}	Elimination Rate Constant
Kg	Kilogram(s)
L	Litre
LC-MS/MS	Liquid Chromatography/ Mass Spectrometer / Mass Spectrometer
LFT	Liver Function Test
Ltd.	Limited
LSM	Least Square Mean
M	Metre
Mg	Milligram
mL	Milliliter
Mm	Millimeter
Mmol	Millimole
µg	Microgram
µL	Microlitre
µm	Micrometer
A	Level of Significance
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin

MCHC	Mean Corpuscular Hemoglobin-concentration
MSV	Missing Sample Values
Ng	Nanogram
No.	Number
NRV	Non-reportable Values
OTC	Over The Counter
PCV	Packed Cell Volume
Pg	Picogram
PK	Pharmacokinetic
QA	Quality Assurance
RBC	Red Blood Cell
RPM	Revolutions per minute
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
SGOT	Serum Glutamate Oxaloacetate Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SOP(s)	Standard Operating Procedure(s)
$t_{1/2}$	Elimination Half-Life
T_{max}	Time to achieve maximum drug concentration in biological matrix
Tbsp	Tablespoon
Tsp	Teaspoon
U/L	Units per litre
USFDA	U.S. Food and Drug Administration
WBC	White Blood Cell
WMA	World Medical Association
WNL	Within Normal Limit

5 ETHICS

5.1 Independent Ethics Committee (IEC)

All the pertinent documents, such as the protocol and the ICF and CRF, were submitted to the Alert IEC for approval on 23/03/2019, and the same was obtained on 03/04/2019. During the course of the study, the Principal Investigator had the right to make minor administrative amendments to the Protocol without changing the meaning of its contents.

The IEC approval letter and related documents are given in **Appendix 16.1.3**. The copy of the approved protocol is appended as **Appendix 16.1.1**.

5.2 Ethical Conduct of the Study

The study was conducted according to the current version of the declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Revised by WMA General Assembly, Seoul, October 2008), current ICH GCP guidelines, and relevant National Laws and Regulations, ICMR guidelines and CDSCO guidelines.

5.3 Subject Information and Consent

The Informed Consent Form was issued to all the volunteers in the language they understand the best before the study conduction. The Medical Officer explained the volunteers about the study procedures, risks and discomforts associated with the study procedures, possible adverse events of the study drugs, the remuneration and duration of the study, number of the subjects included, voluntary participation and withdrawal from the study and subject's confidentiality of his identity. The consent was obtained from each subject in the presence of Principal Investigator/Co-investigator/medical officer. All the subjects voluntarily gave the written consent for participation in the study. The eligible subjects were allotted a subject number to maintain the confidentiality of their identity. (For specimen copy of the informed consent form, **refer to Appendix 16.1.3.1**).

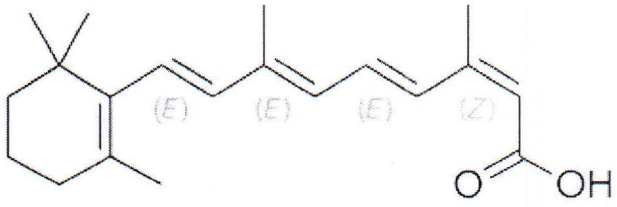
6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Study Personnel	Name & Affiliation
1. Principal Investigator	**Dr. Trahar Srinivasan, MBBS** (Signature) 02/06/2019 (Date)
2. Co- Investigator	**Dr. Manish Jhadhav, MBBS** (Signature) 02/06/2019 (Date)
3. Biostatistician	**Mr.Trupti Deshmukh** (Signature) 02/06/2019 (Date)
4. Bio-analytical Investigator	**Mr. R.S Saravasan** (Signature) 02/06/2019 (Date)
5. QA Reviewer (Head QA)	**Mr. Yashodhan B. Warke** (Signature) 02/06/2019 (Date)
STUDY CENTER **RAPTIM RESEARCH LIMITED** A-242, T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai-400 701, INDIA Tel: + 91 22 27781889	
Sponsor's Representative	Dr. Hardik Shah
Sponsor OLIVE HEALTHCARE Unit-II,163/2, Athiyawad, Village Dabhel, Daman-396210 India	

7. INTRODUCTION

Isotretinoin, also known as 13-cis-retinoic acid (and colloquially referred to by its former brand name Accutane or Roaccutane), is a medication primarily used to treat severe acne. Rarely, it is also used to prevent certain skin cancers (squamous-cell carcinoma), and in the treatment of other cancers. It is used to treat harlequin-type ichthyosis, a usually lethal skin disease, and lamellar ichthyosis. It is a retinoid, meaning it is related to vitamin A, and is found in small quantities naturally in the body. Its isomer, tretinoin, is also an acne drug.

Isotretinoin is primarily used as a treatment for severe acne. The most common adverse effects are a transient worsening of acne (lasting 1–4 months), dry lips (cheilitis), dry and fragile skin, and an increased susceptibility to sunburn. Uncommon and rare side effects include muscle aches and pains (myalgias), and headaches. Isotretinoin is known to cause birth defects due to in-utero exposure because of the molecule's close resemblance to retinoic acid, a natural vitamin A derivative which controls normal embryonic development. It is also associated with psychiatric side effects, most commonly depression but also, more rarely, psychosis and unusual behaviours. Other rare side effects include hyperostosis, and premature epiphyseal closure, have been reported to be persistent.



