REPORT ON BIOEQUIVALENCE STUDY

(Protocol No.: BEQ-532-CAND-2010, Version No.: 05 Date: 16th May 2011)

Study Title:

Bioequivalence study of single dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

Study Design:

An open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 36 healthy, adult, human subjects under fasting condition.

Investigational Product Details		**Dose**
i) Test Formulation (T) :	Candesartan cilexetil tablets 32 mg Macleods Pharmaceuticals Ltd., India	1 x 32 mg
ii) Reference Formulation (R):	Atacand® (candesartan cilexetil) tablets 32 mg for AstraZeneca, LP, USA	1 x 32 mg

Duration of Clinical Phase	:	18th May 2011 – 13th June 2011
Duration of Bioanalytical Phase	:	11th June 2011 – 21st June 2011
Duration of Statistical Phase	:	02nd July 2011
Report Status	:	Final
Version	:	01
Dated	:	14th July 2011
Supersedes Version	:	None
Dated	:	Not Applicable

Sponsor	**Study Centre:**
Macleods Pharmaceuticals Ltd., G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093, India Telephone No.: 91-22-28306435 / 28314611 Fax No.: 91-22-28304641	Macleods Pharmaceuticals Ltd., Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093, India Telephone No.: 91-22-28306435 / 28314611 Fax No.: 91-22-28304641 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 : Mr. Amol Choulwar

2.0 SYNOPSIS OF THE REPORT

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Candesartan cilexetil tablets 32 mg **Name of Active Ingredient:** Candesartan cilexetil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Title of Study: Bioequivalence study of single dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

Investigator: Dr. Rajendra Sonde, Principal Investigator

Study Centre: Macleods Pharmaceuticals Ltd., Bioequivalence Department

Publication (reference): Not Applicable

Study period:

Date of Screening	:	30th April 2011 - 16th May 2011
Duration of Clinical Phase	:	18th May 2011 – 13th June 2011
Period 1	:	18th May 2011 – 20th May 2011
Period 2	:	25th May 2011 – 27th May 2011
Duration of Bioanalytical Phase	:	11th June 2011 – 21st June 2011
Duration of Statistical Phase	:	02nd July 2011

Objectives:

Pharmacokinetic: To evaluate the comparative oral bioavailability of single dose Candesartan cilexetil tablets 32 mg Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India with Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

Safety: To monitor the safety and tolerability of single oral dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) when administered in healthy, adult, human subjects under fasting condition.

Methodology: Serial blood samplings (pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours post-dose) were done before and up to 36.00 hours post-drug administration. Analysis of plasma samples for candesartan concentrations 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.

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Candesartan cilexetil tablets 32 mg **Name of Active Ingredient:** Candesartan cilexetil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Number of Subjects (planned and analysed): A total of 36 subjects were planned and enrolled. Of these 36 subjects, subject number 23 did not report to the facility for period 2, thus considered dropped-out from the study. Thus thirty-five subjects completed both the periods. The data of thirty-five completing subjects (01 to 22 and 24 to 36) 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/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) and having absence of significant disease, clinically significant laboratory values, 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.

i) Test Formulation (T):

Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg)
Batch No.: ECD8101A
Manufacturing Date: 04/2011
Expiry Date: 03/2013
Manufactured by: Macleods Pharmaceuticals Ltd. India
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

ii) Reference Formulation (R):

Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg)
Lot No.: E008171
Manufacturing Date: N/AV
Expiry Date: 04-2013
Manufactured by: AstraZeneca AB, S-15185, Sweden
Manufactured for: AstraZeneca LP, Wilmington, DE 19850
NDC-0186-0032-31
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

Duration of treatment	Single dose in both periods.

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Candesartan cilexetil tablets 32 mg **Name of Active Ingredient:** Candesartan cilexetil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Criteria for Evaluation:

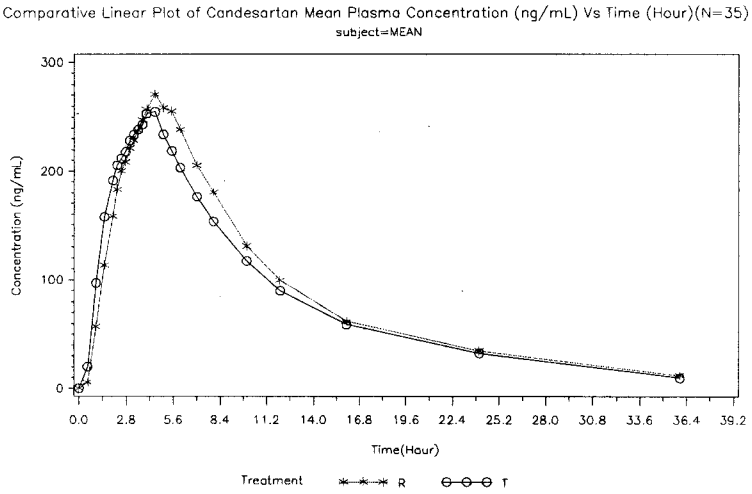
Efficacy: The 90% confidence interval for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Candesartan formed the basis for concluding the equivalence of candesartan in product R and T. If the confidence intervals are entirely included in the range of 80 – 125% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ log-transformed then the treatments would be claimed to be bioequivalent.

Safety: To monitor the safety and tolerability of single oral dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) when administered in healthy, adult, human subjects under fasting condition.

Statistical Methods: The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) are analysed using an ANOVA model. Calculated 90% confidence interval for the ratio of both the products averages (geometric means) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference are expressed in percentage and power test is performed using SAS® version 9.2.

SUMMARY - CONCLUSION

EFFICACY RESULTS:



The 90 % confidence intervals of ln-transformed parameters for Candesartan summarized below:

Geometric mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Candesartan

Pharmacokinetic Parameters	Geometric mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90 % Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	263.242	281.408	93.54	24.00	96.74	85.00 - 102.95
AUC_{0-t} (ng*hrs/mL)	2714.936	2876.430	94.39	13.45	100.00	89.41 - 99.64
$AUC_{0-\infty}$(ng*hrs/mL)	2932.065	3045.322	96.28	13.09	100.00	91.33 - 101.50

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Candesartan cilexetil tablets 32 mg **Name of Active Ingredient:** Candesartan cilexetil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

SAFETY RESULTS:

No adverse event occurred during entire course of the study. During post-study safety assessment adverse event was reported for three subjects.

CONCLUSION:

The test product, Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent to the reference product, Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition. Both the formulations are well tolerated following a single dose administration of the investigational products.

Date of the report: 14th July 2011

3.0 TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

µL	:	Microlitre
ANOVA	:	Analysis of Variance
AUC	:	Area under Curve
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 zero to infinity
BLQ	:	Below Limit of Quantification
BMI	:	Body Mass Index
B.P	:	Blood Pressure
BPM	:	Beats per Minute
CBC	:	Complete Blood Count
CCF	:	Congestive Cardiac Failure
CSF	:	Cerebrospinal Fluid
C_{max}	:	Concentration Maximum
CNS	:	Central Nervous System
COA	:	Certificate of Analysis
CPU	:	Clinical Pharmacology Unit
CV	:	Coefficient of Variance
^0C	:	Degree Centigrade
D	:	Day
DLC	:	Differential Leucocyte count
DNA	:	Deoxyribonucleic acid
ECG	:	Electro-Cardiogram
EDTA	:	Ethylene diamine tetra-acetic acid
ESR	:	Erythrocyte Sedimentation Rate
GABA	:	Gamma Amino Butyric Acid
GCP	:	Good Clinical Practices
GGT	:	Gama Glutamyl Transpeptidase
GMP	:	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 on Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee
IP	:	Investigational Product

