1.0 TITLE PAGE

Clinical Study Report

Project No. 0683-17

Key Pharmaceuticals Ltd., UK.

AN OPEN LABEL, BALANCED, RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, SINGLE ORAL DOSE, CROSSOVER, BIOEQUIVALENCE STUDY OF SPIRONOLACTONE 100 mg TABLETS IN NORMAL, HEALTHY, ADULT, HUMAN SUBJECTS UNDER FED CONDITION

Clinical Study Dates

Study initiation date : 25 September 2018

Study completion date : 08 October 2018

Bio-analytical Study Dates

Experimental start date : 27 October 2018

Experimental completion date : 29 November 2018

Version : 00 **Supersedes Version** : None

Date : 22 January 2019 **Date** : Not Applicable

Development Phase of the Study: Phase-I (Bioequivalence)

The study, including the archiving of essential documents has been conducted as per the IEC approved protocol, GCP and based on the applicable principles of Good Laboratory Practice (GLP) and SOPs of Lambda Therapeutic Research Ltd. We accept the responsibility for the scientific correctness of the project and validity of the data produced in this clinical study report.

[redacted]	[redacted]
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CONFIDENTIAL

The content of this document as well as the objectives and the results of this BA/BE study are confidential and must not be made accessible to third parties.

2.0 SYNOPSIS

Name of Sponsor / Company: Key Pharmaceuticals Ltd., UK.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Spironolactone 100 mg film coated tablets		
Name of Active Ingredient: Spironolactone		

Title of study:

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Spironolactone 100 mg tablets in normal, healthy, adult, human subjects under fed condition.

Principal Investigator:

[redacted]

Co-Investigators:

[redacted]

Study centre(s):

Clinical Facility, Bio-analytical, Pharmacokinetic, Bio-statistics & Programming, Quality Assurance and Clinical Laboratory Services at:

[redacted]

Back-up Contractual Clinical Laboratory Services at:

[redacted]

Publication (reference): None

Study period

Group-I

Period-I : 25 September 2018 to 28 September 2018

Period-II : 02 October 2018 to 05 October 2018

Group-II

Period-I : 26 September 2018 to 29 September 2018

Period-II : 03 October 2018 to 06 October 2018

Group-III

Period-I : 28 September 2018 to 01 October 2018
Period-II : 05 October 2018 to 08 October 2018

Phase of development:

Phase-I Study (Bioequivalence)

Objectives:

Efficacy: To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fed condition and to assess the bioequivalence.

Safety: To monitor the adverse events and to ensure the safety and tolerability of the study subjects.

Methodology:

The study was an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study in normal, healthy, adult, human subjects under fed condition, with a screening period of 28 days prior to IMP administration in Period-I. In each study period, 24 blood samples, including one pre-dose blood sample, were collected from each subject except for the discontinued/ withdrawn subjects to analyze the pharmacokinetic profile of the test as well as the reference product.

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 6.4 (Certara L.P.) for Spironolactone. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

Number of subjects (planned and analysed):

Planned for inclusion			132
Pre-dose discontinued/ withdrawn			04
Dosed	Group-I	Period-I	44
		Period-II	40
	Group-II	Period-I	44
		Period-II	37
	Group-III	Period-I	42*
		Period-II	39
Post-dose withdrawn			14
Analyzed			130 (In which, withdrawn Subject Nos. [redacted] & were also analysed as per protocol requirement)
Considered for statistical analysis			116

*A total of 04 subjects discontinued/ were withdrawn prior to dosing of Period-I. However, out of those 04 subjects, 02 subjects of Group-III were not replaced. Hence, the study was conducted on 130 subjects instead of 132 subjects.

Diagnosis and main criteria of inclusion:

Non-smoking, normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 kg / m^2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (posterior-anterior view) recordings.

Volunteers who complied with all the inclusion criteria were checked in for the study.

Test and Reference product

Test Product-T: Spironolactone 100 mg film coated tablets

Manufactured & Distributed by: [redacted]

Reference Product-R: Aldactone® (Spironolactone tablets 100 mg)

Marketing Authorization Holder: Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.

Dose and mode of administration:

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed within 30 minutes.

A single oral dose (100 mg) of either of the test product or the reference product was administered at 30 minutes after serving of the breakfast to the subjects in sitting posture with 240 ± 02 mL of drinking water at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

The tablet was swallowed whole without chewing or crushing.

Duration of treatment:

Period	Dosing Dates		
	Group-I	Group-II	Group-III
Period-I	27 September 2018	28 September 2018	30 September 2018
Period-II	04 October 2018	05 October 2018	07 October 2018

A washout period 07 days was maintained between the successive dosing days.

Criteria for evaluation:

Pharmacokinetic:

For Pharmacokinetic evaluation, a total of 24 blood samples were collected in each period at the time points specified in the protocol. Standard non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.) was used to derive pharmacokinetic parameters for Spironolactone.

Safety:

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examinations, vital signs assessment, oral body temperature, 12-lead electrocardiogram (ECG), chest X-ray (posterior-anterior view), clinical laboratory parameters (e.g., hematology, biochemistry, urine analysis and immunological tests), subjective symptomatology and monitoring of adverse events.

Statistical methods:

Descriptive statistics are computed and reported for the pharmacokinetic parameters of Spironolactone.

ANOVA, power and ratio analysis are computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Using two-one sided tests for bioequivalence, 90% confidence intervals for the ratio of the geometric least-squares means between drug formulations are calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of Test Product-T vs. Reference Product-R is concluded, if the 90% confidence interval falls within the acceptance range as defined below for ln-transformed pharmacokinetic parameters for Spironolactone.

Parameters	Acceptance Range of 90% CI
C_{max} and AUC_{0-t}	80.00-125.00%

All statistical analyses for Spironolactone are performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA).

Summary:

PHARMACOKINETIC RESULTS

Subject No. [redacted] (Period-I) had all zero concentration in the reference product-R. Hence, period specific data of the same was excluded from the pharmacokinetic and statistical analysis for the assessment of bioequivalence as per the criteria set in the protocol. However, results including the same was provided for supportive information only.

The pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R are summarized in the following table:

Descriptive Statistics of Formulation Means for Spironolactone
[Excluding subject no [redacted] (period-I, R)]

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 116)	Reference Product-R (N = 115)
T_{max} (h)*	2.250 (0.750 - 6.000)	2.000 (0.750 - 6.000)
C_{max} (ng/mL)	148.736 ± 68.0385	149.063 ± 64.2997
AUC_{0-t} (ng.h/mL)	381.047 ± 148.6725	368.610 ± 135.0201
$AUC_{0-\infty}$ (ng.h/mL)	396.496 ± 149.5979^	380.453 ± 139.2814
λ_z (1/h)	0.139 ± 0.0649^	0.143 ± 0.0797
$t_{½}$ (h)	6.115 ± 2.9038^	6.270 ± 3.1643
AUC_%Extrap_obs (%)	3.064 ± 1.6829^	3.097 ±1.5659

*T_{max} is represented as median (min-max) value.

^N = 115; Terminal rate constant (λ_z) cannot be estimated based on obtained concentration data for subject no. [redacted] (Period-II, T). Hence, $AUC_{0-\infty}$ and other elimination phase dependent parameters cannot be calculated.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for Spironolactone are summarized in the following table:

Relative Bioavailability Results for Spironolactone
[Excluding subject no. [redacted] (period-I, R)]

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T (N = 116)	Reference Product-R (N = 115)	Ratio (T/R)%			
$\ln C_{max}$	132.093	130.503	101.2	94.56 - 108.34	31.8	100.0
$\ln AUC_{0-t}$	343.539	330.098	104.1	100.16 - 108.14	17.6	100.0
$\ln AUC_{0-\infty}$	369.987^	355.668	104.0	100.12 - 108.09	17.6	100.0

^N = 115.

Relative Bioavailability Results for Spironolactone (N = 116)
[Including subject no. [redacted] (period-I, R)]

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$\ln C_{max}$	132.093	130.503	101.2	94.56 - 108.34	31.8	100.0
$\ln AUC_{0-t}$	343.539	330.098	104.1	100.16 - 108.14	17.6	100.0
$\ln AUC_{0-\infty}$^	369.987	355.668	104.0	100.12 - 108.09	17.6	100.0

^N = 115.

Safety results:

Adverse events

Seventeen (17) adverse events (AEs) were reported by nine (09) subjects during the conduct of the study. Thirteen (13) AEs were reported in Period-I, one (01) AE was reported in Period-II and three (03) AEs were reported during post-study safety assessment.

Ten (10) AEs were reported in the subjects after administration of Reference Product-R and seven (07) AEs were reported in the subjects after administration of Test Product-T.

All the AEs were mild in nature and the subjects were followed up until resolution of their AEs except for Subject Nos. [redacted] They did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

The causality assessment was judged as possibly related for eleven (11) AEs, as unlikely related for five (05) AEs and as not related for one (01) AE.

There were no deaths or serious AEs reported during the conduct of the study.

However, out of the total reported seventeen (17) AEs, eight (08) AEs were significant. The subjects were withdrawn from the study on medical grounds. The subjects were treated appropriately and followed up until resolution of their AEs. The causality assessment was judged as unlikely related for five (05) AEs, as possibly related for two (02) AEs and as not related for one (01) AE.

Conclusion:

Test Product-T when compared with the Reference Product-R meets the bioequivalence criteria with respect to C_{max} and AUC_{0-t} for Spironolactone under fed condition as per criteria set in the protocol.

Data from this study demonstrated that the test and the reference products were well tolerated. Seventeen (17) adverse events (AEs) were reported by nine (09) subjects during the conduct of the study, out of which, eight (08) AEs were significant. There were no deaths or serious AEs during the conduct of the study.

There were no clinically significant findings in the vital signs assessment, 12-lead ECG recording or in the laboratory tests in any of the subjects in the study except for Subject Nos. [redacted] and [redacted] They had abnormal laboratory values during post-study safety assessment. However, they did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, the abnormal values were considered as clinically significant, adverse events were recorded for the same and the subjects were considered to be lost to follow-up.

Moreover, Subject Nos. [redacted], [redacted] [redacted] and [redacted] did not report for their post-study safety assessment and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

Date of the report: 22 January 2019

3.0 TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_{ez}	:	First order rate constant associated with the terminal (log-linear) portion of the curve
°C	:	Degree Celsius
AE	:	Adverse Event
ANOVA	:	Analysis of variance
AUC_%Extrap_obs	:	Residual area in percentage
$AUC_{0-\infty}$	:	Area under the plasma concentration versus time curve from time zero to infinity
AUC_{0-t}	:	Area under the plasma concentration versus time curve from time zero to the last measurable plasma concentration
BA	:	Bioavailability
BE	:	Bioequivalence
BMI	:	Body Mass Index
CI	:	Confidence interval
C_{max}	:	Maximum measured plasma concentration
CPMA	:	Clinical Pharmacology and Medical Affairs
CRO	:	Contract Research Organization
CV	:	Coefficient of Variation
ECG	:	Electrocardiogram
eCRF	:	Electronic Case Report Form
EMA	:	European Medicines Agency
GCP	:	Good Clinical Practices
GLM	:	General Linear Model
GLP	:	Good Laboratory Practices
h	:	Hour(s)
HIV	:	Human Immunodeficiency Virus
ICF	:	Informed Consent Form

Contd...

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ICH	:	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee
IMP	:	Investigational Medicinal Product
IRB	:	Institutional Review Board
ISCV	:	Intra subject coefficient of variation
K_2EDTA	:	Di Potassium Ethylene Diamine Tetra-Acetic acid
LC-MS/MS	:	Liquid Chromatography/ Tandem Mass Spectrometry
ln	:	Logarithmic value to the base '*e*'
LTR	:	Lambda Therapeutic Research
MedDRA	:	Medical Dictionary for Regulatory Activities
MS	:	Method SOP
MV	:	Method Validation
N	:	Number
ng/mL	:	Nanogram per milliliter
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs
PK	:	Pharmacokinetic(s)
PROC	:	Procedure
QA	:	Quality Assurance
rcf	:	Relative Centrifugal Force
SAE	:	Serious Adverse Event
SAS	:	Statistical Analysis System
SOP	:	Standard Operating Procedure
$t_{½}$	:	Terminal half-life
T_{max}	:	Time of the maximum measured plasma concentration

5.0 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The Anveshhan Independent Ethics Committee reviewed the study Protocol (Version 1.0, dated 05 September 2018), Informed Consent Form (ICF-English) (Version 1.0, dated 06 September 2018), Product Information, Undertaking by the Investigator and gave approval for the study on 17 September 2018.

Informed Consent Form (ICF-Gujarati) (Version 1.0, dated 19 September 2018), List of Changes No. 01 in Protocol (dated 10 September 2018) and List of Changes No. 01 in ICF-English (dated 18 September 2018) were submitted separately to the Anveshhan Independent Ethics Committee for review, which were approved on 20 September 2018.

The Independent Ethics Committee was kept informed about the progress of the study and the adverse events reported during the conduct of the study. The copy of the IEC Approval Letter and the IEC Approved Protocol are appended in Appendix No. 16.1.1 (Protocol and protocol amendments). The composition of IEC and the IEC approved sample copy of ICF are appended in Appendix No. 16.1.3 [List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for subject and sample consent forms].

5.2 ETHICAL CONDUCT OF THE STUDY

This study was carried out in accordance with the IEC approved protocol, all relevant SOPs and was compliant with all the requirements regarding the obligations of investigators and all other pertinent requirements of the Schedule Y (with subsequent amendments) of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India, 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants', ICMR [Indian Council of Medical Research (2017)], ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) 'Guideline for Good Clinical Practice' 2016, Declaration of Helsinki (Brazil, October 2013) and as per the EMA guidelines for bioequivalence studies.

5.3 SUBJECT INFORMATION AND CONSENT

Subjects willing to participate in the study underwent a screening procedure within 28 days prior to IMP administration in Period-I. Written informed consent for the screening procedure was obtained from each subject prior to screening.

Those subjects found eligible for participation in the study underwent a study specific informed consent presentation on the day of check-in for Period-I. The presentation was carried out in a simple language that was understood by the subjects. All the relevant aspects of the study were clearly explained to the subjects with the help of the ICF.

The ICF contained the following points:

- Objectives and conduct of the study.
- Possible risks for health as a result of participation in the clinical study.

- The right of every subject to withdraw his / her consent without having any medical or other disadvantages.
- Possible adverse effects of the planned medication.
- Offer of further information.
- The kind of treatments and the mode of assignment (randomization).
- The information about providing complete medical care along with compensation to the subjects in case of study related injury or death.
- Responsibilities of the subject during study period.
- Details of the investigational medicinal product (IMP).
- Study duration and study details (fasting, postural restrictions, meals etc.).
- Compensation details.

The subjects were encouraged and provided an opportunity to seek clarification to their satisfaction.

Subjects who were willing to participate in the study gave their consent by signing / putting their thumb impression on the ICF. Signature of impartial witness was taken in case of illiterate subjects. One copy of the signed ICF was given to the subjects and the original copy of the ICF was retained in Lambda's study binder.

A copy of the IEC approved ICF is appended in Appendix No. 16.1.3 [List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for subject and sample consent forms].

6.0 INVESTIGATOR AND THE STUDY ADMINISTRATIVE STRUCTURE

The following persons were responsible for the overall conduct of the study.

Principal Investigator	:	[redacted]
Co-Investigators	:	[redacted]
Bioanalytical Responsible Person	:	[redacted]
Clinical Research Physician	:	[redacted]
Quality Assurance	:	[redacted]
Biostatistics and Programming	:	[redacted]
Pharmacokinetic Data Analysis	:	[redacted]
Clinical Laboratory	:	[redacted]
Sponsor's Responsible Person	:	[redacted]

The curriculum vitae of the Investigators and other responsible persons are provided in the Appendix No. 16.1.4 [List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study].

7.0 INTRODUCTION

General pharmacology

Pharmacotherapeutic group: potassium-sparing agents

Mechanism of action

Spironolactone, as a competitive aldosterone antagonist, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

Absorption, Distribution, Metabolism and Excretion

Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulfur containing metabolites (80%) and partly canrenone (20%). Although the plasma half-life of spironolactone itself is short (1.3 hours) the half-lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours). Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}), peak plasma concentration (C_{max}), and elimination half-life ($t_{1/2}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, tmax was 3.2 hr. and 4.3 hr., C_{max} was 391 ng/mL and 181 ng/mL, and $t_{1/2}$ was 13.8 hr. and 16.5 hr., respectively.

The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 hours.

7.1 DOSAGE

Administration of Aldactone once daily with a meal is recommended.

Initial dose usually 100 mg/day to 200 mg/day for treatment of Congestive cardiac failure with oedema, Severe heart failure, Hepatic cirrhosis with ascites and oedema, Malignant ascites, Nephrotic syndrome.

In severe cases the dosage may be gradually increased up to 400 mg/day.

7.2 INDICATION

Therapeutic indications of Spironolactone are as below:

- Congestive cardiac failure
- Hepatic cirrhosis with ascites and oedema
- Malignant ascites
- Nephrotic syndrome
- Diagnosis and treatment of primary aldosteronism.

7.3 CONTRAINDICATION

Spironolactone is contraindicated in adult and paediatric patients with the following:

- Acute renal insufficiency, significant renal compromise, anuria
- Addison's disease
- Hyperkalaemia

- Hypersensitivity to spironolactone or to any of the excipients of Spironolactone tablets
- Concomitant use of eplerenone or other potassium sparing diuretics.

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

Spironolactone should not be administered concurrently with other potassium conserving diuretics and potassium supplements should not be given routinely with spironolactone as hyperkalaemia may be induced.

7.4 RATIONALE AND AIMS

The aim of the study was to compare the bioavailability and assess the pharmacokinetic profile of the sponsor's test formulation in comparison with the reference formulation after single oral dose administration in non-smoking, normal, healthy, adult, human subjects under fed condition and to assess the bioequivalence.

The use of generic preparation of a therapeutically well-established active drug principle has to be justified by the appropriate bioequivalence study, because the proof of bioequivalence of the test and reference products assures the equal therapeutic efficacy.

To establish this, a two-period, single dose fed study in non-smoking, normal, healthy, adult, human subjects was planned based on the EMA requirements.

7.5 TARGET POPULATION AND DURATION OF THE STUDY

As per the protocol, 132 non-smoking, normal, healthy, adult, human, subjects who complied with all the inclusion and none of the exclusion criteria were the target population in the study. However, due to pre-dose discontinuations/ withdrawals, the study was conducted on 130 subjects. The study was conducted in three groups.

The subject population for bioequivalence studies is selected with the aim to minimize variability and permit detection of differences between pharmaceutical products.

The duration of the clinical part of the study was about 14 days (36 hours prior to the IMP administration in Period-I of Group-I until the last pharmacokinetic sample in Period-II of Group-III).

8.0 STUDY OBJECTIVES

Efficacy: To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fed condition and to assess the bioequivalence.

Safety: To monitor the adverse events and to ensure the safety and tolerability of the study subjects.

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

This study was an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study in normal, healthy, adult, human subjects under fed condition.

Based on the in-house study data, statistical analysis and considering the possible dropouts and/or withdrawals, a sample size of 132 volunteers was considered sufficient to establish bioequivalence between the test product and reference product under fed conditions with adequate power. Hence, a crossover study of 132 subjects was proposed.

Thus, a sufficient number of volunteers were asked to report on the day of check-in for Period-I in order to ensure that at least 132 subjects were checked in at the beginning of the study. However, due to pre-dose discontinuations/ withdrawals, the study was conducted on 130 subjects.

The study was conducted in three groups.

Group-I

A total of 46 subjects (Subject Nos. [redacted] and [redacted]) were checked in for Period-I of the study.

Group-II

A total of 45 subjects (Subject Nos. [redacted] and [redacted]) were checked in for Period-I of the study.

Group-III

A total of 45 subjects (Subject Nos. [redacted] and [redacted]) were checked in for Period-I of the study.

The treatment sequences were followed as given below:

Treatment-T: Spironolactone 100 mg film coated tablets

Manufactured & Distributed by: [redacted]

Treatment-R: Aldactone® (Spironolactone tablets 100 mg)

Marketing Authorization Holder: Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.

Table 9.1 (A) Treatment sequence

	Period-I	Period-II
Sequence	Treatment-R (Reference)	Treatment-T (Test)
	Treatment-T (Test)	Treatment-R (Reference)

The screening phase was carried out within 28 days prior to the scheduled dosing day of Period-I. The subjects were administered the study drug in each period except for the discontinued/ withdrawn subjects (Subject Nos. [redacted]). The sequence of administration was determined by the randomization schedule (Appendix No. 16.1.7). A washout period of 07 days was considered sufficient between the successive dosing days. The duration of the clinical part of the study was about 14 days (36 hours prior to the IMP administration in Period-I of Group-I until the last pharmacokinetic sample in Period-II of Group-III).

The schedule of events planned is depicted in the following table:

Table 9.1 (B) Schedule of Events

Time-point (hours)	ICF (Period-I only)	Comp-liance	Check-in	Clinical exami-nation	Meals	Vitals recording	Well-being assess-ments	Dosing	Blood sampling	Blood sample collection for post-study safety assessments (Period-II)	Check-out
Before check-in	X	X	-	-	-	-	-	-	-	-	-
Before 36 hours	-	-	X	-	-	-	-	-	-	-	-
After check-in	-	-	-	X	-	X	X	-	-	-	-
-24.000	-	-	-	-	-	X	X	-	-	-	-
Before 10.5 hours	-	-	-	-	Dinner	-	-	-	-	-	-
Pre-dose	-	-	-	-	-	X	X	-	X	-	-
-0.500	-	-	-	-	Breakfast	-	-	-	-	-	-
0.000	-	-	-	-	-	-	-	X	-	-	-
0.250	-	-	-	-	-	-	-	-	X	-	-
0.500	-	-	-	-	-	-	-	-	X	-	-
0.750	-	-	-	-	-	-	-	-	X	-	-
1.000	-	-	-	-	-	X	X	-	X	-	-
1.250	-	-	-	-	-	-	-	-	X	-	-
1.500	-	-	-	-	-	-	-	-	X	-	-
1.750	-	-	-	-	-	-	-	-	X	-	-
2.000	-	-	-	-	-	X	X	-	X	-	-
2.250	-	-	-	-	-	-	-	-	X	-	-

Time-point (hours)	ICF (Period-I only)	Comp-liance	Check-in	Clinical exami-nation	Meals	Vitals recording	Well-being assess-ments	Dosing	Blood sampling	Blood sample collection for post-study safety assessments (Period-II)	Check-out
2.500	-	-	-	-	-	-	-	-	X	-	-
2.750	-	-	-	-	-	-	-	-	X	-	-
3.000	-	-	-	-	-	-	-	-	X	-	-
3.500	-	-	-	-	-	-	-	-	X	-	-
4.000	-	-	-	-	-	-	-	-	X	-	-
4.500	-	-	-	-	-	-	-	-	X	-	-
5.000	-	-	-	-	-	-	-	-	X	-	-
After 5 hours	-	-	-	-	Lunch	-	-	-	-	-	-
6.000	-	-	-	-	-	X	X	-	X	-	-
7.000	-	-	-	-	-	-	-	-	X	-	-
8.000	-	-	-	-	-	-	-	-	X	-	-
10.000	-	-	-	-	-	-	-	-	X	-	-
12.000	-	-	-	-	-	X	X	-	X	-	-
16.000	-	-	-	-	-	-	-	-	X	-	-
24.000	-	-	-	-	-	-	-	-	X	-	-
Before check-out	-	-	-	X	-	X	X	-	-	X	-
After 24 hours	-	-	-	-	-	-	-	-	-	-	X

Continued....

Screening was carried out within 28 days prior to the IMP administration in Period-I.
Hematology, biochemistry, urine analysis and immunological tests were done during screening.
12-lead ECG recording was done at the time of screening and at 03 hours post-dose in each period.
Urine scan for drugs of abuse and breath test for alcohol consumption were carried out prior to check-in of each period.
No water except for the 240 ± 02 mL drinking water given during drug administration was allowed from 01 hour before to 01 hour after IMP administration.
The subjects were in sitting posture at chair side for the first 04 hours post-dose in each period unless medically necessary due to adverse event or procedurally required or natural exigency.
Lunch was served after 05 hours post-dose. Further meals after 05 hours post-dose were served at appropriate interval then on until check-out.
A washout period of 07 days was maintained between the successive dosing days.
Tests for hematology and biochemistry (except random glucose, sodium, potassium and chloride) were done at the end of the study (i.e. at the time of check-out of Period-II) to assess the post-study safety.