Contraindications

Isotretinoin is contraindicated in women who are pregnant or breast-feeding.

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Isotretinoin is also contraindicated in patients

With hepatic insufficiency

With excessively elevated blood lipid values

With hypervitaminosis A

With hypersensitivity to isotretinoin or to any of the excipients

Receiving concomitant treatment with tetracyclines

Allergic to peanut or soya oil as isotretinoin contains soya-bean oil

Effects on ability to drive and use machines

Isotretinoin could potentially have an influence on the ability to drive and use machines.

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

Fertility, pregnancy and lactation

Pregnancy

Pregnancy is an absolute contraindication to treatment with isotretinoin. Women of childbearing potential have to use effective contraception during and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the fetus

The fetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Breast-feeding

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, isotretinoin is contraindicated during breast-feeding.

Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

8 STUDY OBJECTIVES

Pharmacokinetic objective was to demonstrate bioequivalence between Test Product of (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in Normal, Healthy Adult, Human Subjects Under Fasting Condition.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study design was a randomized, open label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study on normal, healthy, adult, male human subjects under fasting condition. The subjects were confined within the facility at least 11.00 hours prior to dosing until 96.00 hours post-dose during each study period. Subjects were fasted for at least 10.00 hours prior to dosing and for 4 hours post-dose. Subjects were administered single oral dose (Isotretinoin Capsules 20 mg) of Olive Healthcare, of test product or single dose capsule of Roaccutane reference product with 240 mL of water at ambient temperature in sitting position. Dosing was done as per randomization schedule in each study period. Physical examination, vital examination (Blood pressure, pulse rate, temperature and respiratory rate) and well being assessment were done at the time of check in, check out of

each study period and during post study assessment. Sitting blood pressure and radial pulse rate were measured at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose ± 45 minutes (except for pre-dose) of scheduled time in each study period, and whenever the physician thinks it necessary throughout the stay of subjects in each period Well being assessment was done at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose in each study period 12 Lead ECGs were recorded during screening. Total of 23 blood samples (05 mL per sample) were collected from the subjects in each period. Blood samples were collected in K2EDTA vacutainers, at Pre-dose (collected within 1 hr prior to dosing) and at 0.00, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.25, 3.50, 4.00, 5.00, 6.00, 12.00, 24.00, 48.00, 72.00 and 96.00 hr (Post-dose) within 2 min. of scheduled sampling time. Approximately 268 mL [including15 mL for clinical laboratory tests (prestudy and post study) and 13 mL as volume discarded during the use of intravenous cannula] of total blood was withdrawn from the male subjects. The blood samples were centrifuged under refrigeration with the machine set at 3500 RPM, 5 min and 10°C and the separated and transferred into polypropylene screw top labeled.

vials and stored at -70°C ± 10°C until quantification.

Drinking water was not allowed to the subjects from 1 hour pre-dose and for 1 hour post-dose except about 240 mL of water at ambient temperature given with drug administration. At all other times water was given ad-libitum.

Subjects were provided standardized meals approximately at check-in night (In such a way to maintain the 10.00 hours pre dose fasting) and at around 0.00, 12.00 and 96.00 hours post dose in each study period. Subjects remained seated for at least 2 hours post dose except for any procedural reason. The subjects were refrained from any strenuous activity during the confinement period at the testing facility.

Demographic profile, clinical history, physical examination (including vital signs), 12 lead ECG, haemogram, biochemistry, Serology (HIV, Hepatitis B and Hepatitis C), breath alcohol test and urinalysis were done at the time of screening. Breath alcohol and urine screen for drug of abuse test were before check-in of each study period.

All the subjects were instructed to abstain from any xanthine containing food or beverages (chocolates, tea, coffee or cola drinks) or alcoholic products and grape fruit juice for 72 hours prior to drug administration and till the last sample collection in last period. Subjects enrolled in this study have not consumed any tobacco products 48 hours prior to dosing and till the last sample collection in last study period.

9.2 Discussion of Study design, including the choice of control groups

This was a randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design study.

The subjects receiving test (or reference) treatment in period I were given reference (or test) treatment in period II i.e. a crossover design was chosen so the subjects served as their own control.

It was an open label study. However, the analysts 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 the biasness 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.

Since there were two treatments, the trial design was two periods and two sequences. Effect of period, treatment and sequence on primary efficacy criteria was analyzed by ANOVA.

The sample size justification was based on the following estimates based on published literature:

T/R ratio = 95-105%

Intra-Subject C.V (%) ~ 16%

Significance Level = 5 %

Power > 80%

Bioequivalence Limits = 80.00-125.00 %

Based on the above estimates, a sample size of 20 subjects would be sufficient to establish bioequivalence between test and reference formulations with adequate power. Considering dropouts and withdrawals 24 subjects were enrolled into the study.

9.3 Selection of Study Population

Total of 39 subjects screened in order to recruit 32 in study.24 fit subjects were selected for statistical analysis. The screening examination was done after obtaining the subject's written consent. The screening examination consisted of demographic profile, clinical history, physical examination (including vital sign),12 Lead ECG and clinical laboratory tests including haemogram, biochemistry, serology (HIV, Hepatitis B and Hepatitis C), Breath alcohol and Urinalysis.

The Assigned Medical Officer examined the subjects before enrolment; the breath alcohol test and the urine test for drug abuse were carried out and the fit subjects were enrolled for the study by taking written consent in the presence of Medical Officer /Co-Investigator. Subjects satisfied the following inclusion criteria and none of the exclusion criteria were selected for the study.