IU	:	International Unit
IUD	:	Intrauterine device
K_{el}	:	Elimination rate constant
LC-MS/MS	:	Liquid chromatography-tandem mass spectrometry
LFT	:	Liver Function Test
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	:	millilitre
oz	:	Ounce
PA view	:	Posterior Anterior View
PCV	:	Packed Cell Volume
PK	:	Pharmacokinetic
QA	:	Quality Assurance
R	:	Reference Product
RBC	:	Red Blood Cell
RFT	:	Renal Function Test
RH	:	Relative Humidity
rpm	:	Revolution Per Minute
SAE(s)	:	Serious Adverse Event(S)
SADR	:	Serious Adverse Drug Reactions
SAS	:	Statistical Analysis System
SGOT	:	Serum Glutamate Oxaloacetate Transaminase
SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP(s)	:	Standard Operating Procedure(S)
SQ	:	Subject Questionnaire
T	:	Test Product
$t_{1/2}$	:	Terminal Half-life
t_{max}	:	Time of maximum measured plasma concentration. If maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period.
TG	:	Triglycerides
UPT	:	Urine Pregnancy Test
USFDA	:	United States Food and Drug Administration
w/v	:	Weight by Volume

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol, BEQ-532-CAND-2010, version No. 02, dated: 04th November 2010, English ICF, version no. 02, dated: 04th November 2010, Hindi and Marathi ICFs version no. 01, dated 15th November 2010 were sent to IEC on 16th November 2010. The Independ ent Ethics Committee in its meeting held on 01st December 2010 gave provisional approval.

Due to changes and few modifications in protocol and ICFs, the protocol, BEQ-532-CAND-2010 version no. 04, dated: 21st April 2011, English ICF, version no. 04, dated: 21st April 2011, Hindi and Marathi ICFs version no. 03, dated 25th April 2011 were sent to IEC on 02nd May 2011. The Independent Ethics Committee in its meeting held on 13th May 2011 gave provisional approval.

The protocol, BEQ-532-CAND-2010 version no. 05, dated: 16th May 2011 English ICF, version no. 05, dated: 16th May 2011, Hindi and Marathi ICFs version no. 04, dated 16th May 2011 along with COA were sent to IEC on 16th May 2011. The Chairperson on behalf of Independent Ethics Committee on 16th May 2011 gave final approval to the submitted protocol and ICFs.

Approval was granted after the review of documents and the approved version bears the following version number and date:

Protocol : Version No. 05, dated: 16th May 2011
English ICF : Version No. 05, dated: 16th May 2011
Hindi ICF : Version No. 04, dated: 16th May 2011
Marathi ICF : Version No. 04, dated: 16th May 2011

Dr. Mrs. K.C.P. Walawalkar chaired the IEC. 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. The IEC summary report regarding the conduct of the study was sent to IEC on 14th June 2011.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the principles of the Declaration of Helsinki, 'ICH GCP', National Regulations (ICMR Guidelines), 'Indian GCP', USFDA guidelines and "Schedule Y" of Indian Drugs and Cosmetics Act.

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

Name : Mr. Amol Choulwar (M. Pharm Pharmacology)
Asst. Manager – Medical Services

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BIOEQUIVALENCE DEPARTMENT PERSONNEL

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Principal Investigator:

Name : Dr. Rajendra Sonde (M.B.B.S.)

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D) Bioanalytical Facility : Macleods Pharmaceuticals Ltd.,
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E) Statistical Operations : Macleods Pharmaceuticals Ltd.,
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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

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis. [1]

Clinical Pharmacokinetics

General

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to Candesartan, a selective AT1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of Candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of Candesartan are linear for oral doses up to 32 mg of Candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of Candesartan cilexetil, the absolute bioavailability of Candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours.

Distribution

The volume of distribution of Candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at Candesartan plasma concentrations well above the range achieved with recommended doses.

Metabolism and Excretion

Total plasma clearance of Candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When Candesartan is administered orally, about 26% of the dose is excreted unchanged in urine.

Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of Candesartan is approximately 9 hours. [1]

Food Effect

Food with a high fat content does not affect the bioavailability of Candesartan after Candesartan cilexetil administration. [1]

Gender Effect

The pharmacokinetics (C_{max} and AUC) were not modified by age, sex or body weight. There is no difference in the pharmacokinetics of Candesartan between male and female subjects. [1]

Indications and Uses

Hypertension

Atacand® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Heart Failure

Atacand® is indicated for the treatment of heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. Atacand® also has an added effect on these outcomes when used with an ACE inhibitor. [1]

Adverse Reactions

Most common adverse reactions (incidence ≥ 2% and greater than placebo) are back pain, dizziness, upper respiratory tract infection, pharyngitis and rhinitis. [1]

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to Atacand®:

Fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with Atacand® are listed below. It cannot be determined whether these events were causally related to Atacand®.

Body as a Whole: asthenia, fever;

Central and Peripheral Nervous System: paresthesia, vertigo;

Gastrointestinal System Disorder: dyspepsia, gastroenteritis;

Heart Rate and Rhythm Disorders: tachycardia, palpitation;

Metabolic and Nutritional Disorders: creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia;

Musculoskeletal System Disorders: myalgia;

Platelet/Bleeding-Clotting Disorders: epistaxis;

Psychiatric Disorders: anxiety, depression, somnolence;

Respiratory System Disorders: dyspnea;

Skin and Appendages Disorders: rash, sweating increased;

Urinary System Disorders: hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Laboratory Test Findings

Hypertension

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia

Hyperuricemia was rarely found

Hemoglobin and Hematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with Atacand® alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium

A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with Atacand® alone but was rarely of clinical importance.

Liver Function Tests

Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to Atacand® in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

Heart Failure

Small increases in serum creatinine (mean increase 0.2 mg/dL in Candesartan treated patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in Atacand® treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in Atacand®-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in Atacand®-treated patients and 0.9% in placebo-treated patients) were observed. [1]

Precautions and Contraindications

Hypotension

In adult or children patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients, symptomatic hypotension may occur. These conditions should be corrected prior to administration of Atacand®, or the treatment should start under close medical supervision.

Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin II receptor antagonists, including Atacand®, due to blockade of the renin-angiotensin system.

Impaired Hepatic Function

Based on pharmacokinetic data which demonstrate significant increases in Candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment.

Hyperkalemia

In heart failure patients treated with Atacand®, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

Contraindications

Atacand® is contraindicated in patients who are hypersensitive to any component of this product.[1]

Study Rationale

The Macleods Pharmaceuticals Ltd. has developed generic alternative to the reference-listed brand of Candesartan cilexetil. Therefore, its bioequivalence with the reference brand must be evaluated in both fasting and fed conditions. In the present study, the single dose of test product Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India was compared with Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

Justification of Choice of Reference Product

Atacand® (candesartan cilexetil) tablets 32 mg is qualified as acceptable reference listed drug by USFDA.

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 single dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India with Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

8.2 Safety

To monitor the safety and tolerability of single oral dose Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) 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, randomized, two-treatment, two-period, two sequence, single dose, crossover bioequivalence study on 36 healthy, adult, human subjects under fasting condition

ADMISSION AND STAY

Period 1:

On 18th May 2011, informed consent was presented to all the volunteers. At the time of check-in, eligibility was assessed by carrying out test for drugs of abuse, medical examination, confirming compliance to protocol based upon inclusion and exclusion criteria and recording vitals. Breath of the volunteer was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty-six subjects who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 16:55 hours to 19:38 hours.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00 and 24.00 hours post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and checkout.

All the subjects enrolled into the study were housed in the Clinical Pharmacology Unit (CPU) until checkout on 20th May 2011.