Restrictions during the study

All the subjects were instructed to abstain from any xanthine containing food or beverages (like tea, coffee, chocolates or cola drinks or any other), tobacco, tobacco containing products (like pan, pan masala, gutkha) for 24 hours prior to check-in till the last pharmacokinetic sample collection of each period.

All the subjects were also instructed to abstain from grapefruit or grapefruit products for 72 hours prior to check-in of Period-I till the last pharmacokinetic sample of Period-II.

All the subjects were also instructed to abstain from alcohol or alcoholic products for 48 hours prior to check-in of Period-I till the last pharmacokinetic sample of Period-II.

All the subjects were instructed to abstain from an unusual diet, for whatever reason (for example, low-sodium) for four weeks prior to check-in of Period-I and throughout their participation in the study.

It was ensured that all the checked in subjects were non-smokers for 6 months prior to start of the study. They were instructed to abstain from the same during the study period.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Based on the in-house study data and statistical analysis, a 2-way crossover study was planned to be conducted on 132 subjects under fed conditions as per the EMA requirements. However, due to pre-dose discontinuations/ withdrawals, a study was conducted on 130 subjects. The study was conducted in three groups.

Based on the available data and elimination half-life of Spironolactone, a washout period of 07 days was kept in between the successive dosing days.

Multiple blood samples were collected according to the protocol to assess the bioequivalence between the test and the reference products. For this bioequivalence study with a crossover design, each subject, except for the discontinued/ withdrawn subjects (Subject Nos. [redacted] and [redacted] received both the treatments (test drug and reference drug) during the study. Hence, every subject acted as his own control and no separate group of subjects was required to act as the control group.

9.3 SELECTION OF STUDY POPULATION

All the subjects willing to participate in the study were screened prior to their enrolment, in order to assess their eligibility by satisfying all of the inclusion and exclusion criteria. During screening, the medical history of the subjects was elicited and they underwent a general clinical examination, clinical laboratory evaluations, measurement of blood pressure, radial pulse rate, oral body temperature, respiratory rate, 12-lead ECG, chest X-ray (posterior-anterior view), immunological tests for HIV (Human Immunodeficiency Virus), HBsAg (Hepatitis B Surface Antigen) and HCV (Hepatitis C Virus). This procedure was conducted within 28 days prior to the IMP administration in Period-I.

9.3.1 Inclusion Criteria

The inclusion criteria as per the protocol were as follows:

- Normal, healthy, adult, human volunteers between 18 and 45 years of age (both inclusive) living in and around Ahmedabad city or western part of India.
- Non-Smoker.
- Having a Body Mass Index (BMI) between 18.5 to 30.0 (both inclusive), calculated as weight in kg / height in m^2.
- Not having any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (posterior-anterior view) recordings.
- Able to understand and comply with the study procedures, in the opinion of the investigator.
- Able to give voluntary written informed consent for participation in the study.
- In case of female subjects:
  - Surgically sterilized at least 6 months prior to study participation.

    Or
  - If of child bearing potential is willing to use a suitable and effective double barrier contraceptive method or intra uterine device during the study.

    And
  - Serum pregnancy test must be negative.

9.3.2 Exclusion Criteria

The exclusion criteria as per the protocol were as follows:

- Known hypersensitivity to Spironolactone or any excipients or any related drug or any substance.
- History or presence of any disease or condition which might compromise the haemopoietic, renal, hepatic, endocrine, pulmonary, central nervous, cardiovascular, immunological, dermatological, gastrointestinal or any other body system.
- Ingestion of medicine [prescribed and over the counter (OTC) medication including herbal remedies] at any time within 14 days prior to check-in of Period-I. In any such case subject selection will be at the discretion of the Principal Investigator.
- Any history or presence of asthma (including aspirin induced asthma) or nasal polyp or NSAIDs induced urticaria.
- A recent history of harmful use of alcohol (less than 2 years) i.e., alcohol consumption of more than 14 standard drinks per week for men and 07 standard drinks per week for women (A standard drink is defined as 360 mL of beer or 150 mL of wine or 45 mL of 40% distilled spirits, such as rum, whisky, brandy etc.), or consumption of alcohol or alcoholic product within 48 hours prior to check in of Period-I.
- Smokers or who have smoked within last 06 months prior to start of the study.

- The presence of clinically significant abnormal laboratory values during screening.
- Use of any recreational drugs or history of addiction to any recreational drugs or testing positive in pre-study drug scans.
- History or presence of seizure or psychiatric disorders.
- A history of difficulty with donating blood.
- Any major illness in the last three months or any significant ongoing chronic medical illness.
- Difficulty in swallowing solid dosage forms like tablets or capsules.
- Donation of blood (1 unit or 350 mL) or receipt of an investigational medicinal product or participation in a drug research study within 90 days prior to receiving the first dose of study medicine. Elimination half-life of the study drug should be taken into consideration for inclusion of the subject in the study.
- A positive hepatitis screen including hepatitis B surface antigen and/or HCV antibodies.
- A positive test result for HIV antibody (I and II).
- Consumption of grape fruit or grape fruit products within 72 hours prior to check-in of Period-I.
- An unusual diet, for whatever reason (e.g. low-sodium), for four weeks prior to check-in of Period-I. In any such case subject selection will be at the discretion of the Principal Investigator.
- Nursing mothers (for female subjects).

All the checked in subjects satisfied all the above inclusion and exclusion criteria.

9.3.3 Removal of Subject from Therapy or Assessment

As per the protocol the investigator could remove a subject from the study for any of the following reasons:

- The subject suffers from significant inter-current illness or undergoes surgery during the course of the study or the subject has any significant symptoms or signs during the course of the study.
- Any subject found to have entered the study in violation of the protocol. This would include pre-study directions regarding alcohol and drug use, fasting/fed or if the subject is non-compliant during the study or un co-operative with study procedures.
- If any subject cross-participates in other drug trial or trial screening.
- If any subject found to hide important medical history which in opinion of Principal Investigator/ Clinical Research Physician may compromise his safety during participation in this study.
- If any subject experiences emesis at or before reported two times median T_{max} (i.e., 05 hours) after dosing of the study drug.
- Found positive in pregnancy test (for female subjects).

- Any subject has consumed high fat high calorie non-vegetarian less than 800 kcal, then subject will be withdrawn from the study as per investigator's discretion.
- Any subject who requires the use of an unacceptable concomitant medicines [prescribed and over the counter (OTC) medication including herbal remedies].
- If it is felt in Principal Investigator's opinion that it is not in the subject's best interest to continue.
- Any subject who wishes to withdraw his/her consent for whatever reasons.
- Any other justifiable reason.

9.4 TREATMENTS

9.4.1 Treatments Administered

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed within 30 minutes.

A single oral dose (100 mg) of either of the test product or the reference product was administered at 30 minutes after serving of the breakfast to the subjects in sitting posture with 240 ± 02 mL of drinking water at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

The tablet was swallowed whole without chewing or crushing.

The time of administration of the investigational medicinal product was the time at which the subject completed drinking 240 ± 02 mL of water and that was captured in the respective source data forms.

This activity was followed by a mouth and hand check to assess the compliance to dosing. The subjects were in sitting posture at chair side for the first 04 hours post-dose in each period unless medically necessary due to adverse events or procedurally required or natural exigency, in such cases it was not considered as protocol deviation. Thereafter, the subjects were allowed to engage only in normal activities while avoiding any strenuous physical activity.

All the planned activities till 04 hours post-dose including the allowed time window to perform such activities were done in sitting posture at chair side.

They were instructed to refrain from drinking water from 01 hour prior to dosing till 01 hour after dosing in each period, except for the water given during IMP administration.

9.4.2 Identity of Investigational Medicinal Product(s)

Test Product-T		
Name of IMP	:	Spironolactone 100 mg film coated tablets
Manufactured & Distributed by	:	[redacted]
Batch No.	:	[redacted]
Batch Size	:	150,000 tablets
Manufacturing Date	:	03 July 2018
Expiry Date	:	30 June 2020
Storage Condition	:	Store in a dry place below 30°C.
Reference Product-R		
Name of IMP	:	Aldactone® (Spironolactone tablets 100 mg)
Marketing Authorization Holder	:	Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom.
Batch No.	:	[redacted]
Expiry Date	:	31 March 2022
Storage Condition	:	Store in a dry place below 30°C.

The accountability of the IMPs is given below:

IMP	Total IMP Units Received	Total Units of IMP Dispensed		Total Units of IMP Remaining
		Period-I	Period-II	
Test Product-T	448	69	69	309 + 06* + 10# + 01$ = 326
Reference Product-R	280	69	69	141 + 06* + 08^ + 01$ = 156

*One extra IMP (each for Reference Product-R and Test Product-T) was dispensed in addition to the required number of IMPs in each period in each group and labelled accordingly. This was done to use the extra IMPs in situations like dropping of the IMPs, etc. Since these products were not used, they were returned to pharmacy and were labelled as "NOT FOR USE" and retained along with the other IMPs of its type.

^Reference Product-R: Subject No. [redacted] was not dosed in Period-I and Subject Nos. [redacted] were not dosed in Period-II. Their

IMPs were returned to the Pharmacy and labelled as "NOT FOR USE" and retained along with the other IMPs of its type.

#Test Product-T: Subject No. [redacted] was not dosed in Period-I and Subject Nos. [redacted] were not dosed in Period-II. Their IMPs were returned to the Pharmacy and labelled as "NOT FOR USE" and retained along with the other IMPs of its type.

$One IMP of reference and test product was taken for verification. These products were labelled as "NOT FOR USE" and retained along with the other IMPs of its type.

9.4.3 Method of Assigning Subjects to Treatment Groups

This was a randomized study design. The order of receiving Test Product-T and Reference Product-R for each subject in each period of the study was determined according to the randomization schedule. The randomization schedule is provided in Appendix No. 16.1.7. Equal allocation of subjects to each sequence was ensured. The study personnel involved in the sample analysis were kept blinded from the randomization code during the entire study. Subjects were sequentially assigned a subject number as per the Arrival Sequence Number, which was allotted on the basis of the subject's reporting time to the facility on the day of check-in for Period-I and compliance to the requirements of the protocol. Replacement subjects were assigned 1000 numbers ahead of the number allotted, e.g. the subject replacing Subject No. [redacted] was allotted Subject No. [redacted].

9.4.4 Selection of Dose in the Study

Spironolactone 100 mg can be safely administered for various indications. The primary objective of the study was to assess the bioequivalence of the test product in comparison to the reference product. Hence, as per the sponsor's recommendation, the aforementioned dose was selected for the study.

9.4.5 Selection and Timing of Dose for Each Subject

Dosing was carried out in the morning at 30 minutes after serving of the high fat high calorie vegetarian breakfast after an overnight fast of at least 10 hours.

9.4.6 Blinding

This was an open label study, hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the Reference Product-R and Test Product-T to the individual subjects.

9.4.7 Prior and Concomitant Therapy

As per the protocol, the subjects were instructed not to take / apply any medication [prescribed and over the counter (OTC) medication including herbal remedies] other than the investigational medicinal product from 14 days prior to dosing in Period-I till completion of the study.

However, few subjects were administered medicines to treat their adverse events. Information on these medications (subject wise) is presented in Appendix No. 16.2.7-Adverse event listings (each subject).

9.4.8 Treatment Compliance

Compliance to dosing was assessed by examination of the oral cavity of the subjects and hand check using a torch and disposable spatula by the trained study personnel immediately after IMP administration in each period.

9.5 PHARMACOKINETIC AND SAFETY VARIABLES

9.5.1 Pharmacokinetic and Safety Measurements Assessed

Pharmacokinetic: Pharmacokinetic was primarily assessed by the pharmacokinetic properties of the test and the reference formulations by measurement of Spironolactone concentrations in plasma.

The following pharmacokinetic parameters were calculated:

Primary pharmacokinetic parameters:

C_{max} and AUC_{0-t}

Secondary pharmacokinetic parameters:

T_{max}, $AUC_{0-\infty}$, λ_z, $t_{½}$ and AUC_%Extrap_obs

These pharmacokinetic parameters were calculated for Spironolactone by non-compartmental model using Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

Safety: The following measures were taken to monitor and assess the safety of the subjects during the study:

- Subjects were monitored throughout the study period for adverse events. They were instructed to bring to the notice of the nurse, clinical custodian or the doctor for any adverse event that occurred during their stay at the clinical facility.
- A physician was available within the clinical facility whenever the subjects were housed (from check-in to check-out in each period). A consultant physician was always available on call during the study period.
- Subjects met the criteria for enrolment in the study.
- Clinical examination of the subjects including recording of vital signs (sitting blood pressure and radial pulse rate) and oral body temperature was done at screening, after check-in and before check-out of each period. Clinical examination before check-out in each period could start within 60 minutes prior to the scheduled time of check-out of each subject.
- Vital signs (sitting blood pressure and radial pulse rate) were recorded at -24 hours, prior to administration of IMP and at 01, 02, 06 and 12 hours post-dose after administration of IMP in each period.

  Note: -24 hours pre-dose and all post-dose vital signs measurements were recorded within ± 40 minutes from the scheduled time.
- Chest X-ray (during the last 6 months) (posterior-anterior view) was performed during screening.
- 12-lead ECG recording was performed at screening and at 03 hours post-dose in each period.
- Post-dose 12-lead ECG measurement was carried out in supine position and within ± 40 minutes of the scheduled time.
- Subjects were questioned for well-being at the time of clinical examination and during recording of vital signs in each period.
- Laboratory assessments were done at the time of screening. Scan for drugs of abuse and breath test for alcohol consumption were done prior to check-in of each period.

- Subjects were instructed not to participate in other clinical research study or donate blood anywhere else during the study.
- Laboratory tests for haematology and biochemistry (except random glucose, sodium, potassium and chloride) were done at the end of the study (at the time of check-out of Period-II) to assess the post-study safety.

  Note: All the planned activities till 04 hours post-dose including the allowed time window to perform such activities were in sitting posture at chair side.

Criteria for assessing the adverse events:

The severity of the adverse events was rated by the principal investigator or the clinical research physician.

A) Severity of the adverse events was determined based on the following:

a. Mild: The adverse event does not limit usual activities; the subject experiences slight discomfort.

b. Moderate: The adverse event results in some limitation of usual activities; the subject experiences significant discomfort.

c. Severe: The adverse event results in an inability to carry out usual activities; the subject experiences intolerable discomfort or pain.

B) Causality Assessment of the Adverse Events to the IMP was done based on the following criteria:

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

Causality term	Assessment criteria
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
Unrelated	• The adverse event is clearly not related to the investigational medicinal product • A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.

For an adverse event with the causality assessment of 'certain, probable/likely', the term "related" and for the 'possible', term "possibly related" was used to denote its relationship with the Medicinal product. For the causality assessments 'unlikely', the term "unlikely related" and for the 'unrelated', the term "Not related" was used. This is not applicable for causality term 'conditional/unclassified' and 'unassessable/unclassifiable'.

9.5.2 Appropriateness of Measurements

Plasma concentration measurements are often used for the calculation of pharmacokinetic parameters. The sampling time-points were planned based on the reported pharmacokinetics of the drug. These time-points were chosen to assess C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_z, AUC_%Extrap_obs and $t_{½}$ appropriately. Based on these evaluations, comparison of the two formulations was carried out.

9.5.3 Primary Pharmacokinetic Variable(s)

Pharmacokinetic of the formulations is assessed based on the following pharmacokinetic parameters.

These parameters are derived individually for each analyzed subject from the concentration vs. time profiles of Spironolactone in plasma using non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

a) C_{max} and T_{max}

The maximum measured plasma concentration (C_{max}) and the time of observing the peak concentration (T_{max}) was calculated from the plasma concentration vs. time profile of the individual subjects.

The units of C_{max} and T_{max} are ng/mL and hour (h) respectively.

b) AUC_{0-t}

Area under the plasma concentration vs. time curve (AUC_{0-t}) in ng.h/mL was calculated by linear trapezoidal rule from measured data points from the time zero to the time of last quantified concentration.

c) $AUC_{0-\infty}$

Area under the plasma concentration vs. time curve ($AUC_{0-\infty}$) in ng.h/mL from time zero to infinity, where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable concentration and λ_z is the terminal rate constant.

The $AUC_{0-\infty}$ was the sum of measurable and extrapolated parts.

d) Terminal rate constant (λ_z)

First order rate constant associated with the terminal (log-linear) portion of the curve. This was estimated via linear regression of time vs. log transformed concentration. This parameter was calculated by linear least squares regression analysis using last three or more non-zero plasma concentration values.

The unit of λ_z is $hour^{-1}$ (1/h).

e) Terminal Half-life ($t_{½}$)

The terminal half-life was calculated using the formula:

$0.693/\lambda_z$

The unit of $t_{½}$ is hour (h).

f) AUC_%Extrap_obs (%)

The residual area in percentage was determined by the formula:

$[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100$

Actual time-points of the sample collection are used for the calculation of pharmacokinetic parameters.

All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations.

The individual pharmacokinetic parameters are tabulated in Table No. 14.2.1.3 for Spironolactone.

The individual pharmacokinetic parameters of data excluded from statistical analysis are tabulated in Table No. 14.2.1.4 for Spironolactone.

The pharmacokinetic outputs from Phoenix® WinNonlin® Version 6.4 (Certara L.P.) are provided in Appendix No. 16.2.5 (Compliance and/or drug concentration data).

9.5.4 Drug Concentration Measurements

As per the protocol, a total of twenty-four (24) blood samples, each of 04 mL were to be collected from each subject in each period.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.500, 4.000, 4.500, 5.000, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000 and 24.000 hours following IMP administration in each period.

Blood samples were collected through an indwelling intravenous cannula (Venflon) placed in a forearm vein of the subjects. Immediately after collection of blood, the collection tube (vacutainer) was inverted gently several times to ensure the mixing of tube contents (i.e., anticoagulant). For precaution purpose, vacutainers were placed upright in a rack kept in ice cold water bath during collection.

As per the protocol, the pre-dose blood samples were collected within a period of 60 minutes before dosing. The post-dose in-house blood samples were to be collected within ± 02 minutes from the scheduled time for all the subjects. Post-dose samples not collected within this time frame from the scheduled time were documented as sampling deviations. The actual time of collection of each blood sample was recorded immediately after blood collection.

Deviations in this regard are appended in Appendix No. 16.3.2 (Other CRFs submitted).

Intravenous indwelling cannula was kept *in situ* as long as possible by injecting 0.5 mL of normal saline solution to maintain the cannula patent (to prevent cannula from clogging) for collection of all blood samples during housing. In such cases blood samples were collected after discarding the first 0.5 mL of normal saline containing blood from the tubing. The blood samples were withdrawn using syringe and transferred into pre-labelled (mentioning Project number, Subject number, Period, Bar Code ID No. and Sampling time point) sample collection tube containing K_2EDTA as the anticoagulant placed upright in a rack kept in ice cold water bath until centrifugation for precaution purpose.

The details regarding the total number of samples collected during the study is given in the below table:

Sr. No.	Subject No.	Total No. of Samples Collected (No. of Samples x No. of Subjects)	Remarks
1.	[redacted]	624 (48 x 13)	All the samples were collected.
2.	[redacted]	24 (24 x 01)	The subject discontinued from the study on his own accord in Period-II.
3.	[redacted]	192 (48 x 04)	All the samples were collected.
4.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.
5.	[redacted] and [redacted]	96 (48 x 02)	All the samples were collected.
6.	[redacted]	24 (24 x 01)	The subject discontinued from the study on his own accord in Period-II.
7.	[redacted] and [redacted]	288 (48 x 06)	All the samples were collected.
8.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.

Sr. No.	Subject No.	Total No. of Samples Collected (No. of Samples x No. of Subjects)	Remarks
9.	[redacted]	1248 (48 x 26)	All the samples were collected.
10.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.
11.	[redacted]	384 (48 x 08)	All the samples were collected.
12.	[redacted]	22 (22 x 01)	The subject was withdrawn from the study on medical grounds in Period-I.
13.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on medical grounds in Period-II.
14.	[redacted]	48 (48 x 01)	All the samples were collected.
15.	[redacted]	22 (22 x 01)	The subject was withdrawn from the study on medical grounds in Period-I.
16.	[redacted]	24 (24 x 01)	The subject discontinued from the study on his own accord in Period-II.
17.	[redacted]	144 (48 x 03)	All the samples were collected.
18.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on medical grounds in Period-II.
19.	[redacted]	576 (48 x 12)	All the samples were collected.
20.	[redacted]	23 (23 x 01)	The subject was withdrawn from the study on medical grounds in Period-I.
21.	[redacted]	240 (48 x 05)	All the samples were collected.
22.	[redacted] and [redacted]	48 (24 x 02)	The subjects discontinued from the study on their own accord in Period-II.
23.	[redacted]	624 (48 x 13)	All the samples were collected.
24.	[redacted]	00 (00 x 00)	After being checked in for Period-I, the subject discontinued from the study on his own accord.
25.	[redacted] and [redacted]	288 (48 x 06)	All the samples were collected.
26.	[redacted]	24 (24 x 01)	The subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.

Sr. No.	Subject No.	Total No. of Samples Collected (No. of Samples x No. of Subjects)	Remarks
27.	[redacted]	288 (48 x 06)	All the samples were collected.
28.	[redacted]	01 (01 x 01)	The subject was withdrawn from the study on medical grounds prior to dosing in Period-I.
29.	[redacted]	528 (48 x 11)	All the samples were collected.
Total No. of samples to be collected as per the protocol: 6336 **Total No. of samples collected during the study: 5900**			

Note: The pre-dose sample of Subject No. [redacted] was collected in Period-I, however, prior to dosing, the subject was withdrawn from the study on medical grounds and was replaced by Subject No [redacted] This sample was not used and was discarded.

Summary of Sample Processing

The blood samples were centrifuged at 3000 rcf for 05 minutes at 2°C to separate plasma. For precaution purpose, the blood samples were kept in ice cold water bath before centrifugation and during separation. The separated plasma was transferred to pre-labelled polypropylene tubes in two aliquots (around 0.6 mL in first aliquot and rest of the volume in second aliquot) and the samples were stored upright in a freezer at a temperature -65 ± 10°C for interim storage till transfer of the same to the bio-analytical department. During transfer, the samples were kept in a box containing adequate amount of dry ice.

All the received samples were transferred to the freezer maintained at -65 ± 10°C at the bioanalytical facility. Before analysis, all the samples were verified.

Summary of Bio-analytical Method

The plasma samples of subjects were analysed using a validated LC-MS/MS method for Spironolactone at the Bioanalytical facility of Lambda Therapeutic Research Ltd., Ahmedabad, India. The method validation report is provided in Appendix No. 16.5.3 (Method Validation Report). The analysis was conducted as per Method SOP No. MS-1228-00. Calibration curve using an 8-point calibration curve standard, with concentrations ranging from 0.752 ng/mL to 303.220 ng/mL were used to determine the concentrations of Spironolactone in the samples of all analysed subjects.

The Bioanalytical Report, Certificates of Analysis of working standards / reference standards, Method Validation Report, Method SOP, Bioanalytical study plan and Bioanalytical SOPs are provided in Appendix No. 16.5 (Bioanalytical Phase Report).

The chromatograms of the subjects are given in Appendix No. 16.5.7.

9.6 DATA QUALITY ASSURANCE

9.6.1 Quality Control

The Principal Investigator or his designate ensured that all the data from subject visits were entered in the eCRFs as per the existing SOPs and applicable guidelines. An explanation for the omission of any required data should appear on the appropriate page. The data on all the eCRFs were checked for correctness, completeness and legibility of the entries by the Quality Control team. The quality control team responsible for audit of data generated by the bioanalytical department ensured the compliance with the existing SOPs and relevant current international guidelines.

Prior to submission of the data to QA for audit, assigned Quality control team performed Quality control checks on the generated data / reports to ensure completeness and correctness of the data.

9.6.2 Monitoring

[redacted] Key Pharmaceuticals Ltd., UK monitored the clinical phase of the study as well as [redacted] CliniServe, India also monitored the clinical phase of the study on behalf of Key Pharmaceuticals Ltd., UK. The details are as below:

Group	Period	Day of visit in particular period	Date of visit	Name of monitor
I	I	Check-in	25 September 2018	[redacted]
II	I		26 September 2018	
I	I	Dosing	27 September 2018	
II	I		28 September 2018	
III	I		30 September 2018	
I	II	Check-in	02 October 2018	
II	II		03 October 2018	
I	II	Dosing	04 October 2018	
II	II		05 October 2018	
III	II		07 October 2018	

9.6.3 Training

The investigator and team are trained in salient feature of ICH-GCP at periodic intervals. Before the start of the study, the study team was trained on various aspects of the study during the protocol training session. They were trained on the protocol, informed consent procedures, randomization procedures, eCRF completion and correction, study drug administration, study drug storage and accountability, source documentation, monitoring procedures, laboratory procedures, completion of study logs, archiving of documents and timelines of subject recruitment and completion.