9.3.1 Inclusion Criteria

1. Healthy males within 18-45 years of age (both inclusive)
2. Weigh at least 45 kg and BMI in the range of 18.5 – 24.99 (both inclusive).
3. Normal health as determined by medical history and clinical examination, laboratory or other tests mentioned in within acceptable range.
4. Willingness to provide written informed consent to participate in the study, ability to comprehend the nature and purpose of the study
5. Willingness to comply with the requirement of the protocol including all the restrictions.
6. Availability of subject for the entire study period.

9.3.2 Exclusion Criteria

1 History of allergy or hypersensitivity to Investigational Product.

2 Abnormalities in vital sign (systolic blood pressure < 90 or > 140 mm Hg or diastolic blood pressure < 50 or > 90 mm Hg or heart rate < 50 bpm or > 100 bpm at screening, at pre-entry and at pre-dose physical examination.

3 Clinically significant cardiovascular, gastrointestinal, liver, renal, pulmonary, hematological, neurological, endocrinal disease.

4 History of epilepsy or psychiatric disorder.

5 Any illness within 21 days or hospitalized or a major illness within the 3 months prior to the first dosing.

6 Any other clinical condition, which may affect the absorption, distribution, biotransformation or excretion of the study drug. (e. g. diarrhoea, vomiting in 3 days prior to or at dosing)

7 Use of any prescribed medication during last two weeks or OTC medical products during the last one week preceding the first dosing

8 Participated in any other clinical investigation requiring repeated blood sampling / a blood donation program / have blood loss of more than 350 ml in the past three months.

9 History of consumption of alcohol for more than two years & drink more than two alcoholic drinks per day or consumed alcohol within 48 hours prior to first dosing [one drink is equal to one unit of alcohol (one glass wine, half pint beer, and one measure i.e. one fluid ounce of spirit)].

10 Smoke more than 10 cigarettes / day or Unable to abstain from smoking during the study.

11 Consumption of products containing xanthine & nicotine within 48 hours before dosing.

12 Intake of grapefruits or products containing grapefruits within 72 hours prior to receiving the dose of study medication in each period.

13 An unusual diet, for whatever reason (e. g. low-sodium or high protein) for four weeks prior to receiving the study medication.

14 Use of any recreational drug or a history of drug addiction.

15 Participation in any clinical study within the past 3 months.

16 History of difficulty in accessibility of veins in arms.

9.3.3 Removal of Subjects from Therapy or Assessment

The subject was free to withdraw from the study at any time without having to give any reasons thereof. The investigator may withdraw a subject from the study for any of the valid reasons which he thinks is appropriate in view of the safety and well-being of subject, GCP principles or objectives of the project, in particular for:

- Any serious side effect

- Any abnormal laboratory test considered to be of clinical significance
- Any serious protocol violation
- Lack of co-operation
- Inter-current illness requiring treatment / inter-current surgery
- If the subject vomits at or before 2 times median T_{max}.

All the subjects have completed the clinical phase of the study and the plasma samples of these subjects were analyzed and were considered to draw statistical conclusion.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were fasted for at least 10 hours prior to dosing and for 4 hours post dose in each study period. Total of 24 subjects were administered a single oral dose of either of the test or reference product as per the randomizationschedule at ambient temperature in sittingposition in each period of product or single dose (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania of reference product was administered with about 240 ml of water. A mouth check was done immediately after dosing using a tongue depressor and torch to assess the compliance of the procedure. The administration of the test and the reference products was done as per the randomization schedule generated through SAS 9.2.

Refer to Appendix 16.1.7.

The test and reference products were administered to the subjects in sitting position. Subjects remained seated for at least 2 hours post dose except for any procedural reason. The subjects were refrained from any strenuous activity during the confinement period at the testing facility. Drinking water was not allowed to the subjects from one hour prior to dosing until one hour post-dose except about 240 mL of water given during administration of the drug. At all other times drinking water was given ad-libitum.

9.4.2 Identity of Investigational Product

A: Test Product (T)

Name of Product	(Isotretinoin Capsules 20 mg)
Label Claim	Each Soft Gelatin Capsule Contains: Isotretinoin USP.....20mg
Batch No.	T18F001
Mfg. Date:	06/2018
Expiry Date:	05/2021
Manufactured By	Olive Healthcare

B: Reference Product (R)

Name of Product	Roaccutane
Label Claim	Each Soft Gelatin Capsule Contains: Isotretinoin.....20mg
Batch No.	B9397805
Expiry Date.	02/2020
Manufactured for	Catalent Germany Eberbach GMBH, Alemania

9.4.3 Method of Assigning Subjects to Treatment Groups

All the 24 subjects were randomized to either of the treatment (Test or Reference) according to the randomization schedule in each study period, which was prepared by the biostatistician prior to the conduct of the study. The subjects were assigned subject number as per check in time of subject for Period-I which remained same throughout the study. For Randomization Schedule Refer Appendix 16.1.7.

The randomization Schedule was generated using SAS® Software (Version 9.2).

9.4.4 Selection of doses in the study

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Based on above recommended doses and safety concerned, this dose (Isotretinoin Capsules 20 mg) has been choosen for the study. This dose was expected to be well tolerated and provided sufficient plasma concentration to measure.