The subjects visited to the clinical facility for ambulatory blood sample collection at 36.00 hours post-dose.

Period 2:

On 25th May 2011, thirty-five subjects reported to the clinical facility. At the time of check-in, eligibility was assessed by carrying out test for drugs of abuse, medical examination, confirming compliance to protocol based upon exclusion criteria and recording vitals. Breath of the volunteer was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty-five subjects who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 17:02 hours to 20:41 hours.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00 and 24.00 hours post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and checkout.

All the subjects enrolled into the study were housed in the Clinical Pharmacology Unit (CPU) until checkout on 27th May 2011.

The subjects visited to the clinical facility for ambulatory blood sample collection at 36.00 hours post-dose.

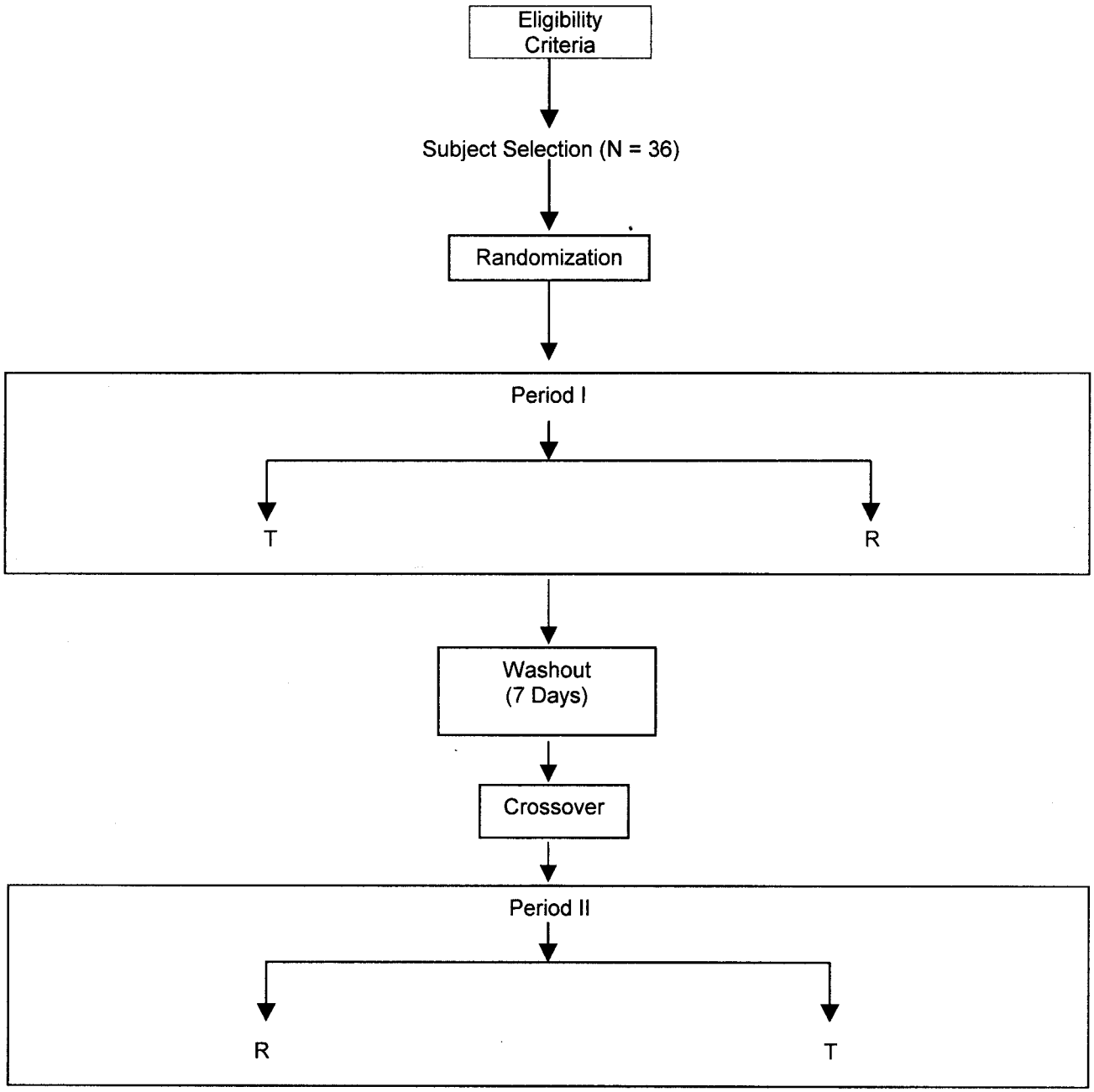
Washout Period:

There was washout period of 7 days from the completion of dosing between two consecutive periods.

The study schematic is given in figure-1.

FIGURE – 1 STUDY PLAN

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 period, two sequence. 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 derived based on variability of the pharmacokinetic data available from "Published literature [2].

With the elimination half-life of candesartan averages 9 hours, the two dosing days i.e. for period 1 and period 2, were separated by a washout period of 7 days.

9.3 Selection of Study Population

The general screening was carried out after obtaining the written consent on IEC approved 'Informed Consent for Screening' from the volunteers. The screening procedure included Demographic data including sex, completed age, height and weight, Body Mass Index (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. Medical examination including recording of vital signs (Blood Pressure (BP), Pulse, Respiration and Temperature), general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Chest X-ray (PA view); Laboratory parameter investigation including Complete complete blood count – Leucocyte count, Erythrocyte count, Haemoglobin, Hematocrit, Platelet count, differential leucocyte count (DLC); and ESR, Blood grouping (if previously not performed by Bioequivalence department of Macleods Pharmaceuticals Ltd.), Biochemistry – blood sugar (fasting), cholesterol and triglycerides, Alkaline Phosphatase, Hepatic Profile – SGPT, SGOT, GGT, and Serum Bilirubin (Total, Direct, Indirect), Renal profile – serum creatinine, BUN, Serum Calcium, Serum Electrolytes (sodium, potassium. chlorides) and Infectious Diseases – HbsAg, HIV, and HCV and routine urine examination.

No clinically significant abnormalities in ECGs, Chest X-ray, (PA view) were reported in subjects who were included in the study. Additionally, serological tests (HIV, Hepatitis B and C, HCV) were negative. 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.

All the baseline clinical and laboratory results are given in appendix 16.2.8. 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. There were few values as given below, which were outside the acceptable limits, however since the results were considered clinically non-significant based on clinical correlation, these subjects were included in the study.

Subject No.	Laboratory Parameter	Results	Reference Range
08	Lymphocytes	45%	20 - 40%
14	Triglycerides	166.2 mg/dL	< 150.0 mg/dL
15	Hematocrit	35.6%	40.0 – 50.0%
27	Triglycerides	175.5 mg/dL	< 150.0 mg/dL
31	Lymphocytes	45%	20 - 40%

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 were found negative for breath alcohol test and urine test for drugs of abuse test [Cocaine (COC), Amphetamines (AMP), Marijuana (THC), Morphine (MOP), Barbiturates (BAR) and Benzodiazepine (BZO)].

Volunteers were given the rank orders based on their reporting time to the facility on pre-study day. Based on their rank orders and depending on the compliance to the requirements of the protocol, subject numbers were allotted serially. Thirty-six 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/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).

9.3.2 Exclusion Criteria

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

1. Personal history of allergy or hypersensitivity to candesartan 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 (Heart failure), Hepatitis, Hypotensive episodes, Hyperglycemia etc.
3. Presence of any clinically significant abnormal values during screening e.g. significant abnormality of liver function test, renal (kidney) function test etc.
4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other condition, 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, any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meats within 7 days of drug 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.
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. Known hypersensitivity to heparin.