9.6.4 Quality Assurance

Quality Assurance assessed compliance to the study requirements as per Good Clinical Practices, Principles of Good Laboratory Practices, Internal Standard Operating Procedures, Protocol and Applicable Regulatory Requirements. As a part of quality assurance audit program, various activities involved during conduct of the study and documents / data / eCRFs generated (Clinical, Statistical phases and final Report Writing) were audited in-process and / or retrospectively to ensure compliance to the study requirements. Audit Certificates assuring compliance to the above requirements was issued by QA. This is included in Appendix No. 16.1.8 (Audit Certificates) of this report.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

Descriptive statistics were to be computed and reported for the pharmacokinetic parameters for Spironolactone.

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were to be subjected to Analysis of Variance (ANOVA) for Spironolactone.

As study was conducted in groups, ANOVA model was to be included Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation and Period (Group) as fixed effects.

Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

The power of the study was to be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Ratio of geometric least squares means of the test and reference formulations was to be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Intra-subject variability was to be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Any missing samples (M) or non-reportable (NR) concentration values were to be disregarded in pharmacokinetic and statistical analysis.

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares means between drug formulations were to be computed for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of Test Product-T vs. Reference Product-R was to be concluded, if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters for Spironolactone.

Parameters	Acceptance Range of 90% CI
C_{max} and AUC_{0-t}	80.00 - 125.00%

All statistical analyses for Spironolactone were to be performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc, USA).

9.7.2 Determination of Sample Size

Based on the in-house study data, the maximum intra-subject variability observed for primary pharmacokinetic parameter was found to be ~ 36%; the sample size computation was determined using SAS by considering the following assumptions:

a) T/R ratio = 90.0-111.1%

b) Intra-Subject C.V (%) ~ 36%

c) Significance Level = 5%

d) Power ≥ 80%

e) Bioequivalence Limits = 80.00 – 125.00%

Based on the above estimates, a sample size of 110 subjects will be required to establish bioequivalence between formulations with adequate power. Considering approximately 20% dropouts and/or withdrawals, a sample size of 132 subjects were sufficient to establish bioequivalence between formulations with adequate power for this study.

9.8 CHANGES IN THE CONDUCT OF STUDY OR PLANNED ANALYSES

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

10.0 STUDY SUBJECTS

10.1 DISPOSITION OF SUBJECTS

The study was conducted in three groups.

Group-I

A total of 46 subjects (Subject Nos. [redacted]) were checked in for Period-I of the study. Subject Nos. [redacted] were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I.

On the day of dosing for Period-I, prior to dosing, Subject No. [redacted] had complaint of loose stool since approximately [redacted] It was associated with abdominal pain. Hence, the subject was withdrawn from the study on medical grounds. He was replaced with Subject No. [redacted], who was later, allotted Subject No. [redacted]

Subject No. [redacted] was checked out of the facility as no more subject discontinued / was withdrawn from the study prior to dosing in Period-I.

No female volunteers were checked in for the study.

Hence, 44 subjects (Subject Nos. [redacted]) were dosed in Period-I of the study.

Subject Nos. [redacted] discontinued from the study on their own accord in Period-II. Subject Nos. [redacted] were withdrawn from the study on the grounds of protocol non-compliance in Period-II.

In all, 40 subjects (Subject Nos. [redacted]) completed the clinical phase of the study successfully.

Group-II

A total of 45 subjects (Subject Nos. [redacted]) were checked in for Period-I of the study. Subject No. [redacted] was checked in for the study, in order to compensate for any dropout prior to dosing in Period-I.

Subject No. [redacted] was checked out of the facility as no more subject discontinued / was withdrawn from the study prior to dosing in Period-I.

No female volunteers were checked in for the study.

Hence, 44 subjects (Subject Nos. [redacted]) were dosed in Period-I of the study.

Subject Nos. [redacted] were withdrawn from the study on medical grounds in Period-I. Subject No. [redacted] was withdrawn from the study on the grounds of protocol non-compliance in Period-II. Subject Nos. [redacted] were withdrawn from the study on medical grounds in Period-II. Subject No. [redacted] discontinued from the study on his own accord in Period-II.

In all, 37 subjects (Subject Nos. [redacted]) completed the clinical phase of the study successfully.

Group-III

A total of 45 subjects (Subject Nos. [redacted]) were checked in for Period-I of the study. Subject No. [redacted] was checked in for the study, in order to compensate for any dropout prior to dosing in Period-I.

On the day of check-in for Period-I, after being checked in, Subject No. [redacted] informed the study personnel that he did not want to continue his further participation in the study due to his personal reason. Hence, he discontinued from the study on his own accord.

On the day of check-in for Period-I, after being checked in, Subject No. [redacted] informed the study personnel that he did not want to continue his further participation in the study due to his personal reason. Hence, he discontinued from the study on his own accord. He was replaced with Subject No. [redacted], who was later, allotted Subject No. [redacted]

On the day of dosing for Period-I, Subject No. [redacted] had a single episode of vomiting at approximately [redacted] while having breakfast prior to dosing. Hence, he was withdrawn from the study on medical grounds.

No female volunteers were checked in for the study.

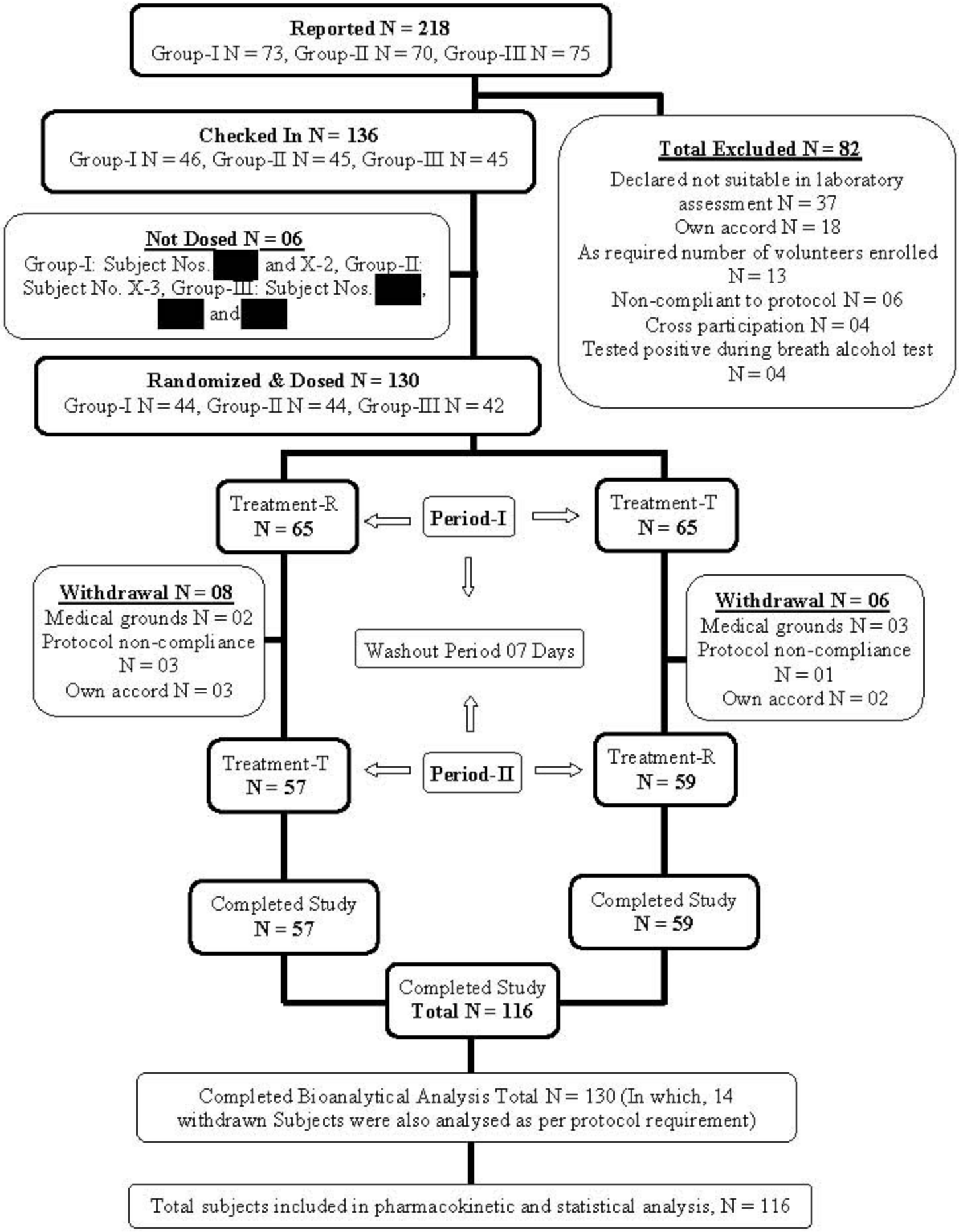
Hence, 42 subjects (Subject Nos. [redacted] and [redacted] were dosed in Period-I of the study.

Subject Nos. [redacted] and [redacted] discontinued from the study on their own accord in Period-II. Subject No. [redacted] was withdrawn from the study on the grounds of protocol non-compliance in Period-II.

In all, 39 subjects (Subject Nos. [redacted] and [redacted]) completed the clinical phase of the study successfully.

In all the groups, 116 subjects (Subject Nos. [redacted] and [redacted]) completed the clinical phase of the study successfully.

Details of discontinued/ withdrawn subjects are presented in Appendix No. 16.2.1 (Discontinued subjects).


Reported N = 218
Group-I N = 73, Group-II N = 70, Group-III N = 75
Checked In N = 136
Group-I N = 46, Group-II N = 45, Group-III N = 45
Total Excluded N = 82
Declared not suitable in laboratory assessment N = 37
Own accord N = 18
As required number of volunteers enrolled N = 13
Non-compliant to protocol N = 06
Cross participation N = 04
Tested positive during breath alcohol test N = 04
Not Dosed N = 06
Group-I: Subject Nos. [redacted] and X-2, Group-II: Subject No. X-3, Group-III: Subject Nos. [redacted], [redacted] and [redacted]
Randomized & Dosed N = 130
Group-I N = 44, Group-II N = 44, Group-III N = 42
Treatment-R N = 65
Period-I
Treatment-T N = 65
Withdrawal N = 08
Medical grounds N = 02
Protocol non-compliance N = 03
Own accord N = 03
Washout Period 07 Days
Withdrawal N = 06
Medical grounds N = 03
Protocol non-compliance N = 01
Own accord N = 02
Treatment-T N = 57
Period-II
Treatment-R N = 59
Completed Study N = 57
Completed Study N = 59
Completed Study Total N = 116
Completed Bioanalytical Analysis Total N = 130 (In which, 14 withdrawn Subjects were also analysed as per protocol requirement)
Total subjects included in pharmacokinetic and statistical analysis, N = 116

10.2 PROTOCOL DEVIATIONS

10.2.1 Protocol Deviations

Protocol deviation	Subjects under each period		
	Period-I	Period-II	End-study
Pre-dose vital (Pre-dose vitals were not recorded within the scheduled time interval)	[redacted] and	-	-
Post-dose vital (01 hour vital was not performed within ±40 minutes of the scheduled time)	[redacted]	-	-
Housing (Subjects were not housed within 36 hours prior to dosing)	[redacted]	[redacted] and	-
Dosing (Hand check was not done after dose administration)	-	[redacted] and	-
End-study safety assessment (Post-study safety assessment was not performed for the subjects)	-	-	[redacted] and

Details of the above mentioned deviations are appended in Appendix No. 16.2.2 (Protocol Deviations).

Impact

Pre-dose vital: Considering time duration of deviation and clinically acceptable value of vital parameters for these subjects, it does not have any significant impact on safety and overall outcome of the study.

Post-dose vital: Considering time duration of deviation and clinically acceptable value of vital parameters for these subjects, it does not have any significant impact on safety and overall outcome of the study.

Housing: Considering that all subjects were compliant during compliance assessment before check-in and they followed all other protocol requirements, it does not have any significant impact on the result of the study.

Dosing: The IMP was given directly in the subject's mouth. Further, after IMP administration, mouth check was done in line with protocol requirement. As the IMP was not given in the subject's hand, the stated deviation is unlikely to have any significant impact on the study outcome.

End-study safety assessment: The concerned subjects had been contacted telephonically several times as well as attempt was done to visit their home to contact them personally, but subjects were not traceable. So eventually subjects were declared as lost to follow-up. However, the safety of the subjects was ensured till their last visit to the facility, hence this deviation is unlikely to have any significant impact on study.

10.2.2 Sampling Deviations

Details of the deviations in sample collection are appended in Appendix No. 16.3.2 (Other CRFs submitted).

Impact

Sampling deviations – Pharmacokinetic sampling deviations may not have any impact on the overall assessment of the study since the actual time is used for computation in pharmacokinetic and statistical analysis.

11.0 PHARMACOKINETIC EVALUATION

11.1 DATA SETS ANALYZED

The study was planned so as to obtain the data from 132 evaluable subjects. However, due to pre-dose discontinuations/ withdrawals, 130 subjects were dosed in Period-I of the study. Out of the 130 dosed subjects, 116 subjects (Subject Nos. [redacted] and [redacted]) completed the clinical phase of the study successfully.

Plasma samples of 130 subjects were analysed. In which, withdrawn Subject Nos. [redacted] & [redacted] were also analysed as per protocol requirement.

Total 116 subjects were included in the pharmacokinetic and statistical analysis.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The mean ± SD of age, height, weight and BMI of 130 subjects (Subject Nos. [redacted] and [redacted]), who were dosed in the study and 116 subjects (Subject Nos. [redacted] who were included in the BE evaluation is as follows:

Parameter (Units)	Mean ± SD	
	N = 130 (Dosed Subjects)	N=116 (Subjects included in BE evaluation)
Age (years)	30.8 ± 5.92	30.7 ± 5.79
Height (cm)	166.46 ± 5.855	166.44 ± 6.018
Weight (kg)	63.465 ± 10.2988	63.167 ± 10.3156
BMI (kg / m^2)	22.845 ± 3.1376	22.734 ± 3.0808

The demographic data of the subjects is listed in Section 14.1 (Demographic Data) and Appendix No. 16.2.4 (Demographic data).

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

The drug concentrations after analysis have been presented in Appendix No.16.2.5.

11.4 PHARMACOKINETIC RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.4.1 Analyses of pharmacokinetic

11.4.1.1 Pharmacokinetic Analysis

The pharmacokinetic parameters are derived individually for each analyzed subject from the plasma concentration vs. time profiles of Spironolactone. Dataset for the calculation of pharmacokinetic parameters has been prepared using Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

Actual time points of the sample collection are used for the calculation of pharmacokinetic parameters. Sampling time points deviations used in the pharmacokinetic evaluation are tabulated in Table No. 14.2.2 (Sampling time point deviations used for pharmacokinetic evaluation).

Subject No. [redacted] (Period-I) had all zero concentration in the reference product-R. Hence, period specific data of the same was excluded from the pharmacokinetic analysis for the assessment of bioequivalence as per the criteria set in the protocol. However, results including the same was provided for supportive information only.

The pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R are summarized in the following table:

Descriptive Statistics of Formulation Means for Spironolactone
[Excluding subject no. [redacted] (period-I, R)]

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T (N = 116)	Reference Product-R (N = 115)
T_{max} (h)*	2.250 (0.750 - 6.000)	2.000 (0.750 - 6.000)
C_{max} (ng/mL)	148.736 ± 68.0385	149.063 ± 64.2997
AUC_{0-t} (ng.h/mL)	381.047 ± 148.6725	368.610 ± 135.0201
$AUC_{0-\infty}$ (ng.h/mL)	396.496 ± 149.5979^	380.453 ± 139.2814
λ_z (1/h)	0.139 ± 0.0649^	0.143 ± 0.0797
$t_{½}$ (h)	6.115 ± 2.9038^	6.270 ± 3.1643
AUC_%Extrap_obs (%)	3.064 ± 1.6829^	3.097 ±1.5659

*T_{max} is represented as median (min-max) value.

^N = 115; Terminal rate constant (λ_z) cannot be estimated based on obtained concentration data for subject no. 1103 (Period-II, T). Hence, $AUC_{0-\infty}$ and other elimination phase dependent parameters cannot be calculated.

(Refer Table No. 14.2.1.3)

11.4.1.2 Statistical Analysis

Statistical analysis on ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Spironolactone are performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA).

Subject No. [redacted] (Period-I) had all zero concentration in the reference product-R. Hence, period specific data of the same was excluded from the statistical analysis for the assessment of bioequivalence as per the criteria set in the protocol. However, results including the same was provided for supportive information only.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for Spironolactone are summarized in the following table:

Relative Bioavailability Results for Spironolactone
[Excluding subject no. [redacted] (period-I, R)]

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T (N = 116)	Reference Product-R (N = 115)	Ratio (T/R) %			
lnC_{max}	132.093	130.503	101.2	94.56 - 108.34	31.8	100.0
$lnAUC_{0-t}$	343.539	330.098	104.1	100.16 - 108.14	17.6	100.0
$lnAUC_{0-\infty}$	369.987^	355.668	104.0	100.12 - 108.09	17.6	100.0

^N = 115.

(Refer Table No. 14.2.1.1)

ANOVA p-values for Spironolactone are summarized in the following table:

ANOVA p-values for Spironolactone

Parameters	ANOVA (p-value)					Subject(Sequence* Group)
	Group	Sequences	Sequence* Group	Formulation	Period (Group)	
lnC_{max}	0.0013	0.0428	0.3779	0.7683	0.4163	<0.0001
$lnAUC_{0-t}$	<0.0001	<0.0001	<0.0001	0.0869	0.0491	<0.0001
$lnAUC_{0-\infty}$	0.0266	0.1222	0.0146	0.0901	0.0636	<0.0001

Note: p-value is statistically significant if it is < 0.05.

(Refer Table No. 14.2.1.1)

Based on the above table, Formulation effect is found to be statistically insignificant for ln-transformed pharmacokinetic parameter C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Sequence effect is found to be statistically insignificant for ln-transformed pharmacokinetic parameter $AUC_{0-\infty}$; but it is found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Spironolactone.

The cause for significant of sequence effect may not be found with certainty. Therefore, under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect is just statistically significant and can be ignored.

Sequence*Group effect is found to be statistically insignificant for ln-transformed pharmacokinetic parameter C_{max}; but it is found to be statistically significant for ln-transformed pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

The cause of the significance of Sequence*Group could not be identified with certainty. However, the present study satisfies all the scientific and statistical criteria and 90% confidence interval for primary pharmacokinetic parameters are well within the acceptance range for Spironolactone, the statistically significance of Sequence*Group effect can be ignored.

Period(Group) effect is found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$; but it is found to be statistically significant for ln-transformed pharmacokinetic parameter AUC_{0-t} for Spironolactone.

In the study, clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed. Hence, appearance of Period (Group) is insignificant in nature and hence this significant period effect for ln-transformed pharmacokinetic parameter AUC_{0-t} of Spironolactone is just statistically significant and can be ignored.

Group and Subject (Sequence*Group) effects are found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Since each subject is assigned only one sequence within the group, subjects are said to be nested within Sequence*Group. This Subject (Sequence*Group) effect is tested by the residual and should be highly significant. This significance is an indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

Relative Bioavailability Results for Spironolactone (N = 116)
[Including subject no. [redacted] (period-I, R)]

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	132.093	130.503	101.2	94.56 - 108.34	31.8	100.0
lnAUC_{0-t}	343.539	330.098	104.1	100.16 - 108.14	17.6	100.0
ln$AUC_{0-\infty}$^	369.987	355.668	104.0	100.12 - 108.09	17.6	100.0

^N = 115.

(Refer Table No. 14.2.1.2)

The detailed outputs of the statistical computations are presented in Appendix No. 16.1.9 (Documentation of statistical methods).

11.4.2 Statistical / Analytical issues

There were no statistical issues in the study.

11.4.2.1 Adjustments for Covariates

This section is not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

There were fourteen (14) post-dose discontinuations/ withdrawals during the conduct of the study.

Subject Nos. [redacted], [redacted] and [redacted] discontinued from the study on their own accord in Period-II. Subject Nos. [redacted] and [redacted] were withdrawn from the study on the grounds of protocol non-compliance in Period-II. Subject Nos. [redacted] and [redacted] were withdrawn from the study on medical grounds in Period-I. Subject Nos. [redacted] and [redacted] were withdrawn from the study on medical grounds in Period-II.

There were no missing samples during the conduct of the study.

Plasma samples of withdrawn Subject Nos. [redacted] & [redacted] were analysed as per protocol requirement. Plasma sample of withdrawn Subject No. [redacted] was not analysed as per protocol requirement.

11.4.2.3 Interim Analyses and Data Monitoring

This section is not applicable.

11.4.2.4 Multicentre Studies

This section is not applicable.

11.4.2.5 Multiple Comparisons / Multiplicity

This section is not applicable.

11.4.2.6 Use of an "Pharmacokinetic Subset" of Subjects

This section is not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This section is not applicable.

11.4.2.8 Examination of Subgroups

This section is not applicable.

11.4.3 Tabulation of Individual Response Data

For this bioequivalence study, the results of the study are drug concentration levels. These are tabulated in Table Nos. 14.2.1.5 to 14.2.1.7 for Spironolactone.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

This section is not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

This section is not applicable.

11.4.6 By-Subject Displays

The linear and semi logarithmic individual plots of plasma concentration versus time curve of Spironolactone are presented in Appendix No. 16.2.6 (Individual pharmacokinetic response data).

11.4.7 Pharmacokinetic Conclusion

Test Product-T when compared with the Reference Product-R meets the bioequivalence criteria with respect to C_{max} and AUC_{0-t} for Spironolactone under fed condition as per criteria set in the protocol.

12.0 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Dosage: Dose variation was not allowed in this study. Treatment regimen consisted one of the following formulations.

Test Product-T : Spironolactone 100 mg film coated tablets

Reference Product-R : Aldactone® (Spironolactone tablets 100 mg)

Subject Exposure: A total of 136 subjects were checked in for the study. Out of these 136 subjects, 130 subjects were dosed in Period-I of the study. The safety assessment includes information for all 130 subjects who were dosed at least once during this study.

The details are provided in the below table:

	Test Product-T	Reference Product-R
Number of subjects (N)	122	124
Exposure	One	One

12.2 ADVERSE EVENTS (AEs)

12.2.1 Brief Summary of Adverse Events

Seventeen (17) adverse events (AEs) were reported by nine (09) subjects during the conduct of the study. Thirteen (13) AEs were reported in Period-I, one (01) AE was reported in Period-II and three (03) AEs were reported during post-study safety assessment.

Ten (10) AEs were reported in the subjects after administration of Reference Product-R and seven (07) AEs were reported in the subjects after administration of Test Product-T.

All the AEs were mild in nature and the subjects were followed up until resolution of their AEs except for Subject Nos. [redacted] and [redacted] They did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

The causality assessment was judged as possibly related for eleven (11) AEs, as unlikely related for five (05) AEs and as not related for one (01) AE.

There were no deaths or serious AEs reported during the conduct of the study.

However, out of the total reported seventeen (17) AEs, eight (08) AEs were significant. The subjects were withdrawn from the study on medical grounds. The subjects were treated appropriately and followed up until resolution of their AEs. The causality assessment was judged as unlikely related for five (05) AEs, as possibly related for two (02) AEs and as not related for one (01) AE.

12.2.2 Display of Adverse Events

A summary of the AEs is presented in Section 14.3.1 (Displays of Adverse events) and the AEs are listed (subject wise) in Appendix No. 16.2.7 [Adverse event listings (each subject)].

12.2.3 Analysis of Adverse Events

The analysis of adverse events was carried out treatment-wise. Nine (09) subjects reported a total of seventeen (17) AEs during the study.

Thirteen (13) AEs were reported in Period-I, one (01) AE was reported in Period-II and three (03) AEs were reported during post-study safety assessment.

Five (05) subjects in the reference group reported a total of ten (10) AEs and four (04) subjects in the test group reported a total of seven (07) AEs.

Of the seventeen (17) AEs reported, the causality assessment was judged as possibly related for eleven (11) AEs, as unlikely related for five (05) AEs and as not related for one (01) AE.

All the AEs were classified as mild in nature.

In the reference group, the most frequently reported AEs were Pyrexia (04 subjects, 3.23%) and Headache (03 subjects, 2.42%). The most frequently reported AEs for both treatment groups combined were Pyrexia (06 subjects, 4.62%) and Headache (05 subjects, 3.85%).