9.4.5 Selection and timing of dose for each subjects

Subjects were randomly assigned to one of the treatment sequences (TR/RT) as per the generated randomization code. All subjects fasted overnight for at least 10.00 hours prior to the scheduled dosing time. Dosing was done in a staggered manner to maintain blood sample collection schedule. The time interval between two subsequent dosing was two minutes. The test or reference formulations were orally administered to the subjects in sitting posture with about 240 ± 5 mL of water at ambient temperature, followed by a mouth-check to confirm the compliance of the procedure.

Dosing was done in a staggered manner to maintain blood sample collection schedule. The time interval between two subsequent dosing was two minutes. The test or reference formulations were orally administered to the subjects in sitting posture with about 240 mL of water at ambient temperature, followed by a mouth-check to confirm the compliance of the procedure.

9.4.6 Blinding

This study comprised of a randomized, open label design. However the analyst was blinded to the sequence of administration of test and reference products to the individual subjects. The plasma samples were stored in labeled vials, which were not identified by product details. The randomization schedule was in the custody of the Pharmacist until the completion of clinical phase of study.

9.4.7 Prior and Concomitant Therapy

No subjects used any medication (Prescription or over the counter), vitamins or minerals for 14 days prior to the study. Subjects did not use any enzyme modifying drugs in the previous 28 days prior to dosing or were not in any medical or surgical conditions which might significantly interfere with the functioning of gastrointestinal tract, blood-forming organs etc. which was confirmed by the clinical history taken by the Medical Officer.

9.4.8 Treatment Compliance

Test or Reference Product containing was administered to the subjects by the assigned study

personnel responsible for the activity, under the observation of Principal Investigator. Subjects were fasted for at least 10.00 hours prior to dosing and for 96.00 hours post dose. Subjects were administered single oral dose (Isotretinoin Capsules 20 mg) of Olive Healthcare. and Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania under fasting condition of reference product was administered with about 240 mL of water at ambient temp. in sitting Positon while dosing, the assigned study personnel responsible for the activity confirmed subject number, study code, photograph authorized signature and the subject registration number from the identity card provided to them during the study. The subject identity card had the information of subject number, study code, subject signature, photograph and the and the subject registration number. A mouth check was performed immediately after drug administration to assess the compliance to this procedure. The labels, identifying the study code study period, subject number, the treatment code (Test A or Reference B) and "For Clinical Research Use Only" were affixed on the case report form (CRF) which as signed by the respectively as signed study personnel responsible for the activity.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

The pharmacokinetic parameters were calculated by non-compartmental method using SAS® 9.2. The following pharmacokinetic parameters of Isotretinoin were estimated for test and reference formulations.

a) C_{max} and T_{max}

The maximum plasma concentration (C_{max}) and the time of the peak concentration (T_{max}) were taken directly from the plasma concentration time profiles of individual subjects. The units of C_{max} and T_{max} are ng/mL and hour (hrs), respectively.

b) AUC_{0-t} and $AUC_{0-\infty}$

AUC_{0-t} = Area under the plasma concentration - time curve measured to the last quantifiable concentration, using the trapezoidal rule.

$AUC_{0-\infty}$ = AUC_{0-t} plus additional area extrapolated to infinity, calculated using the formula $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.

Subjects excluded from the Efficacy Analysis:

No Subject was excluded from study and thus the data of all 24 subjects were considered to draw statistical conclusion. Refer to Appendix 16.2.3.

Safety Measurements Assessed:

Safety was evaluated by monitoring adverse events during each study period. The supervising Medical Officer or nursing staff measured vital signs. Physical examination. Vital examination and well being assessment were done at the time of check in, check out of each study period. Sitting blood pressure and radial pulse rate were measured at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose ± 45 minutes (except for pre-dose) of scheduled time in each study period, and whenever the physician thinks it necessary throughout the stay of subjects in each period. Well being assessment was done at pre-dose

and at 0.00, 12.00 and 96.00 hours post-dose in each study period. The subjects were monitored for adverse events, complaints if any, throughout the course of the study.

The following parameters were done at the time of screening:

- Demographic data
- Clinical history
- Physical examination (including vital signs)
- 12 Lead ECG
- Haemogram, Biochemistry, Serology (HIV, Hepatitis B and Hepatitis C).
- Breath alcohol test and urinalysis.

As a part of check-in in each study period the following examinations were done:

- Physical examination (including vital signs)
- Breath alcohol test

As a part of post-study evaluation or early discontinuation of subject, the following examinations were done:

- Physical examination (including vital signs)
- Haemogram, Biochemistry and Urine analysis

The subjects reported spontaneously in case of any inconvenience or adverse events to the monitoring study personnel, during the study, wash out period and after check-out as applicable for the study.

9.5.2 Appropriateness of Measurements

The blood samples were collected at Pre dose (collected within 1 hr prior to dosing) and at prior to dosing) and at 0.00, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.25, 3.50, 4.00, 5.00, 6.00, 12.00, 24.00, 48.00, 72.00 and 96.00 (Post-dose) within 2 minutes of scheduled sampling time in each study period. To assess subject's safety, Physical examination, vital examination (Blood pressure, pulse rate, temperature and respiratory rate)and well being for the assessment were done at the time of check in, check out of each study period and during post study assessment. Sitting blood pressure and radial pulse rate were measured at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose ± 45 minutes (except for pre-dose) of scheduled time in each study period, and whenever the physician thinks it necessary throughout the stay of subjects in each period. Well being assessment was done at pre-dose and at 0.00, 12.00 and 96.00 hrs post-dose.

in each study period 12 Lead ECG were recorded during screening.