19. Use of oral contraceptive in last 90 days (for females).
20. Pregnant / lactating volunteers (for females).

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 reason if a subject would not satisfactorily completed the study 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 (R) or test product (T) was administered at 0.00 hour during each period with the 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 has received both the treatments test and reference each at the end of the study.

Subjects were dosed while in sitting posture and were instructed to avoid any strenuous activity following the investigational product administration. Subjects were in supine position up to 6.00 hours post-dose. 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 if any adverse event occurs 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) : Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg)
Batch No.: ECD8101A
Manufacturing Date: 04/2011
Expiry Date: 03/2013
Manufactured by: Macleods Pharmaceuticals Ltd. India
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

ii) Reference Formulation (R) : Atacand® (candesartan cilexetil) tablets 32 mg (each tablet contains candesartan cilexetil 32 mg)
Lot No.: E008171
Manufacturing Date: N/AV
Expiry Date: 04-2013
Manufactured by: AstraZeneca AB, S-15185, Sweden
Manufactured for: AstraZeneca LP, Wilmington, DE 19850
NDC-0186-0032-31
Dose: 1 tablet
Mode of administration: Administered orally with 240 mL of drinking water.

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 or reference product for each subject during the study was determined according to randomization schedule (generated using SAS® version 9.1.3).

Subject number was allocated as per the rank order of the reporting time of the subject to the clinical facility.

9.4.4 Selection of Doses in the Study

The available strength of Atacand® (candesartan cilexetil) tablets is 4 mg, 8 mg, 16 mg and 32 mg. The recommended adult oral single dose of Atacand® (candesartan cilexetil) tablets is 32 mg. Therefore Single, oral dose of 1 tablet (contains 32 mg of candesartan cilexetil) should be reasonably well tolerated. It was expected to provide adequate plasma concentrations for assay.

9.4.5 Selection and Timing of Dose for Each Subject

The dosing was done at 08:00 hrs to 08:34 hrs (0.00 hours) in the batch of two subjects. The dosing interval between successive subjects was 2 minutes.

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

Fasting was continued for 4 hours post-dose, and then meals were provided at specified intervals. Drinking water was disallowed for 1 hour pre-dose and post-dose administration. 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 plasma 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 the custody of principal investigator and 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 ± 2°C and 60 ± 5% RH.

The dispensed investigational products were transferred to the drug-dispensing containers as unit doses. The IP dispensing containers used for dispensing were properly labelled for the study number, period number, subject number, treatment code, initial and date of the person dispensing the product. The IP dispensing containers along with duplicate label (similar to that 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 are stored in stability chamber at 22 ± 2°C and 60 ± 5% RH and inventory are 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 – 16.1.14.

9.4.7 Prior and Concomitant Therapy

Receipt of any other prescription drug or over-the-counter products (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 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). While dosing, the staff on duty confirmed 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 was performed under supervision of medical officer to assess the compliance to this procedure and the same was noted in the investigational product administration form of each subject. An additional label was affixed to the investigational product administration form in the appropriate place to confirm correct administration of Investigational Product. The time of actual dose administration was recorded in the investigational product administration form.

Investigational product accountability record and evaluation of the plasma 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 Candesartan were estimated after drug administration under fasting conditions:

Primary Efficacy Variables

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary Efficacy Variables

$T_{1/2}$, K_{el} and T_{max}

These parameters were derived individually for each subject from their Candesartan concentration in plasma. 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 if they preceded quantifiable samples in the initial portion of the profile. A BLQ that occurred at the end of the profile was set to zero. A BLQ or zero concentration

that was embedded between two quantifiable points was assigned a value of missing. If consecutive BLQs in the terminal portion of the profile were followed by quantifiable determinations, these quantified values were excluded from PK analysis by assigning them a value of missing. In the calculations of PK parameters, missing values was ignored. Plasma concentrations used to determine PK parameters would be listed.

The pharmacokinetic parameters were calculated by non-compartmental methods using SAS® version 9.2

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

C_{max} : Maximum measured plasma concentration following each treatment.

AUC_{0-t} : The area under the plasma concentration versus time curve from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.

$AUC_{0-\infty}$: The area under the plasma concentration versus time curve, from zero to 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.

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

K_{el} : Apparent first order elimination or terminal rate constant calculated from semi log plot of the plasma concentration versus time curve. The parameters were calculated by linear least square regression analysis using at least the last three non-zero plasma concentration.

$T_{1/2}$: Time required for the plasma drug concentration to decrease to one half.

Safety Measurements Assessed

Safety was evaluated by monitoring clinical adverse events during study periods. Vital signs and subject questionnaire was done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 24.00 and 36.00 hours post-dose. Medical examinations were carried out at the time of check-in, checkout and at 36.00 hours post-dose (Time points being relative to the investigational product dosing).

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

- Medical examination (vital signs, 12 lead ECG, general and systemic examination).
- Clinical laboratory tests (haematology, clinical biochemistry) and urine analysis (only during pre-study screening).

9.5.2 Appropriateness of Measurements

The plasma samples of subjects were analyzed by a validated LC-MS/MS method. The limit of quantification of 5.00 ng/mL for candesartan was enough to quantify the analyte from the plasma samples collected up to 36.00 hours after drug administration. The linearity range of 5.00 ng/mL

to 601.35 ng/mL for candesartan was enough to quantify the expected concentration range of candesartan from subject plasma with the proposed dose of 32 mg of Candesartan cilexetil.

9.5.3 Primary Efficacy Variable(s)

The following pharmacokinetic parameters were assessed as primary efficacy variables, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

1.	Peak plasma concentrations	C_{max}
2.	Area under plasma concentration-Time curve from time of administration until the time of last quantifiable concentration	AUC_{0-t}
3.	Area under plasma concentration-Time curve up to infinity	$AUC_{0-\infty}$

9.5.4 Drug Concentration Measurements

Concentration of candesartan was measured in plasma samples of the subjects. Blood samples (1 × 5 mL) were collected in 5 mL blood collection tube containing K_2EDTA as anticoagulant. The venous blood samples were withdrawn pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours post dose (time points being relative to the investigational product dosing). Blood collection was done at bedside till 6.00 hours post-dose.

Post-dose samples up-to 24.00 hrs collected through an indwelling cannula placed in a forearm vein. The pre-dose samples were collected within one hour prior to investigational product dosing. The post-dose samples up to 24.00 hours in house stay were collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute was recorded. Similarly the post-dose samples during ambulatory visit were collected by direct prick using disposable syringe and needle within one hour of the scheduled time where the end time of collection to the nearest minute was recorded. However there were few deviations in this regard. Refer section 10.2 'Protocol Deviation'. During each ambulatory visit, the blood sample was collected up to two hours of specified schedule time of blood collection. No ambulatory blood sample collection was made after 2 hours of specified schedule time of blood collection for any subject.

Intravenous indwelling cannula was kept in place as long as required by injecting not more than 0.5 mL of 5 IU/mL of heparin in normal saline solution during the collection of multiple samples. The blood sample was collected after discarding the first 0.5 mL of heparinised blood from the tubing. Blood was also withdrawn from vein by using disposable syringe and needle if the cannula was blocked or the cannula is removed for other reasons.

Each blood sample (1 x 5 mL) was collected into 5 mL blood collection tube containing K_2EDTA solution as anticoagulant. The blood samples collected at each time point were centrifuged between 4 to 8°C at 4000 rpm for 10 minutes to separate plasma, after receiving the blood samples from all the subjects (For ambulatory samples, the samples collected till the scheduled time of last subject were centrifuged together and the samples collected later were centrifuged separately according to their collection time). Blood samples were centrifuged within 30 minutes after collection of last blood sample; if there was any delay in centrifugation then samples were

kept in cold condition. The separated plasma was aliquoted in duplicate in prelabelled polypropylene tubes during each period. These tubes were labeled with study number, period number, subject number, sample number, time point (hrs), and aliquot number. These tubes were then transferred to a deep freezer maintained below –50°C or colder for storage.