A total of fourteen (14) adverse events resolved, with majority of the AEs requiring treatment with medication. The outcome for other three (03) AEs was unknown as the subjects did not report for their post-study safety assessment and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

12.2.4 Listings of Adverse Events by Subjects

The listing of the adverse events is given in Appendix No. 16.2.7 [Adverse event listings (each subject)].

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

12.3.1.1 Deaths

There were no deaths during the conduct of the study.

12.3.1.2 Other Serious Adverse Events

There were no other serious AEs during the conduct of the study.

12.3.1.3 Other Significant Adverse Events

There were eight (08) significant AEs reported during the study. The subjects were withdrawn from the study on medical grounds. The subjects were treated appropriately and were followed up until resolution of their AEs. The causality assessment was judged as unlikely related for five (05) AEs, as possibly related for two (02) AEs and as not related for one (01) AE.

A listing of the significant AEs is given in Section 14.3.2 (Listings of Deaths, Other Serious and Other Significant Adverse Events).

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse events

There were no deaths or serious adverse events during the conduct of the study. However, eight (08) significant AEs were reported during the conduct of the study.

Subject No. [redacted] (Pyrexia and Headache)

The subject had complaint of fever and headache since approximately [redacted] He had no other complaints. The adverse events were gradual at onset, continuous in occurrence and mild in severity.

He was withdrawn from the study on medical grounds. He was treated appropriately and was followed up till resolution of his AEs. His AEs were resolved since approximately [redacted]

The adverse events were mild in nature and the relationship of the adverse events to the study drug was considered to be unlikely related.

Subject No. [redacted] (Pyrexia and Headache)

The subject had complaint of fever and headache since approximately [redacted] He had no other complaints. The adverse events were gradual at onset, continuous in occurrence and mild in severity.

He was withdrawn from the study on medical grounds. He was treated appropriately and was followed up till resolution of his AEs. His AEs were resolved since approximately [redacted].

The adverse events were mild in nature and the relationship of the adverse events to the study drug was considered to be possibly related.

Subject No. [redacted] (Thrombophlebitis superficial)

The subject reported to the facility with complaint of pain and mild swelling at the cannulation site over left forearm since approximately [redacted]. He had no other complaints. The adverse event was gradual at onset, continuous in occurrence and mild in severity.

He was withdrawn from the study on medical grounds. He was treated appropriately and was followed up till resolution of his AE. His AE was resolved since approximately [redacted]

The adverse event was mild in nature and the relationship of the adverse event to the study drug was considered as not related.

Subject No. [redacted] (Pyrexia and Headache)

The subject had complaint of fever and headache since approximately [redacted] He had no other complaints. The adverse events were gradual at onset, continuous in occurrence and mild in severity.

He was withdrawn from the study on medical grounds. He was treated appropriately and was followed up till resolution of his AEs. His AEs were resolved since approximately [redacted].

The adverse events were mild in nature and the relationship of the adverse events to the study drug was considered to be unlikely related.

Subject No. [redacted] (Pain in Jaw)

The subject had complaint of pain and swelling over right-side jaw near his chin since approximately [redacted] He had no other associated complaints. The adverse event was gradual at onset, continuous in occurrence and mild in severity.

He was withdrawn from the study on medical grounds. He was treated appropriately and was followed up till resolution of his AE. His AE was resolved since approximately [redacted].

The adverse event was mild in nature and the relationship of the adverse event to the study drug was considered as unlikely related.

The significant AEs have been narrated in Section 14.3.3 (Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events).

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse events

There were no deaths or serious adverse events during the conduct of the study. However, eight (08) significant AEs were reported during the conduct of the study.

Five (05) AEs occurred after administration of Test Product-T and three (03) AEs occurred after administration of Reference Product-R.

All the AEs were mild in nature. The relationship of the adverse events to the study drug was considered to be unlikely related for five (05) AEs, possibly related for two (02) AEs and not related for one (01) AE.

The significant AEs have been listed in Section 14.3.2 (Listing of Deaths, Other serious and Significant Adverse Events) and narrated in Section 14.3.3 (Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events).

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Subjects (16.2.8) and Each Abnormal Laboratory Values (14.3.4)

All the subjects underwent a pre-enrolment laboratory parameters evaluation including tests for hematology, biochemistry urine analysis and immunology. The laboratory reports were reviewed by a physician and were found to be clinically acceptable (including all the out of reference range reports) for all the subjects.

The post-study safety assessments included tests for hematology and biochemistry (except random glucose, sodium, potassium and chloride). The laboratory reports were reviewed by a physician and were found to be clinically acceptable (including all the out of reference range reports) for all the subjects except for Subject Nos. [redacted] and [redacted] Subject No. [redacted] had abnormal laboratory values (Increase in alanine aminotransferase and aspartate aminotransferase) and Subject No. [redacted] had abnormal laboratory value (Increase in alanine aminotransferase) during post-study safety assessment. However, they did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, the abnormal values were considered as clinically significant, adverse events were recorded for the same and the subjects were considered to be lost to follow-up.

Moreover, Subject Nos. [redacted] and [redacted] did not report for their post-study safety assessment and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

The values of all the laboratory parameters in the study are presented in Appendix No. 16.2.8 (Listing of individual laboratory measurements by subject, when required by regulatory authorities).

12.4.2 Evaluation of Each Laboratory Parameter

All the laboratory parameters were measured in accordance with the SOPs and were authenticated by the pathologist. The laboratory parameters obtained during the conduct of the study were evaluated by the physician.

12.4.2.1 Laboratory Values Over Time

This section is not applicable.

12.4.2.2 Individual Subject Changes

This section is not applicable.

12.4.2.3 Individual Clinically Significant Abnormalities

Subject No. [redacted] had abnormal laboratory values (Increase in alanine aminotransferase and aspartate aminotransferase) and Subject No. [redacted] had abnormal laboratory value (Increase in alanine aminotransferase) during post-study safety assessment. However, they did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, the abnormal values were considered as clinically significant, adverse events were recorded for the same and the subjects were considered to be lost to follow-up.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs

Sitting blood pressure and radial pulse rate were recorded during each clinical examination, at -24 hours, at pre-dose (0.000 hours) and at 01, 02, 06 and 12 hours after administration of IMP in each period. Oral body temperature was measured at the time of screening, after check-in and before check-out in each period.

None of the subjects had any clinically significant abnormalities.

ECG

12-lead ECG was recorded at screening and at 03 hours post-dose in each period.

None of the subjects had any clinically significant abnormalities.

Other safety evaluations

Subjects were questioned for well-being at the time of clinical examination and during vital signs examination in each period.

None of the subjects had any clinically significant abnormalities.

12.6 SAFETY CONCLUSION

In general, the clinical portion of the study was completed with seventeen (17) AEs, out of which eight (08) AEs were significant. The investigational products were well tolerated by healthy subjects, as a single dose administration. There were no deaths or serious AEs during the conduct of the study.

There were no clinically significant findings in the vital signs assessment, 12-lead ECG recording or in the laboratory tests in any of the subjects in the study except for Subject Nos. [redacted] and [redacted] They had abnormal laboratory values during post-study safety assessment. However, they did not report for their post-study safety assessment follow-up and were not traceable even after several attempts. Hence, the abnormal values were considered as clinically significant, adverse events were recorded for the same and the subjects were considered to be lost to follow-up.

Moreover, Subject Nos. [redacted], [redacted], [redacted] and [redacted] did not report for their post-study safety assessment and were not traceable even after several attempts. Hence, they were considered as lost to follow-up.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

13.1 PHARMACOKINETIC

Based on the data analyzed from 116 subjects for Spironolactone, the pharmacokinetics was assessed for the comparison of Test Product-T vs. Reference Product-R.

The pharmacokinetic data were analyzed as per the statistical method defined in the protocol. As per approach specified in the protocol, the data of 116 subjects were analyzed using ANOVA model with the terms Group, Sequence, Sequence*Group, Subject (Sequence*Group), Formulation and Period(Group) as fixed effects.

Group and Subject(Sequence*Group) effects are found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Sequence effect is found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Spironolactone.

Sequence*Group effect is found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameter AUC_{0-t} and $AUC_{0-\infty}$ for Spironolactone.

Period(Group) effect is found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameter AUC_{0-t} for Spironolactone

All other ANOVA effects were found to be statistically insignificant (i.e. p-value > 0.05) for Spironolactone.

Overall conclusions:

The results of this study demonstrate that, the criteria used to assess bioequivalence between the test and reference formulations were fulfilled for Spironolactone.

The test to reference geometric least square means with corresponding 90% CI for ln-transformed pharmacokinetic parameter C_{max} and AUC_{0-t} was within the acceptance range of 80.00-125.00%.

Therefore, the Test Product-T is considered to be bioequivalent to the Reference Product-R under fed condition.

13.2 SAFETY

Seventeen (17) adverse events were reported by nine (09) of the 130 subjects, who received at least one dose of the study drug (safety population). The breakdown by treatment group is as follows:

Ten (10) AEs were reported by 4.03% (N=05) of the 124 subjects who received Treatment-R and seven (07) AEs were reported by 3.28% (N=04) of the 122 subjects who received Treatment-T.

The causality assessment was judged as possibly related for eleven (11) AEs, as unlikely related for five (05) AEs and as not related for one (01) AE.

Upon conclusion of the clinical portion of the study, the results from all subjects, who completed post-study procedures including laboratory tests, ECG recording and vital signs measurements and confirmed the absence of significant changes in the subjects' state of health.

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

14.1 Demographic Data

N = 130 (Subjects who were dosed in the study)

Parameters	Age (Years)	Height (cm)	Weight (kg)	BMI Value (kg/m^2)
Mean	30.8	166.46	63.465	22.845
±SD	5.92	5.855	10.2988	3.1376

N = 116 (Subjects included in BE evaluation)

Parameters	Age (Years)	Height (cm)	Weight (kg)	BMI Value (kg/m^2)
Mean	30.7	166.44	63.167	22.734
±SD	5.79	6.018	10.3156	3.0808

14.2 Pharmacokinetic Data
14.2.1 Plasma Spironolactone data
Table No. 14.2.1.1
Summary Statistics for Pharmacokinetic Parameters of Spironolactone
Spironolactone 100 mg film coated tablets
[Excluding Subject No. [redacted] (Period - I, R)]
Dosing: Single Oral Dose; Condition: Fed; Population: Healthy Subjects

Measures		Tmax (h)	Cmax (ng/mL)	AUC0-t (ng.h/mL)	AUC0-inf (ng.h/mL)
Test Formulation-T					
N		116	116	116	115
Mean		2.340	148.736	381.047	396.496
SD		1.0154	68.0385	148.6725	149.5979
CV(%)		43.4	45.7	39.0	37.7
Geometric Mean		2.139	131.855	343.445	370.457
Reference Formulation-R					
N		115	115	115	115
Mean		2.457	149.063	368.610	380.453
SD		1.1538	64.2997	135.0201	139.2814
CV(%)		47.0	43.1	36.6	36.6
Geometric Mean		2.238	135.364	345.313	356.396
ANOVA p-value					
ln-transformed	Group	-	0.0013	<0.0001	0.0266
	Sequence	-	0.0428	<0.0001	0.1222
	Group*Sequence	-	0.3779	<0.0001	0.0146
	Formulation	-	0.7683	0.0869	0.0901
	Period(Group)	-	0.4163	0.0491	0.0636
	Subject(Group*Sequence)	-	<0.0001	<0.0001	<0.0001
Geometric Least Squares Means					
ln-transformed	Test-T	-	132.093	343.539	369.987
	Reference-R	-	130.503	330.098	355.668
Ratio of Geometric Least Squares Means(%)(T/R)					
ln-transformed		-	101.2	104.1	104.0
Intra Subject Variability (%)					
ln-transformed		-	31.8	17.6	17.6
90% Confidence Interval(T Vs. R)					
ln-transformed	Lower	-	94.56	100.16	100.12
	Upper	-	108.34	108.14	108.09
	Power(%)	-	100.0	100.0	100.0
Bioequivalence		-	Yes	Yes	N/AP

Table No. 14.2.1.2
Summary Statistics for Pharmacokinetic Parameters of Spironolactone
Spironolactone 100 mg film coated tablets
[Including Subject No. [redacted] (Period - I, R)]
Dosing: Single Oral Dose; Condition: Fed; Population: Healthy Subjects

Measures	Tmax (h)	Cmax (ng/mL)	AUC0-t (ng.h/mL)	AUC0-inf (ng.h/mL)
Test Formulation-T				
N	116	116	116	115
Mean	2.340	148.736	381.047	396.496
SD	1.0154	68.0385	148.6725	149.5979
CV(%)	43.4	45.7	39.0	37.7
Geometric Mean	2.139	131.855	343.445	370.457
Reference Formulation-R				
N	115	116	116	115
Mean	2.457	147.778	365.432	380.453
SD	1.1538	65.4985	138.7199	139.2814
CV(%)	47.0	44.3	38.0	36.6
Geometric Mean	2.238	135.364	345.313	356.396
ANOVA p-value				
ln-transformed Group	-	0.0013	<0.0001	0.0266
Sequence	-	0.0428	<0.0001	0.1222
Group*Sequence	-	0.3779	<0.0001	0.0146
Formulation	-	0.7683	0.0869	0.0901
Period(Group)	-	0.4163	0.0491	0.0636
Subject(Group*Sequence)	-	<0.0001	<0.0001	<0.0001
Geometric Least Squares Means				
ln-transformed Test-T	-	132.093	343.539	369.987
Reference-R	-	130.503	330.098	355.668
Ratio of Geometric Least Squares Means(%)(T/R)				
ln-transformed	-	101.2	104.1	104.0
Intra Subject Variability (%)				
ln-transformed	-	31.8	17.6	17.6
90% Confidence Interval(T Vs. R)				
ln-transformed Lower	-	94.56	100.16	100.12
Upper	-	108.34	108.14	108.09
Power(%)	-	100.0	100.0	100.0

Note: N =115 subjects were considered in all statistical calculations of Cmax and AUC0-t for Reference formulations except mean, SD and %CV.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	RT	2.000	2.500	94.487	57.315	164.9	184.958	147.527	125.4	189.231	150.304	125.9
	TR	3.500	2.500	176.358	205.979	85.6	646.043	710.441	90.9	659.488	722.852	91.2
	TR	3.500	2.000	69.351	141.308	49.1	241.801	316.591	76.4	245.637	325.665	75.4
	RT	1.750	0.750	84.597	159.238	53.1	231.758	265.077	87.4	237.029	275.533	86.0
	RT	2.250	3.000	158.376	286.244	55.3	533.168	578.529	92.2	542.331	590.507	91.8
	TR	2.750	2.000	292.242	296.577	98.5	603.609	617.211	97.8	610.166	622.199	98.1
	RT	2.250	2.750	216.074	140.537	153.7	555.381	404.431	137.3	564.439	410.160	137.6
	TR	2.500	1.750	289.861	173.937	166.6	606.767	540.258	112.3	618.560	552.177	112.0
	TR	1.500	2.500	312.383	119.063	262.4	581.107	319.102	182.1	588.261	322.695	182.3
	RT	3.500	3.000	354.977	316.083	112.3	872.288	827.023	105.5	899.477	856.093	105.1
	TR	4.000	4.017	91.108	80.335	113.4	342.693	257.677	133.0	351.720	266.366	132.0
	RT	3.500	3.500	74.780	56.818	131.6	299.032	197.635	151.3	303.881	204.156	148.8
	TR	2.500	1.500	115.754	242.703	47.7	334.829	414.190	80.8	354.120	423.359	83.6
	TR	1.000	1.000	159.171	148.137	107.4	254.250	231.402	109.9	261.277	237.058	110.2
	RT	2.250	2.000	97.819	93.917	104.2	158.195	240.178	65.9	165.160	250.878	65.8
	RT	1.500	1.750	226.874	189.453	119.8	435.473	400.680	108.7	446.674	412.927	108.2
	TR	1.250	1.000	179.069	282.742	63.3	373.524	548.049	68.2	381.493	555.355	68.7
	TR	1.250	1.500	124.269	150.242	82.7	282.524	305.623	92.4	290.825	321.059	90.6
	TR	3.000	2.750	107.945	103.983	103.8	385.635	192.706	200.1	394.718	196.597	200.8
	RT	2.000	3.517	271.300	112.931	240.2	788.958	479.307	164.6	806.757	498.856	161.7
	RT	1.500	2.000	76.262	65.912	115.7	202.368	210.979	95.9	208.351	213.948	97.4

Contd.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	TR	2.000	2.000	59.437	87.738	67.7	163.315	182.004	89.7	171.275	187.323	91.4
	TR	5.000	2.500	71.924	176.845	40.7	347.936	385.679	90.2	354.503	391.307	90.6
	RT	4.000	2.000	83.716	176.919	47.3	332.881	420.915	79.1	352.563	444.483	79.3
	TR	2.500	6.000	204.495	100.983	202.5	612.400	489.186	125.2	657.065	523.044	125.6
	RT	3.000	3.500	121.304	141.222	85.9	405.679	384.072	105.6	413.276	392.026	105.4
	TR	1.500	1.500	194.532	318.485	61.1	554.340	542.138	102.3	568.059	563.652	100.8
	RT	1.533	1.250	158.381	160.830	98.5	284.147	285.546	99.5	289.200	292.148	99.0
	TR	1.250	1.750	141.578	117.723	120.3	251.880	226.593	111.2	257.922	234.287	110.1
	TR	1.750	1.750	101.905	76.768	132.7	407.340	356.016	114.4	431.394	366.013	117.9
	RT	3.000	2.750	67.729	63.008	107.5	214.545	185.277	115.8	217.833	195.810	111.2
	TR	1.250	3.000	182.497	132.287	138.0	496.683	462.155	107.5	511.675	480.980	106.4
	RT	1.250	2.750	197.933	104.688	189.1	363.140	262.448	138.4	370.642	266.444	139.1
	RT	1.017	2.267	288.600	163.910	176.1	456.183	391.592	116.5	465.986	395.644	117.8
	TR	2.500	2.000	142.405	133.290	106.8	319.581	397.843	80.3	329.560	413.895	79.6
	RT	1.750	2.250	116.779	291.840	40.0	337.694	598.590	56.4	347.079	616.681	56.3
	TR	2.750	4.000	77.461	49.416	156.8	278.551	292.450	95.2	284.461	298.498	95.3
	TR	4.000	2.000	136.476	145.170	94.0	406.226	537.198	75.6	432.688	572.322	75.6
	RT	3.533	2.000	76.208	113.730	67.0	198.042	223.332	88.7	205.165	226.077	90.8
	TR	1.250	1.750	120.035	145.877	82.3	288.276	286.969	100.5	301.091	298.078	101.0
	RT	6.000	6.000	95.865	139.997	68.5	382.271	440.000	86.9	415.918	450.698	92.3
	RT	3.000	2.500	87.346	112.585	77.6	227.768	258.040	88.3	232.410	262.217	88.6

Contd.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	TR	2.750	3.500	356.592	239.718	148.8	835.885	558.786	149.6	878.210	590.970	148.6
	RT	1.500	1.250	94.211	141.042	66.8	181.046	264.224	68.5	184.312	271.447	67.9
	TR	2.000	2.000	194.610	122.223	159.2	507.305	313.480	161.8	514.334	319.098	161.2
	RT	1.500	1.750	212.614	138.096	154.0	410.196	273.062	150.2	429.671	292.111	147.1
	TR	1.500	1.750	199.455	131.972	151.1	340.433	285.366	119.3	362.708	305.169	118.9
	RT	3.000	4.500	138.492	187.040	74.0	591.767	590.276	100.3	609.048	612.604	99.4
	TR	2.000	2.250	109.478	162.556	67.3	273.239	328.519	83.2	276.993	338.461	81.8
	TR	3.500	3.500	119.293	125.167	95.3	432.403	318.006	136.0	438.222	325.766	134.5
	TR	2.250	2.250	177.196	214.357	82.7	609.831	651.023	93.7	635.086	687.014	92.4
	RT	2.000	1.750	107.753	181.837	59.3	311.352	327.299	95.1	330.511	337.212	98.0
	TR	3.000	2.000	172.474	157.869	109.3	407.401	340.612	119.6	419.767	358.854	117.0
	RT	2.750	1.750	136.178	230.376	59.1	387.888	393.026	98.7	399.978	407.366	98.2
	TR	3.000	2.500	135.002	135.664	99.5	262.158	282.737	92.7	269.608	299.655	90.0
	RT	2.000	2.750	244.050	207.273	117.7	475.599	572.251	83.1	482.888	578.078	83.5
	RT	2.250	2.000	112.952	119.597	94.4	351.600	341.324	103.0	382.093	357.897	106.8
	TR	2.500	2.000	100.483	185.979	54.0	351.315	370.754	94.8	360.148	382.481	94.2
	RT	4.000	1.750	105.208	174.846	60.2	415.522	453.287	91.7	424.621	464.037	91.5
	RT	4.000	4.500	88.587	90.972	97.4	398.160	370.619	107.4	409.049	385.036	106.2
	TR	1.000	0.750	119.057	147.351	80.8	208.876	223.162	93.6	227.038	241.763	93.9
	RT	0.750	1.000	68.002	126.356	53.8	166.042	225.360	73.7	171.558	235.088	73.0
	RT	1.500	1.750	283.037	294.525	96.1	603.890	657.020	91.9	613.909	673.539	91.1

Contd.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	TR	1.500	2.250	242.692	141.607	171.4	445.804	389.824	114.4	453.037	394.248	114.9
	RT	1.750	2.000	235.285	236.075	99.7	605.110	529.087	114.4	637.645	540.667	117.9
	TR	1.750	1.500	128.829	222.936	57.8	291.136	410.720	70.9	304.707	438.275	69.5
	RT	3.000	2.250	117.347	107.027	109.6	351.371	305.401	115.1	360.148	309.298	116.4
	TR	1.250	2.000	142.394	132.973	107.1	259.341	336.696	77.0	265.335	342.469	77.5
	RT	2.783	3.500	89.014	69.985	127.2	240.831	263.346	91.5	264.165	273.566	96.6
	TR	2.250	4.000	95.199	119.530	79.6	255.483	273.654	93.4	260.885	288.377	90.5
	RT	1.500	1.750	150.736	145.774	103.4	366.081	431.054	84.9	376.274	441.851	85.2
	RT	1.500	1.500	185.787	166.372	111.7	496.868	576.422	86.2	506.368	596.071	85.0
	TR	1.750	1.500	155.049	133.045	116.5	335.762	304.608	110.2	351.541	322.657	109.0
	TR	2.767	1.750	174.735	130.415	134.0	516.800	497.337	103.9	537.740	513.271	104.8
	RT	1.750	5.000	223.572	64.224	348.1	561.998	330.897	169.8	574.333	342.343	167.8
	TR	1.000	6.000	83.203	55.024	151.2	397.058	244.828	162.2	403.390	251.969	160.1
	RT	3.000	2.500	123.693	152.062	81.3	313.884	516.135	60.8	320.268	525.220	61.0
	TR	1.750	2.250	158.543	127.155	124.7	288.940	383.838	75.3	292.460	391.793	74.6
	RT	2.250	2.000	180.790	128.371	140.8	340.752	240.529	141.7	348.043	243.950	142.7
	TR	2.500	4.000	159.745	90.665	176.2	465.035	261.133	178.1	472.718	269.808	175.2
	RT	2.500	2.250	100.591	140.095	71.8	289.550	318.211	91.0	293.079	323.683	90.5
	TR	2.767	1.750	145.297	252.626	57.5	412.958	406.155	101.7	420.028	413.472	101.6
	TR	2.000	2.750	143.271	146.990	97.5	355.706	388.887	91.5	373.069	395.702	94.3
	RT	1.267	2.500	179.713	94.186	190.8	403.387	279.896	144.1	416.612	288.479	144.4

Contd.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	RT	4.500	1.500	218.917	244.757	89.4	709.850	517.332	137.2	727.327	537.007	135.4
	TR	2.000	1.250	140.475	181.103	77.6	382.465	310.046	123.4	398.587	314.712	126.7
	TR	1.500	1.500	115.260	140.249	82.2	310.483	295.423	105.1	315.244	302.879	104.1
	RT	2.000	2.500	133.213	93.278	142.8	314.066	297.406	105.6	331.881	313.011	106.0
	RT	3.500	-	1.971	-	-	2.073	-	-	-	-	-
	TR	2.000	2.250	187.514	108.386	173.0	380.728	317.886	119.8	397.878	325.286	122.3
	TR	2.250	2.750	268.697	177.934	151.0	444.513	420.106	105.8	456.630	443.342	103.0
	RT	3.000	2.250	112.044	148.143	75.6	318.457	297.038	107.2	322.631	301.252	107.1
	RT	0.817	1.250	318.934	283.563	112.5	430.006	433.012	99.3	436.054	441.378	98.8
	TR	1.250	1.750	184.430	131.838	139.9	347.913	308.957	112.6	357.830	312.736	114.4
	RT	1.500	3.000	81.829	35.138	232.9	207.145	125.131	165.5	213.181	129.214	165.0
	TR	3.000	2.750	108.315	189.564	57.1	433.194	508.143	85.3	452.421	518.776	87.2
	RT	2.750	6.000	113.786	87.439	130.1	375.899	315.500	119.1	383.128	325.826	117.6
	RT	3.500	6.000	126.599	62.335	203.1	274.453	237.390	115.6	280.236	246.615	113.6
	TR	1.750	1.250	141.249	208.348	67.8	448.407	508.930	88.1	463.439	526.186	88.1
	TR	2.000	1.750	101.478	179.281	56.6	335.450	383.935	87.4	346.072	423.821	81.7
	RT	2.250	4.000	106.197	93.726	113.3	375.078	292.329	128.3	394.410	300.899	131.1
	TR	3.000	2.500	106.877	73.067	146.3	326.901	374.841	87.2	334.311	386.274	86.5
	RT	1.000	1.500	210.299	174.886	120.2	358.543	343.365	104.4	363.722	357.720	101.7
	TR	2.250	5.000	60.358	44.833	134.6	215.359	222.076	97.0	226.366	230.479	98.2
	TR	3.500	2.250	207.903	151.742	137.0	448.402	425.027	105.5	465.867	441.093	105.6

Contd.