9.5.3 Primary efficacy variable(s)

The pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were taken as primary variables for establishing the bioequivalence of the Test Product, (Isotretinoin Capsules 20 mg) of Olive Healthcare. Compared with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in terms of rate and extent of absorption under Fasting condition.

9.5.4 Drug Concentration Measurements

Analysis was done atRAPTIM RESEARCH LIMITED .

9.6 Data Quality Assurance

The entire proceedings of the study, the raw data generated for the study including scientific, nonscientific data (e.g. correspondence), clinical, bioanalytical and statistical data and final reports were liable for the following.

- 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.

The Quality Assurance personnel of RAPTIM RESEARCH LIMITED . performed the quality audits. **Refer to Appendix 16.1.8.**

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

9.7.1 Statistical and Analytical Plans

All statistical analysis was performed using SAS® 9.2. The plasma concentrations at each sampling time points were tabulated for each subject and product combination. Descriptive statistics for each product at each scheduled sampling time point was done. All the BLQ values were considered as zero for the computation of pharmacokinetic parameters and statistical calculations. MSV (Missing sample value) was given an arbitrary code as 999999 in calculation of pharmacokinetic parameters using SAS® Version 9.2.

For Individual subject's plasma concentration tables, **Refer Appendix 16.2.5.**

The mean plasma concentration of Isotretinoin versus time profiles for each product was presented graphically on both the scales i.e. on the untransformed and log-transformed data **(Refer Efficacy/ Bioequivalence Data 14.2).** The actual blood sampling time points **(ReferAppendix 16.1.9.2)** were considered for the calculation of pharmacokinetic parameters. ANOVA was performed onlog transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

ANOVA model included sequences, subjects nested within sequence, period, and treatment as factors. Each analysis of variance also included calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences. The significance of the sequenc effect was tested using the subjects nested within the sequence as the error term. The 90% confidence intervals for the difference between treatments, Geometric means (GM) were calculated for log-transformed C_{max}, AUC_{0-t} an $AUC_{0-\infty}$. The confidence interval was expressed as a percentage relative to the least square mean (LSM) of the reference treatments. The geometric least square mean ratios of the test and reference product of and its 90% confidence interval for pharmacokinetic parameters- C_{max} and AUC0-t were computed and bioequivalence was concluded if the 90% confidence interval lay within the acceptable range of 80%-125% for log transformed Cmax, AUC0-t and AUC0-Inf for Isotretinoin.

9.7.2 Determination of Sample Size

The sample size justification was based on the following estimates based on published literature:

T/R ratio = 95-105%

Intra-Subject C.V (%) ~ 16 %

Significance Level = 5 %

Power > 80%

Bioequivalence Limits = 80.00-125.00 %

Based on the above estimates, a sample size of 20 subjects would be sufficient to establish bioequivalence between test and reference formulations with adequate power. Considering dropouts and withdrawals, 24 subjects were enrolled into the study.

9.8 Changes in the Conduct of the Study or Planned Analyses

There was no change in the conduct of the study or planned analysis.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

Forty nine (39) volunteers that were most likely to meet the requirements of this study and who were willing to participate in the study were screened.32 subjects were recruited in study. Total of 24 fit and consenting subjects were enrolled in the study. No Subjects were withdrawn from the study. So total of 24 subjects completed the study. The randomization schedule isappended in **Appendix 16.1.7**.

The data of all subjects were used to demonstrate bioequivalence of test product with reference product. Pharmacokinetic and Statistical analysis results are appended in **Appendix 16.1.9.4**.

10.2 Protocol Deviations

- Blood Sample Time Point Deviation. **Refer to Appendix 16.2.2**.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

Plasma samples of all the subjects were analyzed and were used to demonstrate bioequivalence of test product with reference product.

11.2 Demographic and Other Baseline Characteristics

Normal, healthy, adult male human subjects in the age range of 18 – 45 years with normal findings were enrolled in the study. Demographic profile, clinical history, physical examination (including vital signs), haemogram, biochemistry, serology (HIV, Hepatitis B and Hepatitis C) urinalysis, breath alcohol test and 12 Lead ECG test were carried out in screening. The demographic data for individual subjects are appended in **Appendix 16.2.4**.

11.3 Measurements of Treatment Compliance

Total of 24 subjects were administered single oral dose of either of the test or reference product as per the randomization schedule with about 240 mL of water at ambient temperature in sitting position in each study period. A mouth-check was done immediately after drug administration to assess the compliance to this procedure.Total 24 subjects completed the clinical phase of the study. Plasma Levels of Isotretinoin in individual subjects at different time points following reference and test products are appended in **Appendix 16.2.5.**

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.4.1 Analysis of Efficacy/Bioequivalence

The mean pharmacokinetic parameters estimated for Isotretinoin for both the Test and Reference products are as follows:

Pharmacokinetics Parameters of Isotretinoin

Obs .No.	Name	Geomean Ref	Geomean Test	MSE	Ratio	Power	Intra_cv	plower	pupper	p	BIO-EQUI
1.	LnC_{max}	0.916	0.916	0.063	99.913	99.367	25.670	92.100	108.388	0.985	Yes
2.	$LnAUC_{0-t}$	2.989	3.034	0.119	101.482	90.851	35.603	90.789	113.434	0.825	Yes
3.	$LnAUC_{0-inf}$	4.380	4.336	0.056	98.986	99.689	24.205	91.659	106.900	0.825	Yes

The summary results of are tabulated in section 14.2 and the individual subjects and mean pharmacokinetic parameters for both the test and reference products have been tabulated in **Appendix 16.2.6.**

The pharmacokinetic and statistical output for from SAS® 9.2 is appended in **Appendix 16.1.9.4**.