Plasma samples were withdrawn and replaced by Bio analytical section as and when required.

The investigational products were administered in fasting conditions and no food was served till four hours post-dose. No fluid, except 240 mL drinking water administered with the investigational products was allowed from 1 hour pre-dose and 1 hours post-dose. The investigational products were administered to the subjects while in sitting posture. Subjects were in supine position up to 6.00 hours post dose. 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 if any adverse event occurs at any time during housing the subjects would be placed in an appropriate posture.

Subjects were 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 were instructed to abstain from grapefruit or grapefruit containing products, any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meats within 7 days of drug administration. Subjects were also 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.

Validated LC-MS/MS method was employed for the estimation of candesartan in plasma. During estimation of candesartan in plasma 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 would be reanalyzed as per the standard test procedure based on method validation report.

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 both Clinical, Bioanalytical and, Pharmacokinetic and Statistical phase of the study. The audits were conducted as per in-house standard operating procedure. 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, mean, SD, CV, minimum, and maximum) to summarize the plasma concentrations at each time of measurement.
- For purpose of descriptive Linear and semi-logarithmic plots of the mean and individual plasma 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 9.2 for estimation of pharmacokinetic parameters and its statistical analysis for Candesartan from their plasma 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, standard deviation and the coefficient of variation for untransformed data and relevant pharmacokinetic parameters are the arithmetic means and the standard deviation for the log-transformed (natural) data.
- Analyze the log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) using an ANOVA model with main effects of sequence, subject nested within sequence, period, and formulation.
- Use a separate ANOVA model to analyze each of the parameters. Use a 5% level of significance to test significance of all effects.
- Include calculation of mean square error, coefficient of variance and the associated degree of freedom for each analysis of variance.
- 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}, AUC_{0-t} and $AUC_{0-\infty}$.
- Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).
- Report the geometric means of the test and reference product. And express ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference in percentage.
- 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 coefficient of variation using $\sqrt{e^{MSE}-1}$ with help of SAS® version 9.2. Where MSE is mean squared error obtained from Analysis of Variance model.

- Calculate a 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 confidence intervals are entirely included in the range of 80% – 125 % for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

9.7.2 Determination of Sample Size

Number of Subjects

Sample size was calculated using SAS® 9.1.3. As estimated from data obtained from "Published literature [2]. Based on 2 x 2 crossover design performed on 50 subjects completed the study. Since, Intra-subject C.V. was not available; it was calculated using the available data as shown below:

The pharmacokinetic parameters and statistical results for Candesartan Cilexetil under fasting condition are as follows:

Pharmacokinetic Parameters	Ratio (T/R) (%)	90 % C.I. (%)	
		Lower	Upper
C_{max} (ng/mL)	102.1	95.5	109.1
AUC_{0-24} (ng*hrs/mL)	99.7	95.9	103.7
$AUC_{0-\infty}$ (ng*hrs/mL)	99.3	95.6	103.0

Calculation:

n1 (Number of TR sequence) =25 and n2 (Number of RT sequence) =25

MSE for Cmax = 0.039383

MSE for AUC0-t = 0.013585

MSE for AUC0-∞ = 0.012350

Intra-subject C.V. for Cmax = $100^* \sqrt{e^{MSE} - 1}$ = 20.04%

Intra-subject C.V. for AUC0-24= $100^* \sqrt{e^{MSE} - 1}$ = 11.70%

Intra-subject C.V. for AUC0-∞ = $100^* \sqrt{e^{MSE} - 1}$ = 11.15%

The highest Intra-subject C.V. was observed to be 20.04%. 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

Coefficient of Variation = 0.2004 Alpha = 0.05

Null Ratio	Power	N per Group
0.95	0.800	18
	0.850	21
	0.900	24
	0.950	30
1.00	0.800	15
	0.850	16
	0.900	18
	0.950	22
1.05	0.800	18
	0.850	20
	0.900	24
	0.950	29

The highest intra subject C.V. for candesartan was observed to be 20.04% for C_{max} (ng/mL) in the published literature. So to achieve 80% power a sample size of 18 per group was concluded sufficient to conclude bioequivalence. Thus accounting for dropout or withdrawal of subjects during conduct of the study, 36 healthy subjects were decided to be recruited in a crossover study design to achieve the desired sample size to conclude bioequivalence.

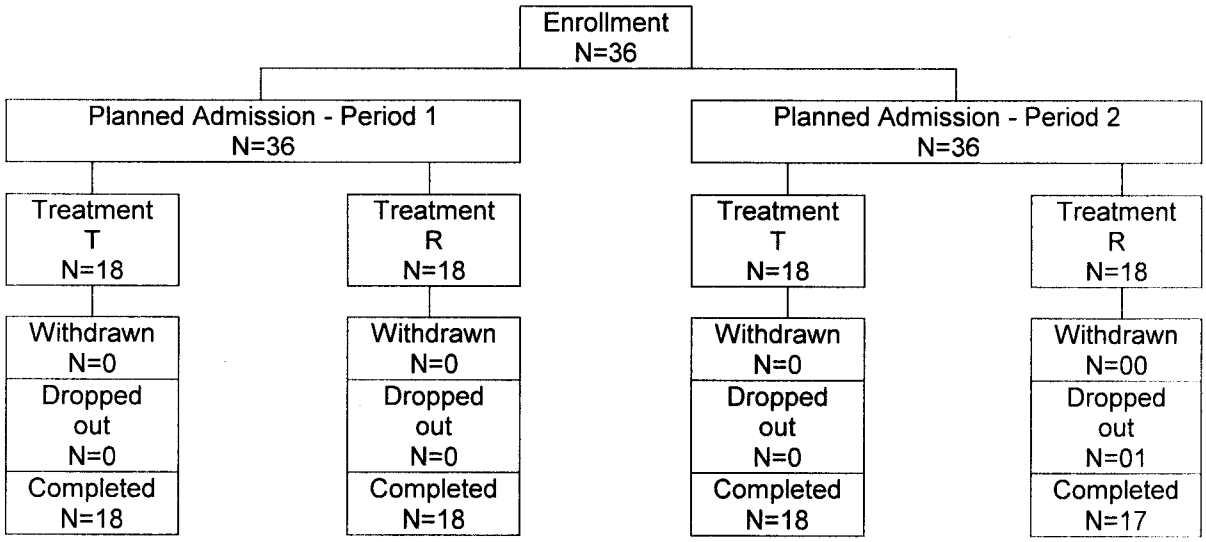
9.8 Changes in the Conduct of the Study or Planned Analyses

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 36 subjects were planned and enrolled. Of these 36 subjects, subject number 23 did not report to the facility for period 2, thus considered dropped-out from the study. Thus thirty-five subjects completed both the periods.



10.2 Protocol Deviations

- As per protocol blood samples should be collected within two minutes of scheduled time for blood collection for in-house samples and within one hour for all ambulatory visit samples. All actual times of the sample withdrawal were recorded in the bleed sheet. However, there were total 3 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 2:						
1	06	3.75	11:55 hrs	11:58 hrs	0.05	Poor blood flow
2	21	2.25	10:19 hrs	10:23 hrs	0.07	Cannula block
3	29	24.00	08:20 hrs	08:23 hrs	0.05	Poor blood flow

- As per protocol total 24 samples should be collected per subject in each period. However there were six deviations reported in period 1. Samples were not collected since the subjects didn't report to the clinical facility.