Table No. 14.2.1.3

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R												
Subject	Sequence	Tmax (h)		Cmax (ng/mL)			AUC0-t (ng.h/mL)			AUC0-inf (ng.h/mL)		
		Formulation		Formulation			Formulation			Formulation		
		T	R	T	R	(T/R) %	T	R	(T/R) %	T	R	(T/R) %
[redacted]	RT	2.500	1.500	169.403	103.971	162.9	376.847	218.687	172.3	388.351	225.063	172.6
	RT	3.000	1.250	181.107	297.751	60.8	532.294	589.861	90.2	545.639	595.956	91.6
	TR	6.000	2.750	97.134	162.538	59.8	525.349	654.749	80.2	571.118	684.381	83.5
	TR	2.500	2.000	64.338	151.903	42.4	209.441	335.221	62.5	213.668	344.402	62.0
	RT	1.000	2.000	210.864	233.562	90.3	680.560	488.139	139.4	705.590	500.169	141.1
	TR	1.500	2.000	58.186	51.850	112.2	145.993	154.092	94.7	150.473	156.858	95.9
	RT	1.250	2.000	200.504	139.935	143.3	331.201	262.919	126.0	340.871	272.956	124.9
	TR	1.250	1.750	148.224	117.773	125.9	331.604	368.776	89.9	341.959	378.797	90.3
	RT	1.750	4.000	133.486	102.659	130.0	415.701	245.880	169.1	422.092	254.532	165.8
	TR	3.500	1.750	70.148	157.188	44.6	241.422	322.409	74.9	247.603	332.991	74.4
	RT	3.500	3.517	83.768	64.825	129.2	212.647	174.023	122.2	221.497	176.358	125.6
N		116	115	116	115	-	116	115	-	115	115	-
Mean		2.340	2.457	148.736	149.063	-	381.047	368.610	-	396.496	380.453	-
SD		1.0154	1.1538	68.0385	64.2997	-	148.6725	135.0201	-	149.5979	139.2814	-
Min		0.750	0.750	1.971	35.138	-	2.073	125.131	-	150.473	129.214	-
Median		2.250	2.000	135.590	140.537	-	357.124	335.221	-	373.069	342.469	-
Max		6.000	6.000	356.592	318.485	-	872.288	827.023	-	899.477	856.093	-
CV%		43.4	47.0	45.7	43.1	-	39.0	36.6	-	37.7	36.6	-
Geometric Mean		2.139	2.238	131.855	135.364	-	343.445	345.313	-	370.457	356.396	-
Note : Subject excluded from statistical analysis are presented in Table No. 14.2.1.4.												

Contd.

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	RT	2.258	1.848	0.194	0.350	8.000	2.750	12.000	16.000	3.564	1.980
	TR	2.039	1.717	0.125	0.121	10.000	12.000	24.000	24.000	5.534	5.739
	TR	1.561	2.786	0.262	0.177	10.000	7.000	16.000	16.000	2.648	3.909
	RT	2.224	3.795	0.144	0.147	10.017	7.000	16.000	12.000	4.826	4.725
	RT	1.690	2.028	0.109	0.099	12.000	12.000	24.000	24.000	6.351	6.983
	TR	1.075	0.802	0.138	0.157	12.000	7.000	24.000	24.000	5.023	4.416
	RT	1.605	1.397	0.112	0.147	12.000	7.000	24.000	24.000	6.192	4.727
	TR	1.907	2.159	0.104	0.103	12.000	10.000	24.000	24.000	6.662	6.706
	TR	1.216	1.113	0.111	0.251	10.000	2.750	24.000	24.000	6.261	2.760
	RT	3.023	3.396	0.087	0.090	12.000	10.000	24.000	24.000	7.925	7.711
	TR	2.567	3.262	0.117	0.100	10.000	12.000	24.000	24.000	5.931	6.931
	RT	1.596	3.194	0.158	0.189	8.000	10.000	24.017	16.000	4.382	3.663
	TR	5.448	2.166	0.132	0.132	10.000	7.000	16.000	24.000	5.240	5.252
	TR	2.690	2.386	0.211	0.158	6.000	10.000	12.000	16.000	3.289	4.376
	RT	4.217	4.265	0.178	0.143	7.000	7.000	12.000	16.000	3.884	4.863
	RT	2.508	2.966	0.104	0.081	7.000	10.000	24.000	24.000	6.693	8.574
	TR	2.089	1.316	0.176	0.123	6.000	12.000	16.000	24.017	3.946	5.621
	TR	2.855	4.808	0.108	0.058	7.000	12.000	24.000	24.017	6.429	11.928
	TR	2.301	1.979	0.085	0.298	12.000	7.017	24.000	12.000	8.134	2.327
	RT	2.206	3.919	0.121	0.090	6.000	10.000	24.000	24.000	5.730	7.717
	RT	2.871	1.388	0.154	0.344	7.000	2.250	16.000	16.000	4.512	2.016

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	TR	4.648	2.839	0.138	0.177	7.000	7.000	16.000	16.000	5.025	3.917
	TR	1.852	1.438	0.137	0.142	12.000	8.000	24.000	24.000	5.047	4.871
	RT	5.583	5.302	0.084	0.076	12.000	12.000	24.017	24.000	8.293	9.172
	TR	6.798	6.473	0.075	0.109	12.000	8.000	24.000	24.000	9.264	6.365
	RT	1.838	2.029	0.199	0.180	8.000	10.000	16.000	16.000	3.476	3.850
	TR	2.415	3.817	0.097	0.062	12.000	12.000	24.000	24.000	7.155	11.137
	RT	1.747	2.260	0.188	0.156	6.000	8.000	16.000	16.000	3.695	4.430
	TR	2.342	3.284	0.138	0.137	4.500	10.000	24.000	16.000	5.009	5.050
	TR	5.576	2.731	0.105	0.177	10.000	10.000	16.000	16.000	6.593	3.908
	RT	1.509	5.379	0.317	0.072	3.500	10.000	16.017	24.017	2.185	9.568
	TR	2.930	3.914	0.088	0.070	10.000	12.017	24.000	24.000	7.861	9.833
	RT	2.024	1.500	0.123	0.350	6.017	3.000	24.000	16.000	5.615	1.979
	RT	2.104	1.024	0.152	0.219	6.000	7.000	16.017	16.000	4.557	3.170
	TR	3.028	3.878	0.090	0.059	8.000	12.000	24.017	24.017	7.677	11.837
	RT	2.704	2.934	0.175	0.076	6.017	12.017	16.000	24.000	3.971	9.120
	TR	2.078	2.026	0.306	0.147	3.000	8.000	16.000	24.000	2.266	4.711
	TR	6.116	6.137	0.099	0.099	7.000	7.000	24.017	24.017	7.003	6.970
	RT	3.472	1.214	0.257	0.368	7.000	2.250	12.000	16.050	2.694	1.881
	TR	4.256	3.727	0.073	0.085	12.000	8.000	24.000	24.000	9.551	8.131
	RT	8.090	2.374	0.048	0.134	12.000	10.000	24.000	24.000	14.586	5.171
	RT	1.997	1.593	0.193	0.206	7.000	8.000	16.000	16.000	3.583	3.366

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	TR	4.819	5.446	0.086	0.077	10.000	12.000	24.000	24.000	8.091	9.046
	RT	1.772	2.661	0.263	0.144	8.000	10.000	12.000	16.000	2.638	4.828
	TR	1.367	1.760	0.115	0.203	12.000	7.000	24.000	16.000	6.030	3.407
	RT	4.533	6.521	0.066	0.048	10.000	12.000	24.000	24.000	10.464	14.494
	TR	6.141	6.489	0.045	0.047	12.017	12.000	24.000	24.000	15.348	14.888
	RT	2.837	3.645	0.109	0.103	12.000	10.000	24.000	24.000	6.348	6.726
	TR	1.355	2.937	0.221	0.078	8.000	12.000	16.000	24.000	3.143	8.846
	TR	1.328	2.382	0.146	0.108	10.000	10.000	24.000	24.000	4.734	6.396
	TR	3.977	5.239	0.091	0.072	10.000	12.000	24.017	24.000	7.628	9.688
	RT	5.797	2.940	0.057	0.089	12.000	12.000	24.000	24.017	12.161	7.799
	TR	2.946	5.083	0.080	0.048	10.000	12.000	24.017	24.000	8.711	14.368
	RT	3.023	3.520	0.097	0.122	12.000	10.000	24.000	16.000	7.120	5.696
	TR	2.763	5.646	0.177	0.063	7.000	10.000	16.000	24.000	3.927	10.990
	RT	1.510	1.008	0.142	0.172	7.017	7.000	24.000	24.017	4.887	4.027
	RT	7.980	4.631	0.041	0.067	12.000	12.000	24.000	24.000	16.815	10.415
	TR	2.453	3.066	0.100	0.076	8.000	12.017	24.017	24.000	6.910	9.153
	RT	2.143	2.317	0.162	0.119	7.000	7.000	24.000	24.000	4.273	5.817
	RT	2.662	3.744	0.133	0.118	8.000	10.000	24.000	24.017	5.231	5.868
	TR	8.000	7.694	0.073	0.067	10.000	10.000	16.000	16.000	9.480	10.373
	RT	3.215	4.138	0.152	0.135	6.000	6.000	16.000	16.000	4.568	5.116
	RT	1.632	2.453	0.123	0.083	6.000	12.000	24.000	24.017	5.651	8.370

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	TR	1.597	1.122	0.118	0.253	7.000	7.000	24.000	16.000	5.878	2.740
	RT	5.102	2.142	0.066	0.126	12.000	7.000	24.000	24.017	10.538	5.505
	TR	4.454	6.287	0.129	0.062	6.000	10.000	16.000	24.017	5.384	11.202
	RT	2.437	1.260	0.215	0.355	6.000	2.517	16.000	16.000	3.229	1.955
	TR	2.259	1.686	0.165	0.133	6.000	6.000	16.000	24.000	4.210	5.224
	RT	8.833	3.736	0.046	0.091	12.000	12.000	24.000	24.000	15.229	7.577
	TR	2.070	5.106	0.326	0.060	2.500	12.000	16.017	24.000	2.126	11.597
	RT	2.709	2.444	0.085	0.096	10.000	10.000	24.000	24.017	8.149	7.196
	RT	1.876	3.296	0.122	0.097	12.000	10.000	24.000	24.000	5.701	7.134
	TR	4.489	5.594	0.115	0.107	10.000	10.033	16.017	16.000	6.050	6.492
	TR	3.894	3.104	0.081	0.094	12.000	12.000	24.000	24.017	8.513	7.412
	RT	2.148	3.344	0.121	0.105	7.000	12.000	24.000	24.017	5.746	6.573
	TR	1.570	2.834	0.134	0.167	10.000	8.000	24.033	24.017	5.182	4.143
	RT	1.993	1.730	0.210	0.224	3.500	2.750	24.000	24.000	3.297	3.088
	TR	1.203	2.031	0.223	0.204	8.000	10.000	16.000	16.000	3.104	3.402
	RT	2.095	1.403	0.214	0.240	6.000	2.250	16.000	24.000	3.239	2.889
	TR	1.625	3.215	0.110	0.142	12.000	8.000	24.000	16.017	6.281	4.889
	RT	1.204	1.691	0.227	0.217	8.000	4.500	16.000	16.000	3.051	3.201
	TR	1.683	1.770	0.116	0.157	10.000	10.000	24.000	16.000	5.969	4.418
	TR	4.654	1.722	0.065	0.133	12.000	7.000	24.000	24.000	10.698	5.202
	RT	3.174	2.975	0.067	0.166	12.000	7.000	24.000	16.000	10.300	4.187

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	RT	2.403	3.664	0.115	0.104	10.000	6.000	24.000	24.000	6.012	6.636
	TR	4.045	1.483	0.069	0.209	12.000	2.500	24.000	24.000	10.049	3.314
	TR	1.510	2.462	0.343	0.146	1.750	7.000	16.000	16.000	2.022	4.746
	RT	5.368	4.985	0.060	0.079	12.000	10.000	24.000	24.000	11.573	8.794
	RT	-	-	-	-	-	-	-	-	-	-
	TR	4.310	2.275	0.122	0.202	10.000	8.000	16.000	16.000	5.674	3.433
	TR	2.653	5.241	0.104	0.080	7.000	8.000	24.000	23.983	6.676	8.645
	RT	1.294	1.399	0.257	0.344	7.000	7.000	16.017	12.000	2.693	2.015
	RT	1.387	1.895	0.198	0.100	8.000	12.000	16.000	24.017	3.502	6.911
	TR	2.772	1.208	0.162	0.236	7.000	2.000	16.000	24.000	4.280	2.933
	RT	2.831	3.160	0.179	0.233	6.000	8.017	16.000	12.000	3.881	2.976
	TR	4.250	2.050	0.088	0.131	12.000	12.000	24.000	24.000	7.900	5.310
	RT	1.887	3.169	0.106	0.113	12.000	12.000	24.000	24.000	6.559	6.118
	RT	2.064	3.741	0.223	0.099	7.000	12.000	16.000	24.000	3.103	7.019
	TR	3.244	3.279	0.104	0.086	10.000	12.000	24.000	24.000	6.670	8.017
	TR	3.069	9.411	0.114	0.033	7.000	12.000	24.000	24.000	6.075	20.850
	RT	4.901	2.848	0.074	0.204	8.000	4.517	24.000	24.033	9.331	3.392
	TR	2.217	2.960	0.109	0.100	12.000	12.000	24.000	24.000	6.373	6.909
	RT	1.424	4.013	0.209	0.160	5.000	8.000	16.000	12.000	3.309	4.339
	TR	4.862	3.646	0.130	0.094	10.000	10.000	16.000	24.000	5.313	7.382
	TR	3.749	3.642	0.095	0.106	10.000	7.000	24.000	24.000	7.297	6.512

Table No. 14.2.1.3 Contd.

Pharmacokinetic parameters of Spironolactone for Test Product-T and Reference Product-R											
Subject	Sequence	AUC_%Extrap_obs (%)		Lambda_z (1/h)		Lambda_z_lower (h)		Lambda_z_upper (h)		t1/2 (h)	
		Formulation		Formulation		Formulation		Formulation		Formulation	
		T	R	T	R	T	R	T	R	T	R
[redacted]	RT	2.962	2.833	0.151	0.167	10.000	7.000	16.000	16.000	4.593	4.146
	RT	2.446	1.023	0.202	0.132	7.000	10.000	16.000	24.000	3.436	5.235
	TR	8.014	4.330	0.066	0.106	12.000	8.000	24.017	24.017	10.446	6.527
	TR	1.978	2.666	0.311	0.091	2.750	12.000	16.000	24.000	2.226	7.621
	RT	3.547	2.405	0.069	0.088	12.000	12.000	24.000	24.017	10.093	7.874
	TR	2.977	1.764	0.224	0.425	8.000	2.250	12.000	12.000	3.096	1.630
	RT	2.837	3.677	0.123	0.104	7.000	10.000	16.000	16.017	5.619	6.664
	TR	3.028	2.645	0.130	0.092	8.000	10.000	16.000	24.000	5.317	7.517
	RT	1.514	3.399	0.126	0.145	7.000	10.000	24.000	16.017	5.496	4.778
	TR	2.496	3.178	0.176	0.098	8.000	8.000	16.000	24.017	3.941	7.108
	RT	3.995	1.324	0.110	0.356	10.000	8.017	16.000	12.000	6.324	1.948
N		115	115	115	115	115	115	115	115	115	115
Mean		3.064	3.097	0.139	0.143	8.796	8.847	20.454	20.978	6.115	6.270
SD		1.6829	1.5659	0.0649	0.0797	2.6486	2.9013	4.2970	4.2591	2.9038	3.1643
Min		1.075	0.802	0.041	0.033	1.750	2.000	12.000	12.000	2.022	1.630
Median		2.567	2.934	0.122	0.121	8.000	10.000	24.000	24.000	5.674	5.739
Max		8.833	9.411	0.343	0.425	12.017	12.017	24.033	24.033	16.815	20.850
CV%		54.9	50.6	46.6	55.9	30.1	32.8	21.0	20.3	47.5	50.5
Geometric Mean		2.703	2.740	0.126	0.125	8.305	8.162	19.964	20.485	5.518	5.549
Note : Subject excluded from statistical analysis are presented in Table No. 14.2.1.4.											

Table No. 14.2.1.4

Pharmacokinetic parameters of data excluded from statistical analysis for Spironolactone								
Subject	Period	Sequence	Formulation	Tmax (h)	Cmax (ng/mL)	AUC0-t (ng.h/mL)	AUC0-inf (ng.h/mL)	AUC_%Extrap_obs (%)
[redacted]	1	RT	R	1.750	80.011	195.344	205.070	4.743
	1	RT	R	3.000	158.307	325.005	344.547	5.672
	1	RT	R	1.750	94.696	290.408	293.638	1.100
	1	RT	R	2.000	243.433	380.211	385.559	1.387
	1	RT	R	2.000	187.687	356.820	369.063	3.317
	1	TR	T	2.000	153.579	256.238	267.336	4.151
	1	RT	R	1.500	150.152	307.199	332.062	7.488
	1	TR	T	1.000	208.740	409.350	422.002	2.998
	1	TR	T	1.250	220.126	476.650	486.481	2.021
	1	TR	T	2.250	140.606	391.261	405.864	3.598
	1	RT	R	1.500	135.594	287.239	295.134	2.675
	1	TR	T	2.500	103.256	175.428	178.875	1.927
	1	RT	R	2.750	198.552	444.666	468.061	4.998
	1	RT	R	-	0.000	0.000	-	-
	1	TR	T	4.500	76.623	241.412	248.916	3.014

Table No. 14.2.1.4

Subject	Period	Sequence	Formulation	Lambda_z (1/h)	Lambda_z_ lower (h)	Lambda_z_ upper (h)	t1/2 (h)
[redacted]	1	RT	R	0.101	10.000	16.000	6.886
	1	RT	R	0.066	12.000	24.000	10.436
	1	RT	R	0.353	2.000	16.000	1.966
	1	RT	R	0.219	7.000	16.000	3.171
	1	RT	R	0.124	10.000	16.000	5.609
	1	TR	T	0.192	7.000	12.000	3.603
	1	RT	R	0.094	7.000	16.000	7.371
	1	TR	T	0.291	2.767	12.000	2.381
	1	TR	T	0.204	5.000	16.000	3.394
	1	TR	T	0.085	8.000	24.000	8.169
	1	RT	R	0.199	4.517	16.000	3.479
	1	TR	T	0.287	7.000	12.000	2.411
	1	RT	R	0.072	12.000	24.000	9.687
	1	RT	R	-	-	-	-
	1	TR	T	0.113	10.000	24.000	6.126

Note 1: ^ subjects were withdrawn.

Note 2: Subject No. [redacted] (Period-I) excluded from statistical analysis as per protocol criteria 11.1.1 (d).

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	1.638	0.000	0.000	2.381	0.000	0.000	0.000	1.497	0.000	0.000
0.500	0.000	7.840	0.000	0.815	13.245	0.882	0.000	0.000	29.802	1.076	0.000
0.750	0.000	8.665	0.000	17.286	43.088	1.079	1.157	1.505	77.792	2.071	5.827
1.000	1.170	14.337	0.000	60.850	64.549	3.102	5.045	7.947	189.371	3.004	19.643
1.250	9.789	15.195	0.000	81.354	86.254	4.173	78.290	9.739	283.675	5.375	20.787
1.500	72.168	23.445	0.000	82.249	125.098	8.819	155.446	12.581	312.383	11.781	20.853
1.750	67.138	29.731	0.000	84.597	118.969	39.469	189.746	81.929	263.884	21.474	25.836
2.000	94.487	49.496	0.000	78.520	111.309	73.834	212.266	198.825	193.678	58.140	25.545
2.250	72.201	72.997	0.000	58.343	158.376	69.799	216.074	203.498	137.006	190.658	24.358
2.500	68.225	79.522	0.783	48.207	135.639	138.050	191.179	289.861	114.219	202.552	28.781
2.750	57.801	111.655	1.092	50.785	118.230	292.242	156.548	244.588	83.689	163.571	52.580
3.000	45.452	151.617	5.524	44.010	119.445	199.448	135.055	217.212	73.342	281.093	59.492
3.500	34.657	176.358	69.351	32.648	97.997	227.891	90.663	125.446	48.453	354.977	88.842
4.000	23.171	142.907	57.383	22.637	79.322	154.923	53.006	81.528	33.282	226.911	91.108
4.500	14.248	91.322	57.431	16.886	58.540	76.079	36.142	56.787	27.330	139.289	63.531
5.000	9.617	74.494	58.025	13.983	42.077	54.399	29.615	42.283	20.839	92.904	46.457
6.000	4.606	90.430	51.186	6.968	26.021	20.750	24.108	20.865	12.170	41.615	30.498
7.000	3.099	34.913	16.988	5.159	14.003	13.246	11.635	13.615	8.363	23.558	15.663
8.000	1.809	20.524	10.209	4.226	10.085	12.041	8.200	9.857	6.480	17.384	9.596
10.000	1.334	9.201	4.854	1.745	6.261	7.590	7.079	7.411	3.393	10.846	5.564
12.000	0.831	7.846	2.801	1.479	3.825	4.814	4.034	4.268	3.427	6.783	4.217
16.000	0.000	3.208	1.004	0.757	2.107	2.568	2.137	2.843	1.755	4.814	3.199
24.000	0.000	1.684	0.000	0.000	1.000	0.905	1.014	1.227	0.792	2.378	1.055