11.4.2.2 Handling of Dropouts or Missing Data

Missing Sample Value(s) was given numeric code "999999" before performing pharmacokinetic calculations. The SAS program recognized this code and the particular value(s) was not considered for estimation of pharmacokinetic parameters.

11.4.2.3 Interim Analyses and Data Monitoring

Not Applicable

11.4.2.4 Multicenter Studies

Not Applicable

11.4.2.5 Multiple Comparisons/Multiplicity

Not Applicable

11.4.2.6 Use of an "Efficacy Subset" of Patients

Not Applicable

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not Applicable

11.4.2.8 Examination of Subgroups

Not Applicable

11.4.3 Tabulation of Individual Response Data

All individual subjects'concentration data of Isotretinoin at each time point is appended in **Appendix 16.2.5**.Individual plasma conc. time curves are presented in **Appendix 16.1.9.3.2.**

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

Only pharmacokinetic parameters were considered in this study. No pharmacodynamic evaluations were performed.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.4.6 By-Patient Display

Not Applicable

11.4.7 Efficacy / Bioequivalence Conclusion

In statistical analysis of Isotretinoin on data of 24 subjects, ratios for geometric least square means and 90% confidence interval of primary variables lie within the acceptance ranges 80-125% for log transform C_{max}, AUC_{0-t}, and AUC_{0-inf}.

Thus it is concluded that the Test Product, (Isotretinoin Capsules 20 mg) of Olive Healthcare. is bioequivalent with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in terms of rate and extent of absorption under fasting condition.

12 SAFETY EVALUATION

12.1 Extent of exposure

Total of 24 subjects in period I and 24 subjects in period II were administered single oral dose of either of the test or reference product as per the randomization schedule with about 240 mL of water at ambient temperature in sitting position. No subject was with drwan from the study. Total 24 subjects has completed the clinical phase of the study. Plasma Levels of Isotretinoin in individual subjects atdifferent time points following reference and test products are appended in **Appendix 16.2.5.** The duration of clinical phase was 20 days, including the washout period of 21 days.

12.2 Adverse events (AEs)

12.2.1 Brief Summary of Adverse Events

Subject number 01 had Itching during Period I, subject number 22 had Nausea during period II. **Refer Appendix 16.2.7.**

12.2.2 Display of Adverse Events

Adverse events reported during the clinical phase of the study were noted in the respective case report forms. **Refer Appendix 16.2.7.** Abnormal laboratory values are listed in **Appendix 16.2.8** and summary of vital signs measurement is listed in **Appendix 16.4.2.**

Incidence of Adverse Events in the Study

Adverse Event Reported	Test Product (T) N = 24	Reference Products (R) N = 24
Itching	00 (00.00 %)	01 (05.10 %)
Nausea	01 (05.16 %)	00 (00.00 %)
Total	**01 (05.16 %)**	**01 (05.10 %)**

12.2.3 Analysis of Adverse Events

No any adverse event was reported during the clinical phase of the study in test product treated subjects and total of two (05.16%) and (05.10%) adverse events were reported during the clinical phase of the study in test and reference product treated subjects. Event was related to the study medication. The adverse event was mild in severity and resolved. No serious adverse event was observed during all the periods of the study. There were a few laboratory values out of the reference ranges which were evaluated as clinically non significant and recorded in the respective CRF of the subject for Summary of Clinical Laboratory Test. Refer Appendix 16.2.8.

12.2.4 Listing of Adverse Events by subjects

LIST OF ADVERSE EVENT

Subject No.	Adverse event	Start Time	Relief Time	Severity	Drug Relation	Measures Taken
During Period- I						
01	Itching	13:06	15:01	Mild	Expected, Probable	Reassurance, keep under observation until resolved
During Period- II						
22	Nausea	16:12	17:03	Mild	Expected, Probable	Reassurance, keep under observation until resolved
Post Study Laboratory Assessment						
No adverse event observed						

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

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

No deaths, or serious adverse events or other significant adverse event was occurred during the study period.

12.3.1.1 Deaths

No death during the study, including the post treatment follow-up period or deaths that resulted from a process that began during the study.

12.3.1.2 Other Serious Adverse Events

No serious adverse event was reported during any of the study period.

12.3.1.3 Other Significant Adverse Events

No significant adverse event was reported during any of the study period.

12.4 Clinical Laboratory Evaluation

The laboratory values outside the reference range were evaluated on the basis of clinical significance. The abnormalities observed in the clinical laboratory tests were evaluated on the basis of clinical significance and comments were written accordingly in the CRF of the subject.

12.4.1 Listing of individual laboratory measurements by subjects and each abnormal value

The summary of clinical laboratory findings is included as bold letter in Appendix 16.2.8 of all the subjects.

12.4.2 Evaluation of Each Laboratory Parameter

No significance of the deaths, other serious adverse events or other significant adverse events found during the study period.

12.5 Vital Signs, Physical Findings, and other observations related to safety

Pre-enrolment health check-up of the subjects were performed during the enrolment for each period. The subjects were checked physically for any illness or health problems at the time of screening and on the check-in day prior to dosing by the Assigned Medical Officer/Co-Investigator and their vital signs were also measured.