Sr. No.	Time Point (Hrs)	Subject Number
		Period 1
1	36.00	06, 07, 14, 16, 32 and 33

The above deviations were duly incorporated during pharmacokinetic analysis.

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

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The data of 35 completing subjects (01 to 22 and 24 to 36) receiving reference and test product were utilized for pharmacokinetic and statistical evaluations.

Subject's 23 plasma samples were excluded from the efficacy evaluation.

Plasma samples of subject number 23 were not analyzed, since the subject was dropped-out from the study.

11.2 Demographic and Other Baseline Characteristics

The demographic characteristics of the 35 subjects completed the study were as follows:

- Age between 18 and 42 years [27.9 mean) ± 6.74 (SD) years].
- Weight between 50.8 and 79.8 kg [61.35 (mean) ± 7.700 (SD) kg].
- Height between 1.57 and 1.81 meters [1.663 (mean) ± 0.0565 (SD) meters].
- BMI between 18.54 and 26.73 kg/m^2 [22.183 (mean) ± 2.5771 (SD) kg/m^2].

The demographic characteristics of the 36 subjects recruited in the study were as follows:

- Age between 18 and 42 years [27.9 mean) ± 6.65 (SD) years].
- Weight between 50.8 and 79.8 kg [61.43 (mean) ± 7.603 (SD) kg].
- Height between 1.57 and 1.81 meters [1.666 (mean) ± 0.0579 (SD) meters].
- BMI between 18.54 and 26.73 kg/m^2 [22.142 (mean) ± 2.5522 (SD) kg/m^2].

The 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 plasma drug concentration of the samples confirmed 100% compliance of the all the subjects from whom the data were analyzed. Plasma levels of candesartan in individual subjects at different time points following reference and 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 Candesartan under fasting conditions are as follows:

Pharmacokinetic Parameters	Test product (N=35)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	280.792	108.7822	38.74	255.70	136.07 - 701.99
AUC_{0-t} (ng*hrs/mL)	2811.39434	770.536021	27.41	2751.8849	1460.5878 - 4526.7575
$AUC_{0-\infty}$ (ng*hrs/mL)	3030.59257	800.584248	26.42	2934.8822	1533.7371 - 4602.9684
T_{max} (hrs)	3.993	1.2240	30.65	4.00	2.00 - 7.00
$T_{1/2}$ (hrs)	8.31580	2.649211	31.86	7.5196	4.7769 - 20.7928
K_{el} (hr^{-1})	0.08890	0.020465	23.02	0.0922	0.0333 - 0.1451

Pharmacokinetic Parameters	Reference product (N=35)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	294.201	85.6630	29.12	286.11	133.33 - 486.75
AUC_{0-t} (ng*hrs/mL)	3005.50555	872.147605	29.02	2910.9808	1560.3488 - 4644.2025
$AUC_{0-\infty}$ (ng*hrs/mL)	3184.53310	939.115483	29.49	3015.7719	1641.5088 - 5008.0144
T_{max} (hrs)	4.322	1.0108	23.39	4.50	2.25 - 6.00
$T_{1/2}$ (hrs)	8.02945	1.923178	23.95	7.7272	4.6343 - 13.3506
K_{el} (hr^{-1})	0.09106	0.021408	23.51	0.0897	0.0519 - 0.1496

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 9.2 is appended in appendix 16.4.1.

The ln-transformed least square mean and 90% confidence interval based on least square mean obtained from ANOVA and ratio of geometric means for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Candesartan under fasting conditions are summarized in the following table:

Geometric mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Candesartan						
Pharmacokinetic Parameters	Geometric mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90 % Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	263.242	281.408	93.54	24.00	96.74	85.00 - 102.95
AUC_{0-t} (ng*hrs/mL)	2714.936	2876.430	94.39	13.45	100.00	89.41 - 99.64
$AUC_{0-\infty}$ (ng*hrs/mL)	2932.065	3045.322	96.28	13.09	100.00	91.33 - 101.50

ANOVA RESULTS:

Formulation Effect

Formulation effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$

Sequence Effect

Sequence effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$

Period Effect

Period effect found to be statistical insignificant for C_{max}, AUC_{0-t} and significant for $AUC_{0-\infty}$.

A significant period effect is caused by the fact that in one of the two periods, the plasma levels $AUC_{0-\infty}$. is higher / lower than in other. This may be due to different conditions in Period 1 and Period 2. Some of the causes for significant period effects are volunteers, meal plan, dosing procedure and environmental conditions. However in this study all the conditions in Period 1 and Period 2 were identical. These are:

- Same volunteers were enrolled in both periods. Moreover, none of the volunteers had taken any medicine between Period 1 and Period 2.
- Same meal plan was given to volunteers in both periods.
- Dosing procedure was same in both periods.
- Environmental condition during dispensing and sample separation were similar in both Periods.

Thus based on the above observations, since the conditions in Period 1 and Period 2 were identical, the period effect appears to be insignificant in nature and may not have any clinical consequences.

RATIO AND 90% CONFIDENCE INTERVAL:

The ratio of geometric mean and 90% confidence interval for the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 93.54% & 85.00% – 102.95%; 94.39% & 89.41% – 99.64% and 96.28% & 91.33% – 101.50%.

POWER AND INTRA SUBJECT VARIABILITY:

The power and intra subject variability for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 96.74% & 24.00%; 100.00% & 13.45% and 100.00% & 13.09%.

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 plasma concentration time curves are presented in linear and log-linear scale in appendix 16.2.5.

11.4.4 Drug Dose, Dose Concentration, and Relationships to Response

In the present bioequivalence study the pharmacokinetic end points were considered for the bioequivalence conclusion and hence the pharmacodynamic was not measured. Thus the drug dose, dose concentration and relationship to response were not evaluated.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.4.6 By-Subject Displays

Not applicable

11.4.7 Efficacy Conclusions

The 90% confidence interval for the ratio (Test/Reference) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of candesartan were within the acceptable limits of bioequivalence 80% - 125%.

Thus it is concluded that the test product, Candesartan cilexetil tablets 32 mg (each tablet contains candesartan cilexetil 32 mg) manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent with the reference product, Atacand® (candesartan cilexetil) tablets 32 mg (each

tablet contains candesartan cilexetil 32 mg) manufactured for AstraZeneca, LP, USA in healthy, adult, human subjects under fasting condition.

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

Thirty-five subjects who completed the study were exposed to Candesartan cilexetil 32 mg, twice as per randomization schedule. Subject number 23 (who did not report to the facility for period 2, thus considered dropped-out from the study) was exposed to Candesartan cilexetil 32 mg, once as per randomization schedule.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

No adverse event occurred during entire course 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 09, 24 and 29. 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

No adverse event occurred during both periods. The clinically significant post-study out of reference range laboratory results are 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

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 Number	Laboratory Parameter	Safety Assessment Results	Reference Range	Remark	Relationship with the Study Drug
09	SGPT	43.1 U/L	4.0 - 36.0 U/L	**Increased**	Possible
24	Haemoglobin	10.9 g/dL	13.0 - 17.0 g/dL	**Decreased**	Possible
	Hematocrit	31.9%	40.0 - 50.0%		
29	Eosinophils	10%	1 - 6%	**Increased**	Unlikely

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

There were no serious adverse events 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 biochemical, hematological 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 09, 24 and 29 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 were few values as given below, which were outside the acceptable limits, however not considered clinically significant based on the clinical co-relation and have not been included as adverse events. For subject number 09, 24 and 29 the laboratory result outside acceptable range are considered as clinically significant based on the clinical co-relation and are reported as adverse events.