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	2.361	0.000	0.000	0.000	2.305	0.000	0.000	0.000
0.500	0.964	1.138	3.850	7.828	0.000	1.640	2.970	8.744	1.551	0.000	0.000
0.750	1.896	3.975	45.834	9.343	2.552	35.135	6.241	16.187	3.212	6.088	2.824
1.000	2.619	7.303	159.171	10.144	104.951	128.915	31.529	32.337	12.639	70.169	5.531
1.250	4.984	5.801	139.047	13.347	143.028	179.069	124.269	35.735	35.883	73.598	9.197
1.500	6.246	33.589	121.834	17.111	226.874	154.840	110.297	63.191	102.923	76.262	16.077
1.750	10.542	41.866	83.974	43.633	197.318	140.080	105.667	75.159	182.706	67.658	42.275
2.000	13.489	51.332	66.316	75.553	182.154	113.558	88.445	88.399	271.300	72.200	59.437
2.250	31.224	72.780	56.551	97.819	118.258	94.283	75.916	90.354	221.079	55.037	57.205
2.500	35.919	115.754	38.563	59.263	97.138	71.188	63.488	98.675	254.140	44.295	57.740
2.750	36.197	98.978	32.131	49.063	73.603	64.758	59.404	96.455	227.092	38.004	59.048
3.000	41.560	93.796	27.443	36.778	66.252	60.824	50.040	107.945	255.978	34.042	51.130
3.500	74.780	72.355	23.990	23.583	44.210	44.907	38.840	93.298	138.528	25.973	31.863
4.000	70.205	52.184	18.057	15.607	36.253	32.690	31.576	61.646	97.722	18.446	19.485
4.500	60.658	44.613	12.381	11.081	25.187	26.674	17.169	39.422	76.224	15.541	14.990
5.000	52.463	33.978	10.426	9.118	19.169	17.431	10.693	35.661	59.473	11.553	10.500
6.000	37.900	22.482	5.551	4.802	9.627	7.921	7.220	19.630	21.548	6.278	6.363
7.000	18.610	11.845	4.313	2.761	6.550	6.098	5.380	11.659	19.275	3.445	3.760
8.000	9.819	11.447	3.628	2.771	5.791	5.567	4.520	7.023	13.694	3.042	3.029
10.000	5.950	5.591	2.611	1.550	3.950	3.685	3.273	4.592	10.719	2.412	2.214
12.000	3.547	4.499	1.481	1.243	2.753	2.315	2.470	2.175	8.956	1.394	1.491
16.000	1.409	2.552	0.000	0.000	1.728	1.400	1.290	1.464	7.056	0.919	1.098
24.000	0.767	0.000	0.000	0.000	1.160	0.000	0.895	0.774	2.153	0.000	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.815	0.000	0.000	0.000	0.000	0.000	1.244	0.000
0.500	3.534	1.097	0.000	8.252	6.241	4.971	0.000	1.489	0.817	11.561	0.000
0.750	3.898	1.442	1.737	17.135	49.997	20.874	2.140	19.190	5.963	57.073	18.454
1.000	3.942	3.538	4.193	21.956	93.103	56.719	23.139	60.638	8.859	144.420	113.484
1.250	5.100	6.222	12.168	44.236	126.327	136.617	141.578	93.629	27.568	182.497	197.933
1.500	6.824	6.273	51.155	61.544	194.532	158.381	140.840	87.354	42.423	142.336	183.794
1.750	7.093	9.112	64.977	70.371	159.936	133.516	116.228	101.905	37.575	112.866	146.224
2.000	8.865	14.720	137.234	61.461	147.393	103.216	92.317	99.032	48.782	115.342	108.351
2.250	11.666	20.819	181.607	72.690	150.964	83.015	72.126	91.872	59.713	105.020	85.215
2.500	15.956	28.903	204.495	87.736	161.638	60.858	54.510	88.187	60.739	107.470	69.309
2.750	48.532	33.706	193.033	110.587	139.174	48.014	43.604	82.853	66.647	97.073	60.931
3.000	70.016	35.503	153.431	121.304	98.527	37.211	33.736	74.763	67.729	78.707	49.802
3.500	56.859	49.862	103.085	101.681	63.251	25.417	24.090	71.595	42.261	71.416	35.516
4.000	60.525	83.716	72.950	82.257	47.351	18.586	16.371	56.450	35.461	66.444	24.544
4.500	62.889	76.284	63.978	65.975	44.930	13.744	11.686	47.403	24.474	46.772	17.504
5.000	71.924	78.082	54.734	43.920	52.804	10.112	9.622	43.827	18.440	30.686	13.105
6.000	54.788	36.682	35.131	19.999	22.556	6.728	6.752	25.026	10.875	17.609	7.799
7.000	22.746	17.079	20.728	10.492	11.643	5.167	4.132	13.089	5.875	11.453	6.510
8.000	14.467	12.014	16.391	7.422	7.819	4.105	3.269	8.941	4.206	7.253	5.156
10.000	7.810	7.119	12.291	4.851	6.110	2.305	2.229	4.816	2.628	4.926	4.392
12.000	4.688	4.549	8.059	2.914	4.314	2.326	1.581	3.652	1.342	3.379	2.302
16.000	2.701	3.055	6.526	1.515	2.711	0.948	0.892	2.529	1.043	2.861	1.373
24.000	0.902	1.645	3.342	0.000	1.329	0.000	0.836	0.000	0.000	1.322	0.926

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	1.328	0.000	0.000	0.000	0.000
0.500	18.648	0.000	6.142	1.901	1.262	0.000	22.602	0.000	0.000	1.274	0.000
0.750	139.379	8.770	71.611	8.739	3.440	0.000	95.815	0.000	0.000	5.586	7.716
1.000	288.600	18.581	93.886	18.279	5.432	0.000	105.192	2.237	1.308	24.937	34.432
1.250	262.745	15.368	111.533	29.281	9.603	0.902	120.035	11.114	1.893	28.252	68.613
1.500	208.796	34.118	107.763	37.651	21.439	1.403	62.700	19.169	3.014	47.673	94.211
1.750	161.040	41.507	116.779	42.223	33.327	3.041	80.327	24.282	13.184	119.503	87.062
2.000	109.082	61.181	104.428	50.484	29.504	12.917	79.248	19.268	16.680	180.652	76.029
2.250	87.750	84.949	87.448	59.182	40.187	19.907	72.606	18.349	38.412	184.826	59.779
2.500	66.310	142.405	72.446	76.737	48.959	42.079	57.254	18.552	60.899	225.786	45.679
2.750	55.394	133.486	68.714	77.461	44.430	50.990	50.291	24.880	58.118	356.592	36.721
3.000	45.722	114.039	76.899	59.825	32.105	64.387	38.553	39.549	87.346	308.514	28.801
3.500	31.609	71.106	44.902	50.938	74.948	76.208	25.451	77.380	75.345	202.223	18.449
4.000	24.471	53.273	29.053	41.430	136.476	60.636	17.376	75.136	64.838	128.323	13.929
4.500	16.663	38.219	20.757	40.996	128.212	39.072	12.615	69.540	44.511	77.184	11.153
5.000	12.934	23.291	15.530	32.397	61.424	27.025	11.643	60.127	28.091	52.226	7.127
6.000	7.628	10.539	9.099	23.417	28.126	11.845	6.921	95.865	10.869	28.310	4.978
7.000	6.466	6.569	6.578	11.358	14.422	6.559	6.500	24.743	5.164	22.152	3.665
8.000	5.223	3.999	5.282	7.179	11.766	4.820	5.464	11.596	3.797	15.746	2.454
10.000	3.679	2.909	3.881	4.371	6.927	2.667	4.266	5.468	2.526	12.046	1.455
12.000	3.874	1.710	2.072	2.271	4.877	1.833	2.221	2.892	1.548	10.028	0.858
16.000	1.491	1.132	1.638	1.808	3.159	0.000	1.664	2.139	0.898	6.762	0.000
24.000	0.000	0.901	0.000	0.000	2.619	0.000	0.930	1.599	0.000	3.626	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	10.113	0.000	0.000	0.000
0.500	0.000	0.000	1.472	1.046	5.481	0.000	7.512	41.708	1.059	0.000	0.000
0.750	1.090	4.582	9.279	2.399	14.705	2.039	16.082	62.832	6.079	1.991	0.000
1.000	23.192	24.661	95.883	10.159	14.878	4.485	31.414	63.943	8.676	2.847	0.000
1.250	101.610	125.739	139.750	30.302	28.427	11.451	36.437	60.327	21.100	11.145	0.000
1.500	186.558	212.614	199.455	32.094	89.945	17.380	73.455	63.308	33.355	43.612	1.775
1.750	183.003	154.034	151.064	44.962	88.658	40.917	129.633	83.342	62.236	67.233	4.992
2.000	194.610	133.543	135.106	64.510	109.478	41.008	138.522	107.753	58.696	91.907	10.513
2.250	170.804	127.327	94.345	61.915	109.301	80.563	177.196	103.625	62.523	98.552	27.583
2.500	151.742	117.463	71.845	72.830	82.871	116.662	165.520	73.708	100.581	126.735	26.210
2.750	138.322	88.330	56.257	123.692	66.171	98.874	151.446	60.967	128.839	136.178	62.702
3.000	122.420	75.431	43.685	138.492	58.172	107.161	127.872	44.906	172.474	105.304	135.002
3.500	77.476	51.375	29.841	123.188	36.698	119.293	115.571	42.276	133.785	92.735	119.612
4.000	49.899	35.699	22.713	125.880	29.436	96.382	101.551	26.058	89.761	60.438	76.922
4.500	34.371	27.729	15.798	120.757	24.010	58.226	73.603	22.705	55.230	43.677	40.641
5.000	24.147	20.835	12.142	91.001	18.766	44.135	54.552	17.688	37.324	32.587	24.899
6.000	13.780	12.982	8.074	45.962	12.106	38.591	32.171	10.013	13.832	17.949	11.090
7.000	9.868	8.532	5.165	22.429	7.393	17.519	17.221	6.682	6.960	9.509	6.712
8.000	9.221	5.887	3.834	17.310	4.634	11.755	12.123	5.922	5.020	7.615	4.426
10.000	6.080	3.261	2.352	11.427	3.265	6.740	8.257	4.229	3.117	5.006	3.800
12.000	3.208	2.798	1.698	6.790	1.721	4.688	6.819	2.230	2.340	3.775	2.052
16.000	2.031	1.898	1.549	5.094	0.828	2.349	4.995	1.528	1.502	2.593	1.315
24.000	0.808	1.290	1.006	1.887	0.000	0.852	2.295	1.092	0.984	1.177	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	1.850	0.000	0.000	5.123	0.000	0.000	0.000
0.500	0.000	7.305	0.000	2.210	7.109	10.455	9.964	15.976	1.268	1.550	3.143
0.750	7.913	15.791	1.603	4.717	9.760	87.111	68.002	69.197	6.772	2.752	45.519
1.000	29.975	23.790	12.187	8.534	13.616	119.057	62.642	178.612	114.026	13.745	82.563
1.250	37.642	41.691	47.895	8.594	17.060	97.408	65.329	277.740	158.502	65.894	126.809
1.500	113.482	70.191	75.377	12.555	25.248	96.833	66.788	283.037	242.692	149.553	126.701
1.750	172.558	74.367	91.910	21.508	38.858	66.968	58.905	207.976	167.979	235.285	128.829
2.000	244.050	99.864	95.741	23.880	40.727	47.535	48.757	232.515	161.940	219.476	94.873
2.250	163.535	112.952	75.932	27.747	46.869	38.851	38.626	168.747	137.529	146.065	77.404
2.500	127.891	90.561	100.483	39.815	54.697	32.362	29.058	142.998	116.113	159.530	63.234
2.750	101.121	84.570	97.771	53.703	57.647	28.103	23.949	110.495	83.081	159.431	55.855
3.000	91.254	75.233	90.877	82.363	43.465	21.276	20.684	88.877	75.409	150.052	41.546
3.500	84.487	74.885	91.001	104.800	53.467	14.324	13.431	56.011	53.027	124.351	27.630
4.000	56.032	56.044	59.779	105.208	88.587	9.680	9.666	37.798	31.555	74.441	20.864
4.500	37.541	37.877	40.477	64.442	88.043	7.606	7.073	27.786	20.123	53.262	14.031
5.000	29.175	23.368	20.519	45.710	55.532	6.615	5.695	21.884	13.154	38.508	11.248
6.000	16.152	16.973	9.755	42.925	48.473	3.735	3.777	9.917	10.456	16.422	5.821
7.000	10.334	10.862	7.059	24.221	18.795	3.845	3.148	9.288	6.522	15.016	4.711
8.000	9.423	5.786	5.128	14.892	12.816	2.753	2.742	7.031	6.154	9.838	4.816
10.000	6.312	3.490	3.453	11.689	7.081	2.072	2.006	5.808	3.952	7.698	3.546
12.000	3.950	2.010	2.462	8.554	7.317	1.736	1.400	3.999	2.435	4.759	2.008
16.000	1.869	1.934	2.354	2.999	3.071	1.328	0.837	1.969	2.167	3.481	1.747
24.000	1.034	1.257	0.886	1.476	1.443	0.000	0.000	1.229	0.853	2.140	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.803	0.000	0.000	3.107	0.000
0.500	1.537	3.534	0.000	0.000	15.973	2.328	20.884	0.000	0.798	32.031	0.000
0.750	3.674	24.956	0.000	0.000	87.677	24.604	73.027	0.000	5.419	67.643	1.516
1.000	4.727	118.878	1.087	0.982	100.538	88.744	94.768	0.000	16.988	83.203	4.673
1.250	8.507	142.394	1.124	19.275	115.261	180.237	89.662	0.000	76.918	75.893	9.773
1.500	15.334	142.211	10.589	44.229	150.736	185.787	104.905	2.205	142.807	72.061	23.971
1.750	24.365	94.614	20.445	40.670	108.022	181.239	155.049	24.531	223.572	65.391	32.385
2.000	43.782	73.211	49.694	53.144	95.992	135.131	106.965	91.308	221.271	51.473	46.512
2.250	65.741	59.973	59.260	95.199	77.936	123.395	88.493	141.711	162.842	47.225	65.374
2.500	116.777	48.864	74.748	93.636	77.622	147.590	67.996	152.723	148.806	52.794	80.493
2.750	113.054	39.740	89.014	77.056	59.110	128.933	60.310	174.735	126.723	52.811	109.061
3.000	117.347	37.931	62.916	60.490	57.453	98.999	50.860	149.407	116.575	63.975	123.693
3.500	99.267	27.140	60.229	39.013	53.317	57.103	38.653	117.919	111.267	55.130	92.110
4.000	82.939	18.460	50.336	42.355	35.018	37.335	25.838	91.113	73.426	49.753	70.959
4.500	56.574	12.143	38.520	30.630	27.523	26.001	18.790	69.418	53.694	44.554	36.380
5.000	34.946	9.547	25.923	24.289	20.190	20.036	16.996	58.373	39.701	42.984	25.687
6.000	15.295	5.144	10.586	21.492	11.273	13.944	10.874	37.859	19.014	36.570	14.986
7.000	11.514	3.721	5.829	7.968	6.460	9.564	7.916	18.385	10.744	17.716	7.575
8.000	8.538	2.607	3.807	4.620	4.756	7.996	5.744	12.855	8.989	14.996	4.732
10.000	5.088	1.812	3.185	3.077	2.946	5.915	3.687	7.073	6.559	5.661	2.809
12.000	2.973	1.206	1.888	2.045	2.219	5.001	2.603	4.516	4.232	3.942	2.124
16.000	1.884	0.987	1.360	1.761	1.392	2.968	1.808	3.310	2.097	1.949	1.278
24.000	0.000	0.000	1.062	0.000	0.867	1.155	0.000	1.705	1.488	0.847	1.342

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T									
	Subject									
	Concentration (ng/mL)									
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	4.025	1.241	0.000	0.000
0.500	1.943	2.214	0.000	0.000	0.000	0.000	37.754	10.563	0.000	0.000
0.750	22.072	5.211	1.159	0.000	0.000	0.000	99.864	13.981	0.000	3.092
1.000	31.495	12.444	1.084	0.000	12.836	4.612	157.627	17.512	3.397	13.401
1.250	75.217	15.820	2.446	2.054	31.663	40.534	179.713	20.911	37.836	30.849
1.500	114.774	32.546	3.930	8.764	69.307	91.920	161.700	25.683	88.897	115.260
1.750	158.543	34.875	5.750	28.404	117.210	141.351	148.248	28.419	106.026	111.438
2.000	96.106	89.648	59.970	87.748	121.790	143.271	133.276	44.194	140.475	107.806
2.250	83.232	180.790	94.533	90.852	130.709	141.406	107.807	50.100	101.616	90.633
2.500	72.709	133.698	159.745	100.591	141.845	117.197	79.963	53.359	111.888	75.639
2.750	57.943	143.131	153.485	94.051	145.297	88.836	56.417	64.481	109.552	70.337
3.000	54.140	104.760	140.874	96.170	130.570	79.044	53.647	91.480	103.638	61.958
3.500	37.010	69.425	113.166	81.361	85.967	52.938	32.712	92.081	84.573	62.615
4.000	28.557	45.879	89.507	57.614	55.448	31.568	22.915	198.698	60.952	42.985
4.500	19.687	31.630	68.738	39.248	33.058	24.981	15.747	218.917	33.573	29.921
5.000	15.947	25.354	75.024	22.104	26.002	21.874	11.161	166.132	26.983	22.498
6.000	9.537	12.391	33.323	15.271	14.872	11.798	8.895	67.347	13.439	13.187
7.000	6.179	8.476	17.387	8.781	8.128	7.861	4.992	31.745	6.841	7.859
8.000	4.662	6.551	9.336	4.909	6.941	7.534	5.773	23.507	5.496	6.640
10.000	3.048	3.320	4.817	3.090	4.293	4.602	3.727	10.130	3.623	4.154
12.000	1.922	1.979	3.180	1.827	3.064	2.496	2.051	7.910	2.594	1.792
16.000	0.786	1.560	2.068	0.802	1.665	1.745	1.367	4.573	1.787	1.632
24.000	0.000	0.000	0.848	0.000	0.821	1.125	0.890	2.015	1.112	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	2.714	1.003	0.942	0.000	0.000	3.993	0.000	0.000	0.000	0.000	0.000
0.500	5.870	1.306	2.541	0.000	0.000	189.528	0.000	0.000	0.000	1.022	0.000
0.750	9.951	0.882	4.426	0.000	0.000	318.934	13.336	3.634	1.101	1.549	0.000
1.000	16.919	0.000	57.476	0.000	0.000	250.473	113.977	41.285	14.902	3.067	1.502
1.250	45.084	0.000	137.975	0.000	0.000	166.952	184.430	76.603	56.420	11.033	0.946
1.500	103.233	0.000	104.450	10.022	1.206	113.503	143.056	81.829	80.779	53.288	1.522
1.750	131.277	0.000	107.950	128.786	1.404	87.811	123.243	66.767	76.225	89.876	3.217
2.000	133.213	0.000	187.514	165.896	21.913	70.666	108.873	59.162	81.771	85.019	4.690
2.250	114.461	0.000	130.786	268.697	80.481	63.745	90.069	57.805	107.520	97.410	10.755
2.500	84.149	0.000	110.491	190.730	90.948	50.242	72.910	61.891	92.161	107.654	19.336
2.750	74.755	0.000	93.215	154.759	109.384	42.473	60.996	47.779	98.610	113.786	19.221
3.000	61.126	0.000	71.175	127.427	112.044	37.235	49.053	39.545	108.315	103.238	57.683
3.500	41.173	1.971	43.926	72.398	74.858	28.979	34.519	25.143	105.418	92.169	126.599
4.000	29.995	1.129	30.318	44.539	80.148	20.215	30.261	20.275	75.795	68.829	92.073
4.500	20.536	0.000	22.006	33.823	61.348	15.502	26.365	15.163	51.928	47.000	68.379
5.000	16.591	0.000	19.175	23.336	40.570	12.295	18.620	11.135	33.591	29.798	52.447
6.000	9.807	0.000	12.831	13.006	24.035	7.672	10.408	5.720	19.033	17.750	20.065
7.000	6.794	0.000	9.184	7.199	10.759	4.757	6.301	5.148	11.736	10.034	9.089
8.000	5.776	0.000	7.742	6.591	7.329	5.961	6.131	4.332	9.502	8.178	6.979
10.000	3.465	0.000	4.320	4.743	3.820	3.449	3.753	2.481	5.944	4.651	3.368
12.000	2.249	0.000	3.544	4.221	1.967	2.091	2.505	1.667	4.845	2.833	1.907
16.000	1.547	0.000	2.095	2.440	1.074	1.197	1.606	1.078	3.370	1.502	1.292
24.000	1.067	0.000	0.000	1.258	0.000	0.000	0.000	0.000	1.687	0.764	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	1.975	0.000
0.500	2.326	1.553	17.699	0.000	21.697	0.000	1.755	10.188	1.323	11.010	2.348
0.750	7.931	9.039	30.170	0.000	189.975	0.000	2.934	12.148	1.991	20.160	8.076
1.000	26.405	36.595	43.083	1.184	210.299	1.583	5.493	14.611	2.732	18.093	10.641
1.250	43.946	56.975	70.897	3.679	171.991	5.243	10.364	35.854	2.705	16.399	14.516
1.500	93.764	97.104	90.586	10.235	130.433	12.317	18.602	58.017	17.035	22.651	20.401
1.750	141.249	98.593	104.280	21.512	106.195	23.629	32.782	91.741	81.999	18.771	33.975
2.000	112.811	101.478	103.580	27.415	77.478	39.158	37.065	115.860	102.239	19.200	36.419
2.250	107.910	82.379	106.197	34.582	61.331	60.358	49.604	144.470	143.326	30.103	59.506
2.500	102.161	70.717	97.619	82.324	54.570	39.837	60.237	169.403	180.485	34.079	64.338
2.750	91.958	53.534	89.934	89.816	45.935	44.459	70.652	105.706	178.474	60.077	44.536
3.000	78.065	55.115	88.285	106.877	41.779	47.475	81.660	88.423	181.107	82.597	42.820
3.500	64.842	54.868	59.445	88.373	29.458	47.776	207.903	62.785	123.766	71.476	37.331
4.000	55.873	46.608	52.903	67.065	21.681	48.320	95.501	47.545	98.130	89.576	32.380
4.500	54.489	35.857	36.121	49.461	16.259	34.604	77.475	37.007	70.823	80.956	31.503
5.000	42.120	31.619	26.195	39.566	10.091	31.808	53.665	24.977	51.199	89.943	24.052
6.000	31.328	16.592	13.358	25.759	8.207	18.719	30.010	18.397	32.967	97.134	21.311
7.000	15.601	8.673	7.866	14.422	5.785	8.168	18.988	9.644	15.836	32.263	8.338
8.000	10.568	6.400	4.945	9.272	4.670	6.149	12.148	8.058	12.421	19.666	5.213
10.000	6.515	4.986	3.709	4.613	2.794	3.217	6.498	4.282	7.592	11.897	2.821
12.000	5.554	3.116	2.404	2.972	1.789	2.200	4.621	3.208	4.280	6.978	1.739
16.000	3.112	1.885	1.719	1.926	1.085	1.436	2.334	1.736	2.692	4.484	1.316
24.000	1.562	1.212	1.436	0.806	0.000	0.000	1.659	0.000	0.000	3.037	0.000

Table No. 14.2.1.5

Time (h)	Plasma concentration of Spironolactone for Test Product-T						
	Subject						
	Concentration (ng/mL)						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	44.123	0.846	0.756	0.000	0.000	0.000	0.000
0.500	169.178	1.707	16.337	18.229	9.045	0.000	0.000
0.750	178.756	14.748	82.409	63.622	40.643	0.000	0.786
1.000	210.864	35.340	157.213	125.723	90.911	1.271	1.189
1.250	175.545	44.459	200.504	148.224	114.462	1.430	1.696
1.500	131.767	58.186	172.263	109.248	106.683	4.346	1.975
1.750	153.345	55.598	135.254	100.588	133.486	44.491	2.401
2.000	120.529	51.304	100.749	96.180	129.433	68.903	3.542
2.250	150.630	43.956	77.524	83.850	119.588	52.874	7.506
2.500	134.467	37.832	59.643	70.297	109.445	54.880	13.493
2.750	109.208	29.491	44.303	60.245	106.682	57.013	25.746
3.000	99.199	27.592	33.164	55.193	84.851	60.310	38.735
3.500	105.468	20.017	23.476	38.896	64.625	70.148	83.768
4.000	61.070	12.929	13.637	29.607	38.523	55.947	82.632
4.500	52.162	9.939	9.915	20.682	30.656	35.467	54.476
5.000	35.714	7.275	8.419	15.429	32.102	26.762	38.610
6.000	33.780	4.730	6.313	8.145	15.883	16.813	18.519
7.000	15.136	2.662	3.522	5.523	7.073	7.945	8.407
8.000	10.492	2.456	3.523	3.946	4.949	4.972	4.523
10.000	6.109	1.631	1.919	2.846	3.088	2.432	1.843
12.000	3.996	1.003	1.941	2.510	2.230	2.336	1.602
16.000	2.755	0.000	1.193	1.350	1.030	1.087	0.970
24.000	1.719	0.000	0.000	0.000	0.806	0.000	0.000