Physical examination & Vital examination were done before check in and check out of each study period. Sitting blood pressure and radial pulse rate were measured at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose ± 45 minutes (except for pre-dose) of scheduled time in each study period, and whenever the physician thinks it necessary throughout the stay of subjects in each period. Well being assessment was done at pre-dose and at 0.00, 12.00 and 96.00 hours post-dose in each study period. 12 Lead ECG were recorded during screening.

At the end of the study, post-study evaluation including physical examination (including vital signs), haemogram, biochemistry and urinalysis were performed.

The abnormalities observed in the clinical laboratory tests were evaluated on the basis of clinical significance. **Refer Appendix 16.2.8.**

The summary of 12 Lead ECG recordings has been appended in **Appendix 16.4.1** and the summary of the recordings of vital signs have been appended in **Appendix 16.4.2.**

12.6 Safety Conclusions

Isotretinoin Capsules was well tolerated and adverse event was mild in severity and resolved Total of two (02) adverse events were observed in test and reference product treated subjects. Event was related to the study medication. The adverse event was mild severity and resolved. No serious adverse event was observed during all the periods of the study.The laboratory values observed out of reference range were evaluated on the basis of clinical correlation.

13 DISCUSSION AND OVERALL CONCLUSIONS

Total of 39 normal, adult, healthy, male human subjects were screeened. 32 volunteers were recruited. 24 fit volunteers were selected. Plasma samples of 24 subjects were analyzed for Isotretinoin the data of all these subjects were considered to draw the pharmacokinetic and statistical evaluation. It is concluded that the Test Product of (Isotretinoin Capsules 20 mg) of Olive Healthcare. is bioequivalent with Roaccutane (Isotretinoin Capsules 20 mg) of Catalent Germany Eberbach GMBH, Alemania in term of rate and extent of absorption under fasting condition.

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

14.1 DEMOGRAPHIC DATA

Refer Appendix 16.2.4

A: Summary data for the subjects enrolled in the study (24 Subjects):

	Age (Yr)	Height (cm)	Weight(Kg)	BMI
Mean	30.50	169.25	63.42	13.27
SD (±)	4.75	4.66	5.37	1.58
CV%	15.56	2.75	8.47	11.88
Geomean	30.12	169.19	63.19	13.17

B: Summary data for subjects included in the final analysis (24 Subjects):

	Age (Yr)	Height (cm)	Weight(Kg)	BMI
Mean	30.50	169.25	63.42	13.27
SD (±)	4.75	4.66	5.37	1.58
CV%	15.56	2.75	8.47	11.88
Geomean	30.12	169.19	63.19	13.17

14.2 EFFICACY / BIOEQUIVALENCE DATA

For Individual data and graphical representation, **Refer to Appendix 16.1.9.3.** Summary statistics of Isotretinoin Capsules pharmacokinetic parameters of test (A) and reference (B) products under fasting condition.

ISOTRETINOIN

SUBJECTS (SEQ) ANOVA (C_{MAX}, AUC_{0-t}, AUC_{0-inf}) Log transformed Data

For LnC_{max}

Source of variation	Degree of Freedom	Mean Squares	Statistic F	p- Value
Sequence	1	0.11579235	1.81	0.1838
Subject (sequence)	22	0.02574084	0.40	0.9993
Period	1	0.00858158	0.13	0.7153
Treatment	1	0.00002023	0.00	0.9859
Residuals	22	0.06381936	---	---

The GLM Procedure

Dependent Variable: LnC_{max}

Source	Pr> F
Seq	0.1838
Subject (Seq)	0.9993
Period	0.7153
Treat	0.9859

Tests of Hypotheses Using the Type III

MS for Subjects (Seq) an as Error Term

Source	DF	Type III SS	Mean Square	F Value
Seq	1	0.11579235	0.11579235	4.50

Tests of Hypotheses Using the Type III

MS for Subjects (Seq) an as Error Term

Source	Pr> F
Seq	0.0387

For Ln AUC_{0-t}

Source of variation	Degree of Freedom	Mean Squares	Statistic F	p- Value
Sequence	1	0.04119530	0.62	0.4361
Subject (sequence)	22	0.03916793	0.59	0.9353
Period	1	0.09472390	1.43	0.2404
Treatment	1	0.00010239	0.00	0.9689
Residuals	22	0.06633275	---	---

The GLM Procedure

Dependent Variable: LnC_{max}

Source	Pr> F
Seq	0.4361
Subject (Seq)	0.9353
Period	0.2404
Treat	0.9689

Tests of Hypotheses Using the Type III

MS for Subjects (Seq) an as Error Term

Source	DF	Type III SS	Mean Square	F Value
Seq	1	0.04119530	0.04119530	1.05

Tests of Hypotheses Using the Type III

MS for Subjects (Seq) an as Error Term

Source	Pr> F
Seq	0.3123

For LnAUC$_{0\text{-inf}}$

Source of variation	Degree of Freedom	Mean Squares	Statistic F	p-Value
Sequence	1	0.08435319	1.48	0.2290
Subject (Sequence)	22	0.01840646	0.32	1.0000
Period	1	0.00677328	0.12	0.7316
Treatment	1	0.00279906	0.05	0.8254
Residuals	22	0.05693894	---	---