Subject Number	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
01	**Triglycerides**	188.3 mg/dL	97.2 mg/dL	<150.0 mg/dL	Clinically not significant
02	**SGPT**	41.9 U/L	38.4 U/L	4.0 - 36.0 U/L	Clinically not significant
05	**Lymphocytes**	13%	20%	20 - 40%	Clinically not significant
	ESR	19 mm/hr	4 mm/hr	<15 mm/hr	
07	**Triglycerides**	201.4 mg/dL	119.9 mg/dL	<150.0 mg/dL	Clinically not significant
09	**Triglycerides**	170.9 mg/dL	65.4 mg/dL	<150.0 mg/dL	Clinically not significant
	SGPT	43.1 U/L	25.1 U/L	4.0 - 36.0 U/L	Clinically significant
10	**Triglycerides**	245.8 mg/dL	76.1 mg/dL	<150.0 mg/dL	Clinically not significant

Subject Number	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
12	**Triglycerides**	205.5 mg/dL	101.7 mg/dL	<150.0 mg/dL	Clinically not significant
14	**Triglycerides**	538.5 mg/dL	166.2 mg/dL	<150.0 mg/dL	Clinically not significant
18	**Triglycerides**	287.9 mg/dL	107.4 mg/dL	<150.0 mg/dL	Clinically not significant
19	**Hematocrit**	34.8%	42.0%	40.0 - 50.0%	Clinically not significant
24	**Haemoglobin**	10.9 g/dL	12.5 g/dL	13.0 - 17.0 g/dL	Clinically significant
	Hematocrit	31.9%	37.7%	40.0 - 50.0%	
25	**Triglycerides**	204.1 mg/dL	100.4 mg/dL	<150.0 mg/dL	Clinically not significant
27	**Triglycerides**	720.1 mg/dL	175.5 mg/dL	<150.0 mg/dL	Clinically not significant
29	**Eosinophils**	10%	8%	1 - 6%	Clinically significant
	Triglycerides	190.3 mg/dL	111.1 mg/dL	<150.0 mg/dL	Clinically not significant
35	**Triglycerides**	240.8 mg/dL	77.5 mg/dL	<150.0 mg/dL	Clinically not significant
36	**Triglycerides**	199.1 mg/dL	84.0 mg/dL	<150.0 mg/dL	Clinically not significant

Note: The triglyceride levels of subject number 01, 07, 09, 10, 12, 14, 18, 25, 27, 29, 35 and 36 are out side acceptable limit. Since the post-study safety assessment samples were collected post-prandially, the triglyceride levels are bound to be high and therefore raised triglyceride levels are clinically acceptable. On Medical Officer's advice, subject number 14 and 27 were contacted over telephone and requested to visit the clinical facility under fasting condition to repeat the test for triglycerides. However subjects did not report to the clinical facility.

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.

12.5 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.

The post-study clinically significant out of reference range laboratory parameters are summarized in the 14.3.4 and the individual recording of laboratory parameters are appended in appendix 16.2.8.

Vital signs and subject questionnaire was done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 24.00 and 36.00 hours post-dose (Time points being relative to the investigational product dosing).

Medical examinations were carried out at the time of check-in and check out and at 36.00 hours post-dose. The individual recording of vital signs for both the periods has been appended as appendix 16.4.2.

All the subjects enrolled and dosed had clinically acceptable vital signs values.

A medical officer was available within the clinical facility whenever the subjects were housed (from check-in to checkout).

At the end of the study period, post-study safety assessments of the subjects completing the study were carried out which included: Medical examination including recording of vital signs [Blood Pressure (BP), Pulse, Temperature and Respiration], general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Laboratory parameter investigation including complete blood count – erythrocyte count, platelet count, haemoglobin, hematocrit, leucocyte count, ESR and differential leucocyte count (DLC); Biochemistry –blood sugar (random), total cholesterol and triglycerides; Hepatic profile – SGOT, SGPT, GGT, alkaline phosphatase and serum bilirubin (total, direct, indirect), Renal profile – serum creatinine, BUN, calcium, electrolytes (sodium, potassium, chlorides).

No clinically significant abnormalities in ECGs were reported in subjects during post-study safety assessments.

Laboratory values outside the reference range were considered clinically not significant based on clinical co-relation and have not been included as adverse events except for few subjects as 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 and the individual recordings of laboratory parameters are appended in appendix 16.2.8.

12.6 Safety Conclusions

No serious adverse event occurred during the conduct of the study.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

A total of 36 subjects were planned and enrolled. Of these 36 subjects 35 subjects completed the study. Single dose administration of Candesartan cilexetil tablets 32 mg was well tolerated and no new safety issues were identified during the study. There were few clinically relevant changes in laboratory safety variables for three subjects, of which two were possibly related to the study drug and other one was unlikely related to the study drug. 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 plasma samples of all the subjects who completed the study were analyzed for candesartan concentration level. Plasma concentration of thirty-five subjects who completed the study was utilised for pharmacokinetic and statistical evaluations.

The mean plasma concentration time profiles of Candesartan for the two treatments are shown in Figure 1 and 2 (Refer section 14.2 'Efficacy Data').

After oral administration of the reference product under fasting condition the drug was rapidly absorbed and median t_{max} was 4.50 hrs where for other PK parameters mean C_{max} 294.201 ng/mL (range 133.33 - 486.75 ng/mL), AUC_{0-t} 3005.50555 ng*hrs/mL (range 1560.3488 - 4644.2025 ng*hrs/mL) and $AUC_{0-\infty}$ 3184.53310 ng*hrs/mL (range 1641.5088 - 5008.0144 ng*hrs/mL).

After oral administration of the test product under fasting condition the drug was rapidly absorbed and median t_{max} was 4.00 hrs where for other PK parameters mean C_{max} 280.792 ng/mL (range 136.07 - 701.99 ng/mL), AUC_{0-t} 2811.39434 ng*hrs/mL (range 1460.5878 - 4526.7575 ng*hrs/mL) and $AUC_{0-\infty}$ 3030.59257 ng*hrs/mL (range 1533.7371 - 4602.9684 ng*hrs/mL).

Bioequivalence was assessed using standard equations. The 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for candesartan were within the usual acceptable limit for 80-125 %.

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

Both the formulations are well tolerated following a single dose administration of the investigational product.

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

14.1 Demographic Data

Demographic Data of Subjects Recruited in the Study:

	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m^2)
Number	36	36	36	36
Median	26.00	1.66	60.50	21.45
Mean	27.9	1.666	61.43	22.142
Standard Deviation	6.65	0.0579	7.603	2.5522
Minimum	18	1.57	50.8	18.54
Maximum	42	1.81	79.8	26.73

Demographic Data of Subjects Completed the Study

	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m^2)
Number	35	35	35	35
Median	26.00	1.66	60.00	21.53
Mean	27.9	1.663	61.35	22.183
Standard Deviation	6.74	0.0565	7.700	2.5771
Minimum	18	1.57	50.8	18.54
Maximum	42	1.81	79.8	26.73

14.2 Efficacy Data

Summary statistics of pharmacokinetic parameters for candesartan after administration of single dose Candesartan Cilexetil tablets 32 mg in 35 healthy, adult human male subjects under fasting conditions.