Table No. 14.2.1.5

Time (h)	N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
0.000	116	0.000	0.0000	0.000	0.000	0.000	-	-
0.250	116	0.838	4.2552	0.000	0.000	44.123	507.9	-
0.500	116	7.790	24.2164	0.000	1.315	189.528	310.9	-
0.750	116	23.466	44.4950	0.000	6.021	318.934	189.6	-
1.000	116	45.361	59.6722	0.000	17.250	288.600	131.5	-
1.250	116	64.285	67.6651	0.000	37.040	283.675	105.3	-
1.500	116	78.790	67.5531	0.000	69.749	312.383	85.7	-
1.750	116	85.499	59.0901	0.000	81.964	263.884	69.1	-
2.000	116	90.554	56.8959	0.000	88.422	271.300	62.8	-
2.250	116	90.570	51.0258	0.000	83.124	268.697	56.3	-
2.500	116	90.673	52.5345	0.000	77.180	289.861	57.9	-
2.750	116	87.526	54.8357	0.000	72.128	356.592	62.7	-
3.000	116	83.637	52.1521	0.000	74.053	308.514	62.4	-
3.500	116	72.043	48.4643	1.971	63.938	354.977	67.3	58.959
4.000	116	56.459	37.3588	1.129	51.260	226.911	66.2	45.211
4.500	116	42.248	30.3328	0.000	36.261	218.917	71.8	-
5.000	116	32.264	23.4324	0.000	25.963	166.132	72.6	-
6.000	116	19.969	17.2759	0.000	14.929	97.134	86.5	-
7.000	116	10.529	6.5299	0.000	8.385	34.913	62.0	-
8.000	116	7.604	4.2166	0.000	6.440	23.507	55.4	-
10.000	116	4.720	2.5270	0.000	4.053	12.291	53.5	-
12.000	116	3.212	1.8813	0.000	2.508	10.028	58.6	-
16.000	116	1.963	1.2823	0.000	1.724	7.056	65.3	-
24.000	116	0.774	0.8127	0.000	0.842	3.626	105.0	-

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]										
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	1.868	0.000	33.228	0.000	0.000	0.000	0.000	0.000	4.401	0.000
0.750	0.000	3.018	0.000	159.238	0.939	0.000	1.544	0.849	0.000	14.814	0.000
1.000	5.547	6.834	0.000	156.419	1.576	1.315	2.187	2.045	3.289	33.454	0.804
1.250	13.418	12.294	0.000	121.992	1.517	9.624	2.826	14.090	10.041	56.317	1.746
1.500	19.244	22.510	65.186	100.653	4.385	139.159	7.190	118.951	20.085	123.748	2.922
1.750	22.927	40.495	133.782	72.267	6.509	177.851	76.677	173.937	47.340	176.634	4.114
2.000	35.155	69.910	141.308	58.696	36.722	296.577	113.276	153.971	92.799	172.110	5.101
2.250	40.696	181.760	118.370	46.831	140.790	288.411	126.548	160.502	113.532	146.122	6.164
2.500	57.315	205.979	105.839	37.119	152.078	212.007	134.647	171.267	119.063	307.241	6.276
2.750	55.553	205.876	86.797	31.118	237.881	149.000	140.537	157.910	106.607	301.287	8.362
3.000	48.582	194.546	73.011	28.872	286.244	127.467	122.229	144.194	110.729	316.083	12.600
3.500	31.578	125.052	55.770	22.134	167.345	127.032	79.488	106.945	77.513	161.861	36.802
4.000	22.637	135.323	39.316	13.644	117.793	88.463	56.460	80.389	51.310	93.796	80.335
4.500	15.955	103.163	29.899	11.484	73.863	55.134	57.104	57.508	39.651	96.934	73.376
5.000	14.928	78.221	18.930	9.955	60.452	33.574	45.235	40.674	23.460	67.769	64.101
6.000	7.159	82.963	12.388	5.496	30.452	16.826	22.514	20.715	12.992	29.017	37.794
7.000	3.372	33.414	7.587	3.382	15.783	11.033	9.773	13.306	7.254	18.132	16.815
8.000	2.138	16.475	6.476	2.585	9.026	9.442	7.670	9.872	4.094	15.652	9.430
10.000	1.187	10.445	4.254	2.191	5.368	7.048	5.554	5.518	3.071	9.383	4.127
12.000	0.836	6.550	2.669	1.534	3.999	5.166	3.037	3.965	1.817	7.217	2.862
16.000	0.972	3.559	1.609	0.000	2.411	2.552	1.569	3.034	0.995	4.307	1.998
24.000	0.000	1.499	0.000	0.000	1.189	0.783	0.840	1.232	0.902	2.613	0.869

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	0.000	2.351	6.946	1.639	64.785	0.000	0.000	0.000	1.828	0.000
0.750	1.169	2.795	59.060	11.577	5.196	248.531	6.274	0.000	1.482	8.148	0.000
1.000	2.138	3.298	148.137	19.614	45.359	282.742	54.851	0.000	2.786	9.807	4.399
1.250	2.152	70.459	140.820	32.110	130.401	219.155	118.528	0.000	3.461	14.061	7.429
1.500	2.665	242.703	107.585	48.561	180.196	175.857	150.242	1.795	7.689	43.823	57.108
1.750	2.943	128.235	84.723	80.582	189.453	148.527	124.502	4.833	19.280	56.104	79.249
2.000	2.984	124.826	50.843	93.917	129.524	138.922	98.895	21.916	38.774	65.912	87.738
2.250	2.334	120.790	40.682	82.543	120.692	92.779	91.878	56.262	55.795	65.337	71.551
2.500	3.930	100.718	27.154	69.428	107.121	82.318	74.124	52.858	61.254	58.175	58.908
2.750	3.981	87.950	23.661	66.724	91.315	83.414	71.560	103.983	85.054	57.962	45.192
3.000	11.677	70.628	19.844	60.701	73.036	61.284	61.413	75.042	95.781	57.177	35.239
3.500	56.818	55.911	14.748	46.567	54.939	48.947	38.561	55.292	112.931	41.363	26.264
4.000	47.917	39.165	11.437	25.721	31.213	39.385	20.800	42.111	96.441	30.300	19.405
4.500	40.269	30.808	8.388	16.234	22.517	23.737	14.266	30.801	102.428	23.485	14.092
5.000	42.953	27.704	7.044	13.177	19.295	18.274	9.681	21.180	87.348	16.343	10.611
6.000	30.002	15.687	6.772	7.332	11.146	10.237	7.256	9.412	54.455	10.280	6.846
7.000	19.936	9.606	5.220	5.231	7.364	8.314	4.713	4.860	21.649	5.508	4.494
8.000	9.258	10.002	3.704	4.561	5.842	7.292	4.041	3.604	12.807	4.720	3.378
10.000	3.751	6.276	2.317	3.264	3.102	5.798	2.846	1.640	6.363	2.493	2.626
12.000	2.890	4.531	1.691	2.096	2.496	3.991	1.839	1.159	4.972	1.507	1.353
16.000	1.234	1.977	0.896	1.525	1.552	2.361	1.322	0.000	3.847	1.021	0.941
24.000	0.000	1.210	0.000	0.000	0.990	0.901	0.897	0.000	1.756	0.000	0.000

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	1.271	0.000	0.000	12.207	12.909	0.000	3.374	1.792	4.861	0.000
0.750	1.544	2.771	0.000	1.570	35.181	62.571	0.000	37.797	3.896	13.114	0.000
1.000	2.501	4.158	0.000	3.511	141.408	155.745	9.372	33.384	5.770	28.000	0.000
1.250	1.783	18.124	1.070	7.315	257.001	160.830	55.652	62.205	10.445	89.626	1.143
1.500	2.443	58.047	1.693	13.665	318.485	147.849	83.137	71.023	14.028	87.861	7.425
1.750	54.606	84.860	1.863	23.849	240.001	118.028	117.723	76.768	13.697	110.942	22.902
2.000	103.870	176.919	3.656	32.382	198.823	77.231	100.235	63.144	19.499	97.575	61.229
2.250	140.748	126.931	9.800	25.137	126.465	53.322	82.981	60.579	23.278	94.273	84.485
2.500	176.845	129.056	11.339	33.754	110.836	45.914	66.395	59.783	52.874	102.740	103.992
2.750	147.570	115.124	14.283	44.337	85.104	35.165	53.772	56.114	63.008	115.091	104.688
3.000	115.704	91.487	24.374	63.436	67.117	27.331	48.691	60.628	52.925	132.287	88.089
3.500	82.310	81.783	51.578	141.222	44.396	19.577	34.502	52.463	43.468	98.352	68.930
4.000	48.306	59.247	87.119	125.783	34.115	13.339	21.542	47.076	32.326	83.494	48.412
4.500	36.003	43.734	84.121	91.326	26.718	11.710	12.888	54.230	27.981	54.813	37.256
5.000	27.104	29.765	84.989	79.458	20.465	8.658	10.283	45.282	20.540	36.695	24.633
6.000	15.994	16.535	100.983	29.664	11.255	5.963	6.493	39.085	13.439	18.380	11.360
7.000	10.530	10.353	43.761	14.299	7.034	3.609	4.621	15.921	6.224	11.046	6.310
8.000	8.034	8.839	21.531	7.326	9.059	3.755	3.537	8.108	4.640	7.514	4.543
10.000	5.245	6.265	14.887	4.276	4.327	2.536	2.392	5.206	2.147	4.867	2.596
12.000	4.762	4.502	11.754	2.784	2.823	2.246	1.872	3.422	1.739	2.988	1.566
16.000	2.342	2.997	6.283	1.432	2.212	1.033	1.056	1.773	1.212	2.659	1.400
24.000	0.801	1.781	3.687	0.000	1.339	0.000	0.000	0.000	0.763	1.327	0.000

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	0.000	1.758	0.865	1.057	0.000	0.000	0.000	1.162	0.000	0.000
0.750	1.419	2.460	9.698	2.526	2.242	0.000	1.450	0.000	4.977	0.000	14.308
1.000	4.452	9.380	26.198	4.618	5.254	1.165	24.699	0.000	13.217	0.000	50.423
1.250	23.705	52.760	58.562	5.937	17.589	4.586	43.993	0.892	28.201	3.763	141.042
1.500	59.651	109.825	105.661	12.686	53.340	56.884	97.085	1.805	26.446	4.407	124.906
1.750	135.570	83.818	220.413	21.349	84.738	99.151	145.877	1.971	23.729	7.338	110.539
2.000	159.410	133.290	237.184	24.892	145.170	113.730	145.280	3.199	28.101	8.188	89.234
2.250	163.910	128.641	291.840	29.646	105.700	92.489	109.909	3.455	56.740	14.936	70.013
2.500	157.130	97.935	237.229	39.816	77.802	83.889	77.171	4.740	112.585	22.875	55.112
2.750	132.811	99.599	203.351	37.518	71.188	70.921	54.261	8.377	87.333	64.064	48.532
3.000	117.405	120.234	133.438	41.950	60.527	51.878	50.647	7.638	95.004	129.882	38.866
3.500	76.525	80.045	89.423	46.035	48.130	34.072	28.626	9.991	63.694	239.718	27.381
4.000	46.814	78.754	57.360	49.416	70.901	28.376	28.591	45.964	47.542	194.909	19.193
4.500	36.947	41.758	39.039	48.069	116.554	14.998	21.731	98.078	34.689	115.795	14.169
5.000	23.593	26.133	26.301	40.544	124.073	12.875	16.218	104.671	23.250	72.919	12.763
6.000	10.709	12.707	16.323	46.416	41.912	7.118	9.182	139.997	10.748	33.159	7.350
7.000	6.975	7.920	13.961	20.030	17.777	4.027	5.918	41.159	6.439	18.802	7.163
8.000	5.004	5.789	10.734	10.081	15.756	2.898	3.853	19.228	4.467	13.600	4.556
10.000	3.165	3.378	6.148	6.971	10.145	1.889	2.650	8.541	2.825	11.290	2.496
12.000	2.583	1.982	3.522	4.266	7.097	1.085	1.908	7.946	1.711	6.209	1.721
16.000	0.886	1.270	2.238	2.936	3.949	1.011	1.099	3.142	0.860	4.481	1.037
24.000	0.000	0.940	1.375	0.890	3.493	0.000	0.947	1.434	0.000	2.466	0.000

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	0.000	0.832	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.750	0.000	4.361	6.381	0.000	0.000	0.000	0.949	1.845	0.000	1.081	1.369
1.000	1.228	25.219	34.593	0.000	0.000	0.870	1.703	8.483	0.000	17.951	3.287
1.250	5.630	50.162	59.234	2.627	5.081	0.911	34.048	102.121	10.730	112.300	5.653
1.500	26.711	114.168	80.016	9.852	31.992	1.405	75.591	168.471	110.239	183.018	11.487
1.750	98.848	138.096	131.972	16.143	74.533	3.965	64.275	181.837	120.148	230.376	18.126
2.000	122.223	128.106	100.822	16.829	125.803	6.090	125.310	131.851	157.869	166.981	37.214
2.250	115.171	79.352	103.656	34.616	162.556	12.488	214.357	93.443	116.837	100.605	78.317
2.500	105.427	72.344	93.155	46.423	101.971	66.500	195.181	76.608	104.533	105.722	135.664
2.750	96.794	59.334	76.629	59.646	94.640	58.724	211.431	60.123	93.993	85.258	124.259
3.000	92.920	47.151	59.770	63.325	84.051	84.309	174.045	47.103	76.020	77.966	117.914
3.500	65.090	33.308	38.855	103.590	71.840	125.167	129.495	33.832	61.231	48.798	74.395
4.000	55.856	24.522	26.724	147.698	47.314	85.597	142.352	23.583	37.618	31.117	46.066
4.500	35.030	19.167	17.613	187.040	33.816	58.461	84.101	16.315	43.463	24.787	26.720
5.000	22.852	12.882	13.465	132.812	25.464	41.415	56.633	14.080	28.949	16.496	17.188
6.000	10.560	7.425	8.515	59.222	13.512	30.495	24.749	9.179	9.850	12.290	9.596
7.000	6.516	5.619	4.867	29.446	8.477	13.239	15.792	7.504	5.576	7.850	5.830
8.000	5.676	3.576	3.681	17.876	4.992	7.007	12.997	6.011	3.371	6.889	5.426
10.000	3.590	2.684	2.282	10.803	2.769	3.782	9.451	3.719	2.475	3.699	2.361
12.000	1.887	1.673	1.649	6.820	2.038	3.058	6.143	2.505	1.621	2.609	2.546
16.000	1.143	1.166	1.222	5.745	1.338	1.606	4.369	1.969	1.139	1.745	1.467
24.000	0.000	0.911	0.922	2.301	0.779	0.841	2.575	0.881	0.880	0.000	1.067

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	5.775	0.000	0.000	0.000	0.000	0.000
0.500	0.000	0.000	0.000	1.450	0.000	113.492	2.882	0.000	0.000	0.000	0.000
0.750	0.000	0.000	1.646	6.371	0.000	147.351	60.535	1.005	1.117	0.859	1.112
1.000	1.261	34.515	10.275	22.744	0.000	133.514	126.356	4.057	3.815	1.503	3.108
1.250	5.509	58.467	20.050	70.043	0.914	96.379	97.808	8.698	8.761	2.769	61.451
1.500	11.567	61.053	68.628	120.447	1.951	71.828	95.756	70.388	31.550	13.485	222.936
1.750	28.721	97.839	177.524	174.846	4.105	45.240	87.611	294.525	48.960	142.297	219.784
2.000	96.364	119.597	185.979	163.728	4.137	33.522	58.848	293.057	125.451	236.075	176.617
2.250	93.602	97.289	144.075	160.951	5.958	24.705	43.536	256.631	141.607	200.930	130.479
2.500	167.577	100.302	121.934	127.579	8.743	19.495	39.878	229.139	117.670	199.254	101.841
2.750	207.273	85.360	109.752	115.912	14.736	17.917	32.976	212.230	114.061	177.215	84.183
3.000	160.587	67.345	95.113	99.705	19.961	16.505	26.419	173.838	123.156	132.367	71.062
3.500	159.018	51.869	58.498	69.491	24.289	10.929	18.031	122.630	97.202	101.142	44.823
4.000	149.002	38.345	40.992	55.772	88.179	9.322	11.774	82.120	68.087	59.832	33.686
4.500	86.711	26.691	27.191	35.787	90.972	7.204	10.639	50.068	46.611	46.478	27.482
5.000	53.190	22.048	17.546	28.265	83.326	7.194	8.791	37.218	38.579	32.079	17.266
6.000	25.631	21.470	9.287	18.066	59.550	3.325	4.703	19.703	21.201	19.397	10.699
7.000	16.437	12.587	5.407	9.437	37.251	2.797	4.054	13.160	10.136	11.544	7.192
8.000	14.468	7.319	4.572	7.155	21.490	2.320	3.518	9.864	7.722	10.806	6.751
10.000	10.338	4.086	3.200	5.318	9.397	1.871	2.657	5.916	4.811	8.312	4.031
12.000	6.340	2.379	2.179	3.091	6.044	1.570	1.598	3.579	2.097	6.219	3.537
16.000	2.390	2.118	1.692	1.648	2.662	1.243	1.318	3.036	1.119	3.294	2.353
24.000	1.003	1.103	0.888	1.281	1.703	0.000	0.000	1.368	0.000	1.458	1.705

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	1.062	0.000	0.000	9.086	8.087	0.000	0.000	0.000	0.000	0.000
0.750	0.000	11.798	2.622	0.000	18.589	29.295	5.789	2.724	1.326	0.000	3.818
1.000	0.000	44.256	5.777	0.000	30.061	38.129	87.224	29.501	7.272	0.000	10.444
1.250	1.175	65.620	7.438	0.000	44.333	73.353	121.523	69.970	17.372	0.000	36.668
1.500	1.571	67.172	12.277	0.000	106.721	166.372	133.045	107.648	25.496	0.000	59.740
1.750	7.368	96.552	14.263	0.000	145.774	125.074	115.041	130.415	28.601	0.913	125.052
2.000	29.010	132.973	16.193	0.793	134.543	96.885	107.602	121.404	35.263	1.620	131.794
2.250	107.027	119.729	22.009	6.256	139.689	67.924	76.418	111.841	51.323	2.366	143.627
2.500	98.814	78.439	36.838	22.539	117.696	69.171	58.848	119.352	45.326	2.982	152.062
2.750	101.734	74.889	42.231	37.171	108.167	74.031	50.957	102.476	39.501	2.520	149.061
3.000	99.838	70.907	57.106	48.350	93.925	111.598	41.364	96.231	38.347	3.672	115.953
3.500	62.064	62.400	69.985	93.214	71.005	134.069	36.250	75.380	50.237	10.085	99.520
4.000	56.610	54.670	59.069	119.530	57.825	134.034	27.148	65.151	61.228	15.556	72.841
4.500	50.168	33.390	68.300	80.465	41.766	89.869	21.800	51.210	46.906	21.509	56.350
5.000	36.279	21.605	49.244	43.381	30.259	51.391	18.140	48.766	64.224	54.464	57.934
6.000	25.022	8.215	17.898	17.644	20.528	29.004	8.374	41.596	37.464	55.024	31.725
7.000	12.058	5.778	8.838	8.873	10.577	15.961	6.422	20.037	20.377	27.112	15.493
8.000	8.002	4.963	5.654	5.955	7.095	11.416	5.549	10.653	13.091	17.255	12.278
10.000	5.361	3.180	3.700	3.588	4.138	7.944	3.633	6.604	7.295	9.815	5.863
12.000	2.225	2.736	2.806	1.825	3.062	5.607	2.988	4.554	4.324	9.077	4.343
16.000	1.382	1.080	1.935	1.350	1.836	4.583	1.927	3.232	2.713	2.789	2.211
24.000	0.000	0.766	0.935	0.880	1.040	1.909	0.000	1.490	1.207	1.195	2.039

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]										
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.904	0.000	0.000
0.500	0.000	1.942	0.000	0.000	0.000	0.000	1.201	1.044	3.138	6.293	5.558
0.750	0.000	3.776	0.000	0.000	2.579	0.000	3.183	2.676	4.380	86.431	9.744
1.000	0.000	6.903	0.000	3.030	5.544	0.000	9.609	21.812	8.226	93.187	16.461
1.250	1.737	7.422	1.248	30.786	83.784	3.472	17.476	154.398	181.103	132.367	24.305
1.500	5.164	52.500	6.862	80.098	191.589	12.753	23.190	244.757	163.015	140.249	37.639
1.750	11.707	85.793	13.486	114.968	252.626	28.337	28.947	226.944	162.930	116.776	44.974
2.000	51.162	128.371	15.824	139.666	210.847	81.756	39.209	208.315	114.846	100.644	83.895
2.250	127.155	79.012	21.860	140.095	158.167	118.170	73.498	160.415	99.927	61.599	66.574
2.500	114.421	76.692	55.749	112.768	104.476	141.199	94.186	117.632	60.472	51.237	93.278
2.750	88.304	69.570	65.236	94.592	82.093	146.990	86.665	100.402	50.016	47.018	75.852
3.000	67.737	56.801	78.267	77.762	69.889	130.002	85.656	86.081	43.499	34.160	72.096
3.500	70.643	37.092	64.889	50.074	45.661	101.242	78.059	76.977	29.518	31.525	63.415
4.000	83.296	29.805	90.665	31.736	30.660	61.896	58.038	42.170	20.874	21.161	46.250
4.500	58.959	17.787	75.796	22.075	28.479	49.037	38.031	29.302	17.092	16.176	28.188
5.000	65.121	14.076	42.393	15.176	19.205	32.444	26.042	24.240	12.691	13.173	25.415
6.000	41.442	9.043	14.027	9.399	10.283	13.376	13.686	13.698	7.650	6.885	15.678
7.000	20.417	5.358	6.968	5.524	7.893	9.265	6.493	9.689	5.300	3.892	8.114
8.000	11.414	3.429	3.990	5.477	5.119	7.531	5.321	8.917	3.526	3.816	5.854
10.000	5.688	2.487	2.368	3.554	3.026	5.864	3.673	5.766	2.470	2.373	3.695
12.000	3.212	1.684	1.582	4.571	1.924	3.663	2.893	3.705	1.851	1.972	3.160
16.000	1.621	0.891	1.230	1.185	1.148	2.710	1.421	2.603	0.933	1.089	2.187
24.000	0.000	0.821	0.000	0.000	0.000	0.908	0.000	2.055	0.976	0.000	1.230

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R									
	Subject									
	Concentration (ng/mL)									
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	2.762	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.463
0.750	6.150	0.000	0.000	149.417	0.000	0.000	1.396	0.000	0.000	17.323
1.000	8.399	0.000	0.000	267.874	3.834	9.562	3.833	0.944	0.000	121.175
1.250	14.193	1.700	2.581	283.563	129.593	16.042	9.165	1.232	0.000	208.348
1.500	14.633	1.697	37.337	168.090	107.085	22.542	25.153	1.182	0.000	203.587
1.750	32.765	2.999	82.191	126.983	131.838	19.552	30.643	2.085	1.099	188.253
2.000	63.230	6.892	131.408	101.252	96.099	23.140	36.140	4.590	3.326	154.009
2.250	108.386	31.898	148.143	79.852	83.773	27.044	37.675	5.121	7.515	148.797
2.500	91.710	73.490	138.160	64.980	62.015	33.069	106.106	9.819	13.124	116.005
2.750	99.328	177.934	97.368	49.269	57.367	24.355	189.564	33.648	12.501	95.906
3.000	90.091	150.401	73.781	39.290	52.408	35.138	145.755	45.060	15.294	84.984
3.500	72.277	138.966	48.992	28.664	39.675	32.772	113.264	33.604	14.028	57.108
4.000	47.182	93.901	32.907	18.750	35.540	25.934	109.509	33.926	41.592	39.090
4.500	37.312	77.414	25.291	14.356	26.950	18.379	86.351	34.154	41.146	30.866
5.000	28.443	60.683	19.370	11.525	21.642	15.572	55.532	32.615	49.218	23.292
6.000	28.944	24.877	16.807	7.475	12.811	6.968	36.689	87.439	62.335	14.882
7.000	12.433	13.158	8.267	8.047	8.167	3.424	19.165	38.877	23.113	7.221
8.000	7.422	7.335	5.951	6.941	5.552	2.405	13.992	20.990	12.109	8.231
10.000	4.912	4.403	3.231	3.781	3.771	1.525	10.411	9.127	5.128	6.473
12.000	2.891	3.707	1.450	2.848	2.435	0.951	6.601	4.873	3.111	4.333
16.000	1.494	2.088	0.000	1.752	1.207	0.000	4.056	2.215	1.684	2.658
24.000	0.000	1.863	0.000	0.839	0.893	0.000	1.388	1.170	0.911	1.492