The GLM Procedure

Dependent Variable: LnAUC$_{0\text{-inf}}$

Source	Pr>F
Seq	0.2290
Subject (Seq)	1.0000
Period	0.7316
Treat	0.8254

Tests of Hypotheses Using the Type III

MS for Subject (Seq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value
Seq	1	0.08435319	0.08435319	4.58

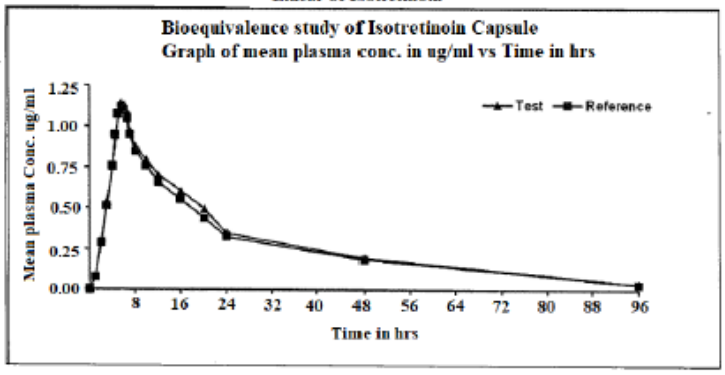
Tests of Hypotheses Using the Type III

MS for Subject (Seq) as an Error Term

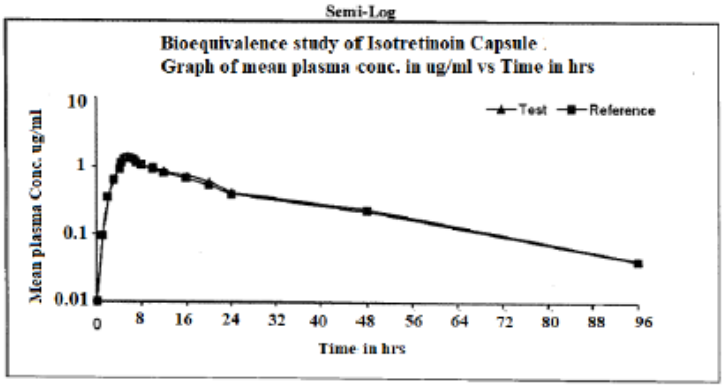
Source	Pr>F
Seq	0.0370

14.2.1 Mean conc Time Profile : Un Transformed and log Transformed (Test and Reference)

Mean Plasma conc. Graph
Linear of Isotretinoin



Semi-Log



14.3 Details of summaries, tables and figures are provided.

14.3.1 Displays of Adverse Events

The adverse events observed during the clinical phase of the study are listed in **Appendix 16.2.7.**

14.3.2 Listings of deaths, other serious and significant adverse events

Not applicable.

14.3.3 Narrative of deaths, other serious and certain other significant adverse events

Not applicable.

14.3.4 Abnormal laboratory value listing

The subjects whose laboratory values were found out of reference range are listed in **Appendix no. 16.2.8.**

15 REFERENCE LIST

1. ICH Harmonized Tripartite Guideline for GCP 1996.
2. Guidance for industry- Statistical Approaches to Establishing Bioequivalence U.S. Department of Health and Human Services, Food and Drug Administration. Jan 2001.
3. Guidance for industry Bioavailability and Bioequivalence studies for orally Administered Drug Products –General considerations U.S. Department of health and Human Services, Food and Drug Administration, Mar 2003.
4. Guidance for Industry- Handling and Retention of BA and BE Testing Samples U.S. Department of Health and Human Services, Food and Drug Administration, May 2004.
5. Generating randomization schedule using SAS® Programming, Chunqin Deng and Julia Graz. PPD, Inc, Research Triangle Park, North Carolina, available on website: - http://www2.sas.com/proceedings/sugi27/p267-27.pdf

16.0 APPENDICES

16.1 STUDY INFORMATION		
	16.1.1	Protocol and Protocol Amendment
	16.1.2	Specimen Copy of Case Record Form
	16.1.3	List of IEC members and IEC approval letter
		16.1.3.1 Specimen of Informed Consent Form
	16.1.4	List of Investigators and CVs
	16.1.5	GCP Compliance Statement
	16.1.6	Listing of subjects receiving test/reference product from specific batches where more than one batch was used.
	16.1.7	Randomization Schedule
	16.1.8	Audit Certificate
	16.1.9	Documentation of Statistical Methods
		16.1.9.1 Sample Size Calculation
		16.1.9.2 Actual Time Point considered
		16.1.9.3 Efficacy / Bioequivalence Data
		16.1.9.4 Pharmacokinetics and Statistical Output
	16.1.10	Quality Assurance Statement for Documentation on inter laboratory standardization methods and quality assurance procedure used.
	16.1.11	Publication based on the study
	16.1.12	Important Publications Referenced in the Report
16.2 SUBJECTS DATA LISTING		
	16.2.1	Discontinued subjects(List of Dropped out/Withdrawn)
	16.2.2	Protocol deviation
	16.2.3	Subjects excluded from the efficacy analysis
	16.2.4	Demographic data of Enrolled and Analyzed subjects
	16.2.5	Compliance and /or Drug Concentration Data Plasma concentration for Test and Reference Product
	16.2.6	Individual efficacy/pharmacokinetic data(Pharmacokinetic parameters for test and Reference Product)
	16.2.7	List of Adverse Event
	16.2.8	Summary of Clinical Laboratory Test
16.3 BIO-ANALYTICAL REPORT		
16.4 METHOD VALIDATION REPORT		