Product/Statistics	C_{max} (ng/mL)	AUC_{0-t} (ng*hrs/mL)	$AUC_{0-\infty}$ (ng*hrs/mL)
Untransformed Reference Product (R)			
Arithmetic Mean	294.201	3005.50555	3184.53310
S.D.	85.6630	872.147605	939.115483
C.V. %	29.12	29.02	29.49
N	35	35	35
Test Product (T)			
Arithmetic Mean	280.792	2811.39434	3030.59257
S.D.	108.7822	770.536021	800.584248
C.V. %	38.74	27.41	26.42
N	35	35	35
Ratio of Arithmetic Mean (% Bioavailability)			
T/R (%)	95.44	93.54	95.17
Ratio (%) for Mean AUC_{0-t} to Mean $AUC_{0-\infty}$			
Reference		94.38	
Test		92.77	
Log Transformed (Natural Log) Least Square Mean			
Reference	5.640	7.964	8.021
Test	5.573	7.907	7.983
Geometric Mean			
Reference	281.408	2876.430	3045.322
Test	263.242	2714.936	2932.065
Ratio of geometric Mean			
T/R (%)	93.54	94.39	96.28
90 % Confidence Interval (T/R)			
Lower limit (%)	85.00	89.41	91.33
Upper limit (%)	102.95	99.64	101.50
Power (%)	96.74	100.00	100.00
D.F.	33	33	33
Intra Subject C.V. (%)	24.00	13.45	13.09
Mean Square Error (MSE)	0.056024	0.017930	0.016981
P-value (ANOVA) for ln-transformed data			
Formulation	0.2469	0.0803	0.2325
Period	0.8156	0.3381	0.0490
Sequence	0.3211	0.8249	0.5484

Figure 1

Comparative Linear Plot of Candesartan Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=35)

subject=MEAN

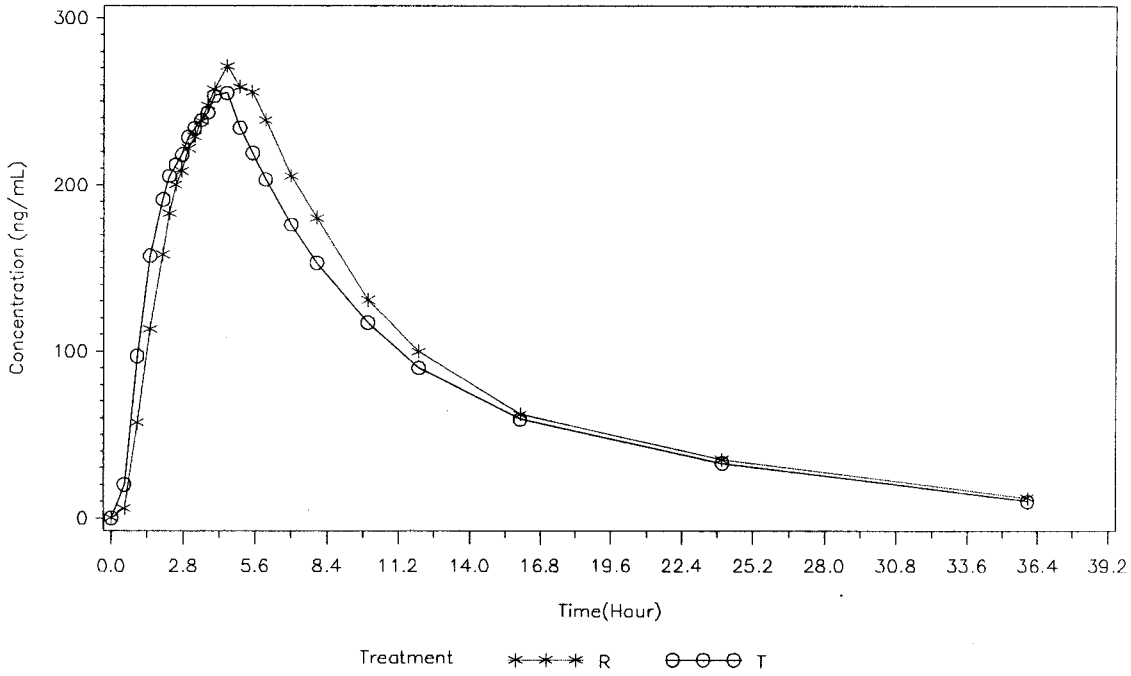
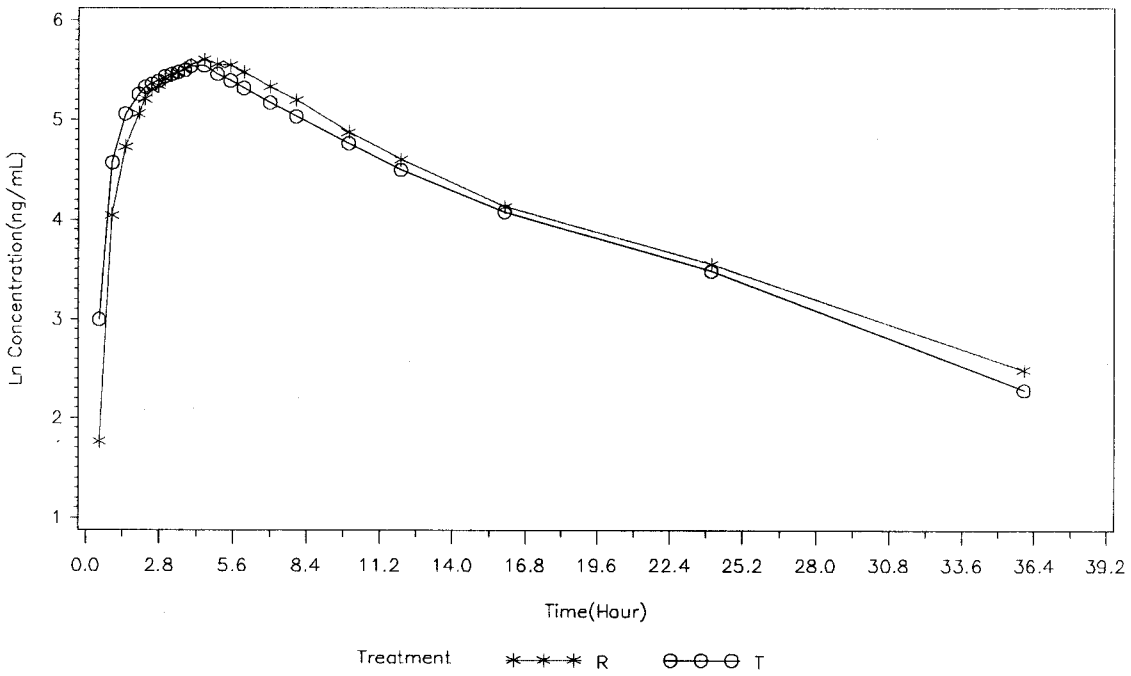


Figure 2

Comparative Semi Log Plot of Candesartan Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=35)

subject=MEAN



14.3 Safety Data

14.3.1 Display of Adverse Events

No adverse event occurred during entire course of the study.

Three subjects (subject number 09, 24 and 29) enrolled in the study were found to have clinically significant post-study laboratory values. The list of clinically significant post-study out of reference range laboratory values 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	Reference Range	Safety Assessment Results	Follow-up Result	Comments
09	SGPT	4.0 - 36.0 U/L	43.1 U/L	Not done	Lost for follow-up
24	Haemoglobin	13.0 - 17.0 g /dL	10.9 g/dL	Not done	Medicated and further lost for follow-up
	Hematocrit	40.0 - 50.0%	31.9%		
29	Eosinophils	1 - 6%	10%	Not done	Lost for follow-up

15.0 REFERENCE LIST

1. U.S. Food and Drug Administration-Drug product label of ATCAND® (NDA) 020838 Approved on 22/10/2009. Cited on 05/08/2010. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020838s031lbl.pdf
2. Product Monograph of ATCAND®. Revised on December 29, 2008. Cited on 10/05/2011. Available from: http://www.astrazeneca.ca/documents/ProductPortfolio/ATACAND_PM_en.pdf