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R										
	Subject										
	Concentration (ng/mL)										
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.500	4.819	0.000	0.000	3.453	2.071	2.526	0.000	0.000	4.205	3.637	0.000
0.750	12.865	1.659	0.825	40.880	12.607	13.746	4.491	18.556	12.039	8.348	0.000
1.000	57.453	3.491	6.305	71.254	16.805	24.464	33.337	134.690	21.276	18.889	6.377
1.250	145.203	6.292	27.630	140.271	22.343	34.363	97.888	297.751	22.726	24.204	51.788
1.500	177.063	4.598	32.131	174.886	23.759	53.237	103.971	259.303	54.202	29.463	124.807
1.750	179.281	4.242	44.097	164.020	26.248	67.619	94.197	231.121	51.576	131.111	181.657
2.000	146.252	5.238	56.668	121.164	21.655	97.186	74.004	173.853	44.068	151.903	233.562
2.250	128.481	7.043	70.216	107.233	21.693	151.742	64.178	150.795	64.050	131.595	176.748
2.500	98.341	9.370	73.067	84.146	18.411	142.075	57.737	131.097	108.823	96.497	126.866
2.750	76.861	11.841	62.385	71.400	18.751	117.339	35.665	101.673	162.538	90.833	113.338
3.000	57.653	11.825	66.008	51.710	19.759	113.567	30.341	91.269	144.376	114.981	119.134
3.500	37.869	37.786	66.285	38.938	24.595	81.033	21.446	63.233	145.582	60.539	78.829
4.000	27.103	93.726	59.862	25.400	34.990	67.990	13.202	37.404	137.167	35.342	60.870
4.500	21.525	89.592	67.786	17.441	40.192	42.677	12.491	35.086	109.352	23.236	39.083
5.000	16.384	79.816	57.466	13.381	44.833	31.106	9.867	28.932	85.568	11.284	29.336
6.000	9.815	35.106	41.409	6.952	36.824	18.552	7.896	20.451	50.639	10.723	20.056
7.000	6.057	15.853	18.092	6.841	13.647	10.424	5.217	13.450	29.368	5.736	9.749
8.000	4.581	9.727	10.078	4.344	6.746	7.823	4.026	10.750	17.808	4.482	8.635
10.000	3.142	5.120	5.941	2.885	2.827	6.464	2.980	5.889	12.384	3.892	4.473
12.000	2.006	2.983	3.930	2.293	2.519	4.234	2.563	3.262	9.347	2.458	3.068
16.000	1.629	2.019	2.292	0.000	1.391	2.375	1.066	2.644	5.303	1.812	2.096
24.000	1.326	1.751	1.147	0.000	0.789	1.710	0.000	0.807	3.147	0.835	1.059

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R					
	Subject					
	Concentration (ng/mL)					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000	0.000
0.500	0.000	0.000	0.000	0.000	0.000	0.000
0.750	3.686	1.593	12.871	0.000	0.000	0.000
1.000	35.195	4.775	41.734	0.000	0.000	0.000
1.250	43.028	77.385	93.456	0.000	1.896	0.000
1.500	38.927	132.282	117.014	2.385	61.550	0.000
1.750	37.511	131.234	117.773	3.714	157.188	0.861
2.000	51.850	139.935	108.116	3.568	119.314	2.052
2.250	51.707	109.050	90.892	5.825	139.990	5.274
2.500	47.145	75.207	106.557	17.163	115.647	15.636
2.750	41.489	64.031	70.795	26.330	82.625	19.794
3.000	38.576	44.775	71.465	19.049	76.858	47.001
3.500	30.347	26.458	57.337	97.849	50.488	64.825
4.000	19.490	17.726	50.435	102.659	33.824	60.593
4.500	11.645	13.097	38.206	60.246	25.583	44.775
5.000	7.413	9.172	27.186	53.198	18.011	34.358
6.000	4.399	5.561	13.447	22.863	12.582	18.584
7.000	2.620	4.776	6.969	8.014	7.318	6.758
8.000	2.205	3.787	5.176	5.391	4.764	3.429
10.000	2.094	1.961	3.684	3.089	3.765	1.681
12.000	1.176	1.557	2.437	2.012	2.726	0.831
16.000	0.000	1.044	2.038	1.255	1.446	0.000
24.000	0.000	0.000	0.924	0.000	1.032	0.000

Table No. 14.2.1.6

Time (h)	Plasma concentration of Spironolactone for Reference Product-R							
	N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
0.000	115	0.000	0.0000	0.000	0.000	0.000	-	-
0.250	115	0.058	0.5443	0.000	0.000	5.775	937.3	-
0.500	115	2.950	12.5511	0.000	0.000	113.492	425.4	-
0.750	115	12.742	35.0080	0.000	1.593	248.531	274.7	-
1.000	115	26.552	49.7522	0.000	5.777	282.742	187.4	-
1.250	115	49.358	63.6669	0.000	20.050	297.751	129.0	-
1.500	115	72.103	69.2318	0.000	56.884	318.485	96.0	-
1.750	115	88.425	70.6127	0.000	83.818	294.525	79.9	-
2.000	115	94.067	66.3540	0.793	97.186	296.577	70.5	58.079
2.250	115	92.054	59.6269	2.334	92.489	291.840	64.8	64.287
2.500	115	89.200	54.6943	2.982	84.146	307.241	61.3	68.143
2.750	115	85.224	54.0561	2.520	76.861	301.287	63.4	66.683
3.000	115	78.664	50.0155	3.672	70.907	316.083	63.6	63.550
3.500	115	65.441	39.1235	9.991	57.108	239.718	59.8	54.943
4.000	115	55.251	35.4700	9.322	47.076	194.909	64.2	45.570
4.500	115	43.765	29.9755	7.204	36.003	187.040	68.5	35.393
5.000	115	34.528	24.9163	7.044	26.301	132.812	72.2	27.428
6.000	115	22.119	20.8567	3.325	14.882	139.997	94.3	16.414
7.000	115	11.431	8.2292	2.620	8.267	43.761	72.0	9.367
8.000	115	7.734	4.4222	2.138	6.751	21.531	57.2	6.688
10.000	115	4.761	2.6555	1.187	3.781	14.887	55.8	4.157
12.000	115	3.271	1.9236	0.831	2.806	11.754	58.8	2.832
16.000	115	1.916	1.1672	0.000	1.629	6.283	60.9	-
24.000	115	0.862	0.8096	0.000	0.890	3.687	93.9	-

Table No. 14.2.1.7

Time (h)	Plasma concentration of data excluded from statistical analysis for Spironolactone				
	Subject				
	Concentration (ng/mL)				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Period-I	Period-I	Period-I	Period-I	Period-I
	Reference -R	Reference -R	Reference -R	Reference -R	Reference-R
0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000
0.500	0.000	1.232	0.000	0.000	0.000
0.750	2.818	10.256	0.852	0.000	0.000
1.000	13.237	14.418	25.164	0.998	0.780
1.250	22.468	14.707	42.879	3.806	2.849
1.500	54.675	12.658	85.648	24.875	45.035
1.750	80.011	14.302	94.696	70.437	172.343
2.000	70.531	13.112	90.392	243.433	187.687
2.250	68.274	21.314	76.826	134.291	150.992
2.500	55.215	24.198	56.954	136.363	134.328
2.750	43.445	70.493	54.022	115.456	108.889
3.000	36.497	158.307	48.438	106.585	83.506
3.500	25.156	107.807	41.246	74.898	59.831
4.000	18.572	74.123	53.959	54.531	36.235
4.500	15.713	51.951	47.577	39.459	30.156
5.000	17.705	36.707	33.674	28.403	21.427
6.000	15.457	16.080	15.581	17.696	12.506
7.000	6.051	9.980	7.740	7.995	8.152
8.000	3.143	7.013	5.530	5.970	4.916
10.000	1.827	4.368	2.415	4.483	3.133
12.000	1.352	2.907	1.663	2.034	2.619
16.000	0.979	2.128	1.139	1.169	1.513
24.000	0.000	1.298	0.000	0.000	0.000
	Note 1: ^ subjects were withdrawn.				
	Note: Subject No. [redacted] (Period-I) excluded from statistical analysis as per protocol criteria 11.1.1(d).				

Table No. 14.2.1.7

Time (h)	Plasma concentration of data excluded from statistical analysis for Spironolactone				
	Subject				
	Concentration (ng/mL)				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Period-I	Period-I	Period-I	Period-I	Period-I
	Test -T	Reference-R	Test -T	Test -T	Test -T
0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	2.160	0.848	0.000
0.500	0.000	5.026	34.734	1.433	0.000
0.750	1.009	38.889	73.421	27.214	0.000
1.000	1.592	99.285	208.740	207.705	6.824
1.250	8.907	129.169	203.654	220.126	38.139
1.500	36.264	150.152	186.007	206.481	104.682
1.750	95.571	111.039	130.851	180.310	107.614
2.000	153.579	113.812	104.331	138.746	108.585
2.250	119.543	73.605	80.147	105.110	140.606
2.500	98.542	62.875	63.538	94.907	127.708
2.750	79.835	56.081	49.138	76.209	116.635
3.000	65.303	43.431	39.727	65.901	89.770
3.500	41.665	28.693	31.268	47.787	62.186
4.000	26.636	20.901	29.289	35.879	64.983
4.500	17.194	15.038	25.575	24.290	47.246
5.000	14.105	13.127	22.579	19.300	31.199
6.000	8.473	7.680	16.501	14.835	13.928
7.000	5.974	5.409	9.999	11.062	8.696
8.000	4.263	4.475	7.013	9.122	4.744
10.000	3.368	3.353	4.639	6.798	3.507
12.000	2.135	2.528	3.683	3.840	2.905
16.000	M	2.338	M	2.008	1.475
24.000	M	0.000	M	0.000	1.239
	Note 1: ^ subjects were withdrawn.				
	Note: Subject No. [redacted] (Period-I) excluded from statistical analysis as per protocol criteria 11.1.1(d).				

Table No. 14.2.1.7

Time (h)	Plasma concentration of data excluded from statistical analysis for Spironolactone				
	Subject				
	Concentration (ng/mL)				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Period-I	Period-I	Period-I	Period-I	Period-I
	Reference-R	Test -T	Reference-R	Reference-R	Test -T
0.000	0.000	0.000	0.000	0.000	0.000
0.250	0.000	0.000	0.000	0.000	0.000
0.500	1.756	0.000	1.430	0.000	0.000
0.750	22.350	0.000	2.274	0.000	0.000
1.000	62.729	0.000	2.907	0.000	0.000
1.250	104.982	0.000	10.215	0.000	0.977
1.500	135.594	1.346	39.353	0.000	2.308
1.750	122.448	14.792	42.911	0.000	3.243
2.000	118.947	66.352	52.354	0.000	5.421
2.250	90.152	64.053	140.837	0.000	5.586
2.500	70.775	103.256	153.979	0.000	7.308
2.750	58.286	88.654	198.552	0.000	10.346
3.000	45.333	61.734	154.199	0.000	12.304
3.500	31.691	41.071	119.435	0.000	37.958
4.000	21.625	22.838	79.337	0.000	55.148
4.500	14.886	14.706	56.749	0.000	76.623
5.000	11.752	11.344	32.263	0.000	67.633
6.000	7.226	6.764	17.955	0.000	35.311
7.000	5.217	4.020	10.532	0.000	13.554
8.000	3.958	3.201	6.660	0.000	7.977
10.000	2.500	1.636	1.533	0.000	4.046
12.000	1.808	0.991	4.117	0.000	3.313
16.000	1.573	0.000	2.516	0.000	1.680
24.000	M	0.000	1.674	0.000	0.849
	Note 1: ^ subjects were withdrawn.				
	Note: Subject No [redacted] (Period-I) excluded from statistical analysis as per protocol criteria 11.1.1(d).				

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	10:16	1	0.017	2.267
	1	15:01	1	0.017	7.017
	2	8:32	2	0.033	0.533
	2	12:31	1	0.017	4.517
	1	13:01	1	0.017	5.017
	2	10:46	1	0.017	2.767
	1	12:03	1	0.017	4.017
	2	18:03	1	0.017	10.017
	1	10:18	1	0.017	2.267
	2	8:34	2	0.033	0.533
	2	9:18	1	0.017	1.267
	2	11:33	1	0.017	3.517
	2	20:03	1	0.017	12.017
	1	14:05	1	0.017	6.017
	2	8:36	2	0.033	0.533
	1	10:20	1	0.017	2.267
	2	8:37	1	0.017	0.517
	2	12:07	1	0.017	4.017
	2	8:52	1	0.017	0.767
	2	10:52	1	0.017	2.767
	2	8:07	1	0.017	24.017
	1	10:54	1	0.017	2.767
	1	8:09	1	0.017	24.017
	2	10:25	2	0.033	2.283
	1	10:09	1	0.017	2.017
	1	12:09	1	0.017	4.017
	2	9:39	1	0.017	1.517
	2	10:09	1	0.017	2.017
	2	10:54	1	0.017	2.767
	2	11:39	1	0.017	3.517
	2	12:09	1	0.017	4.017
	2	12:39	1	0.017	4.517
	2	13:09	1	0.017	5.017
	1	8:11	1	0.017	24.017

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	0:12	2	0.033	16.033
	2	10:11	1	0.017	2.017
	2	11:41	1	0.017	3.517
	1	12:11	1	0.017	4.017
	2	12:11	1	0.017	4.017
	2	8:11	1	0.017	24.017
	1	14:17	5	0.083	6.083
	1	0:13	1	0.017	16.017
	2	15:13	1	0.017	7.017
	2	8:13	1	0.017	24.017
	1	8:43	1	0.017	0.517
	1	9:43	1	0.017	1.517
	1	10:28	1	0.017	2.267
	1	12:13	1	0.017	4.017
	1	0:13	1	0.017	16.017
	2	8:59	2	0.033	0.783
	2	15:13	1	0.017	7.017
	2	8:13	1	0.017	24.017
	1	8:45	1	0.017	0.517
	1	18:15	1	0.017	10.017
	1	11:45	1	0.017	3.517
	1	0:15	1	0.017	16.017
	2	11:17	3	0.050	3.050
	2	12:15	1	0.017	4.017
	2	12:46	2	0.033	4.533
	2	11:18	2	0.033	3.033
	2	12:48	2	0.033	4.533
	1	9:47	1	0.017	1.517
	1	0:17	1	0.017	16.017
	2	15:17	1	0.017	7.017
	1	12:22	4	0.067	4.067
	1	0:19	1	0.017	16.017
	2	8:19	1	0.017	24.017
	1	20:19	1	0.017	12.017

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	10:34	1	0.017	2.267
	2	9:51	3	0.050	1.550
	2	11:49	1	0.017	3.517
	1	12:21	1	0.017	4.017
	1	0:21	1	0.017	16.017
	1	15:21	1	0.017	7.017
	2	9:52	2	0.033	1.533
	2	10:21	1	0.017	2.017
	2	11:51	1	0.017	3.517
	2	18:21	1	0.017	10.017
	1	9:53	1	0.017	1.517
	1	11:23	1	0.017	3.017
	1	12:24	2	0.033	4.033
	1	13:23	1	0.017	5.017
	1	0:23	1	0.017	16.017
	2	8:53	1	0.017	0.517
	2	9:33	11	0.183	1.183
	1	8:53	1	0.017	0.517
	1	9:09	2	0.033	0.783
	1	9:26	4	0.067	1.067
	1	10:09	2	0.033	1.783
	1	8:23	1	0.017	24.017
	2	0:23	1	0.017	16.017
	1	12:25	1	0.017	4.017
	1	20:25	1	0.017	12.017
	2	20:25	1	0.017	12.017
	2	8:56	2	0.033	0.533
	2	11:10	1	0.017	2.767
	2	11:55	1	0.017	3.517
	2	13:25	1	0.017	5.017
	2	14:25	1	0.017	6.017
	2	15:25	1	0.017	7.017
	2	16:25	1	0.017	8.017
	1	10:10	1	0.017	1.767

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	10:40	1	0.017	2.267
	2	9:25	1	0.017	1.017
	2	10:25	1	0.017	2.017
	2	20:25	1	0.017	12.017
	2	0:25	1	0.017	16.017
	1	9:12	1	0.017	0.767
	1	9:27	1	0.017	1.017
	1	10:43	2	0.033	2.283
	1	18:28	2	0.033	10.033
	1	0:27	1	0.017	16.017
	1	8:27	1	0.017	24.017
	2	16:27	1	0.017	8.017
	2	8:27	1	0.017	24.017
	1	9:27	1	0.017	1.017
	1	16:28	2	0.033	8.033
	1	20:27	1	0.017	12.017
	1	0:27	1	0.017	16.017
	2	8:58	2	0.033	0.533
	2	9:57	1	0.017	1.517
	2	11:12	1	0.017	2.767
	2	14:27	1	0.017	6.017
	1	9:12	1	0.017	0.767
	1	12:57	1	0.017	4.517
	2	10:27	1	0.017	2.017
	2	14:27	1	0.017	6.017
	1	10:44	1	0.017	2.267
	1	13:29	1	0.017	5.017
	1	18:29	1	0.017	10.017
	1	8:29	1	0.017	24.017
	2	8:29	1	0.017	24.017
	1	12:29	1	0.017	4.017
	1	16:29	1	0.017	8.017
	1	18:29	1	0.017	10.017
	1	0:31	3	0.050	16.050

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	2	9:00	2	0.033	0.533
	2	10:44	1	0.017	2.267
	2	11:29	1	0.017	3.017
	2	12:00	2	0.033	3.533
	2	12:59	1	0.017	4.517
	2	14:29	1	0.017	6.017
	2	8:29	1	0.017	24.017
	2	8:31	1	0.017	0.517
	2	9:31	1	0.017	1.517
	1	8:31	1	0.017	0.517
	1	8:46	1	0.017	0.767
	2	8:46	1	0.017	0.767
	2	9:31	1	0.017	1.517
	2	12:01	1	0.017	4.017
	2	18:01	1	0.017	10.017
	1	0:03	1	0.017	16.017
	2	9:18	1	0.017	1.267
	2	11:03	1	0.017	3.017
	1	12:33	1	0.017	4.517
	1	14:03	1	0.017	6.017
	2	9:03	1	0.017	1.017
	2	0:03	1	0.017	16.017
	2	8:33	1	0.017	0.517
	2	9:18	1	0.017	1.267
	1	15:05	1	0.017	7.017
	1	20:05	1	0.017	12.017
	1	0:05	1	0.017	16.017
	2	8:22	1	0.017	0.267
	1	0:07	1	0.017	16.017
	2	8:52	1	0.017	0.767
	2	10:23	2	0.033	2.283
	1	11:07	1	0.017	3.017
	1	0:09	1	0.017	16.017
	1	8:09	1	0.017	24.017

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	2	8:24	1	0.017	0.267
	2	8:54	1	0.017	0.767
	2	12:39	1	0.017	4.517
	1	8:09	1	0.017	24.017
	2	8:28	5	0.083	0.333
	2	10:24	1	0.017	2.267
	1	0:09	1	0.017	16.017
	1	8:09	1	0.017	24.017
	1	9:11	1	0.017	1.017
	1	8:26	1	0.017	0.267
	1	8:41	1	0.017	0.517
	2	10:26	1	0.017	2.267
	2	15:11	1	0.017	7.017
	1	8:41	1	0.017	0.517
	1	9:26	1	0.017	1.267
	1	0:11	1	0.017	16.017
	1	8:11	1	0.017	24.017
	2	12:11	1	0.017	4.017
	2	15:11	1	0.017	7.017
	2	0:11	1	0.017	16.017
	1	0:13	1	0.017	16.017
	2	18:13	1	0.017	10.017
	1	8:13	1	0.017	24.017
	2	10:43	1	0.017	2.517
	2	14:13	1	0.017	6.017
	2	18:13	1	0.017	10.017
	2	20:13	1	0.017	12.017
	2	9:45	1	0.017	1.517
	1	11:00	1	0.017	2.767
	1	11:45	1	0.017	3.517
	1	8:17	1	0.017	24.017
	1	10:47	1	0.017	2.517
	1	11:02	1	0.017	2.767
	1	12:17	1	0.017	4.017

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	2	20:17	1	0.017	12.017
	1	10:35	2	0.033	2.283
	1	20:19	1	0.017	12.017
	1	18:20	2	0.033	10.033
	1	0:19	1	0.017	16.017
	1	8:19	1	0.017	24.017
	2	13:19	1	0.017	5.017
	2	8:51	1	0.017	0.517
	2	10:21	1	0.017	2.017
	2	10:51	1	0.017	2.517
	1	8:21	1	0.017	24.017
	2	11:21	1	0.017	3.017
	1	8:36	1	0.017	0.267
	1	11:21	1	0.017	3.017
	1	18:22	2	0.033	10.033
	2	14:21	1	0.017	6.017
	2	8:21	1	0.017	24.017
	1	8:53	1	0.017	0.517
	1	10:53	1	0.017	2.517
	1	11:53	1	0.017	3.517
	2	9:53	1	0.017	1.517
	2	18:23	1	0.017	10.017
	1	18:23	1	0.017	10.017
	2	11:09	2	0.033	2.783
	1	12:28	4	0.067	4.067
	1	20:26	2	0.033	12.033
	1	0:25	1	0.017	16.017
	2	11:55	1	0.017	3.517
	2	13:25	1	0.017	5.017
	2	18:25	1	0.017	10.017
	2	0:25	1	0.017	16.017
	1	8:56	2	0.033	0.533
	1	16:25	1	0.017	8.017
	1	0:25	1	0.017	16.017

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	8:25	1	0.017	24.017
	2	0:25	1	0.017	16.017
	1	0:25	1	0.017	16.017
	2	8:55	1	0.017	0.517
	2	11:10	1	0.017	2.767
	2	0:25	1	0.017	16.017
	1	12:28	2	0.033	4.033
	1	20:27	1	0.017	12.017
	1	0:27	1	0.017	16.017
	1	8:28	2	0.033	24.033
	2	10:42	1	0.017	2.267
	2	11:57	1	0.017	3.517
	2	18:28	2	0.033	10.033
	2	8:27	1	0.017	24.017
	1	8:57	1	0.017	0.517
	1	11:12	1	0.017	2.767
	1	11:27	1	0.017	3.017
	1	14:27	1	0.017	6.017
	1	15:27	1	0.017	7.017
	2	10:25	-1	-0.017	1.983
	2	11:27	1	0.017	3.017
	2	0:27	1	0.017	16.017
	2	8:27	1	0.017	24.017
	1	8:43	2	0.033	0.283
	1	9:13	2	0.033	0.783
	1	9:27	1	0.017	1.017
	1	12:57	1	0.017	4.517
	1	16:27	1	0.017	8.017
	1	11:14	1	0.017	2.767
	1	12:30	2	0.033	4.033
	1	8:29	1	0.017	24.017
	2	18:31	3	0.050	10.050
	2	0:31	3	0.050	16.050
	1	8:44	1	0.017	0.267

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	11:30	2	0.033	3.033
	1	11:59	1	0.017	3.517
	1	12:29	1	0.017	4.017
	1	14:29	1	0.017	6.017
	1	20:29	1	0.017	12.017
	1	8:30	2	0.033	24.033
	2	8:29	1	0.017	24.017
	1	12:31	1	0.017	4.517
	1	15:58	-2	-0.033	7.967
	2	12:31	1	0.017	4.517
	1	9:31	1	0.017	1.517
	1	12:31	1	0.017	4.517
	2	8:01	1	0.017	24.017
	1	12:31	1	0.017	4.517
	1	8:34	2	0.033	0.533
	1	9:48	1	0.017	1.767
	1	10:03	1	0.017	2.017
	1	10:18	1	0.017	2.267
	1	10:33	1	0.017	2.517
	1	13:03	1	0.017	5.017
	1	0:03	1	0.017	16.017
	2	14:03	1	0.017	6.017
	2	0:03	1	0.017	16.017
	1	8:20	1	0.017	0.267
	1	11:05	1	0.017	3.017
	1	16:05	1	0.017	8.017
	1	8:35	1	0.017	0.517
	1	10:50	1	0.017	2.767
	1	16:05	1	0.017	8.017
	2	12:05	1	0.017	4.017
	2	14:05	1	0.017	6.017
	1	0:05	1	0.017	16.017
	1	8:53	2	0.033	0.783
	2	9:22	1	0.017	1.267

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	2	9:35	-1	-0.017	1.483
	1	11:05	-1	-0.017	2.983
	2	8:25	4	0.067	0.317
	1	13:07	1	0.017	5.017
	1	8:54	1	0.017	0.767
	1	11:39	1	0.017	3.517
	2	20:09	1	0.017	12.017
	1	10:54	1	0.017	2.767
	1	14:09	1	0.017	6.017
	2	8:24	1	0.017	0.267
	1	0:09	1	0.017	16.017
	1	8:09	1	0.017	24.017
	2	9:09	1	0.017	1.017
	1	10:41	1	0.017	2.517
	1	10:56	1	0.017	2.767
	1	11:41	1	0.017	3.517
	2	9:41	1	0.017	1.517
	2	8:09	-1	-0.017	23.983
	1	18:11	1	0.017	10.017
	1	0:11	1	0.017	16.017
	1	8:11	1	0.017	24.017
	2	0:11	1	0.017	16.017
	1	8:13	1	0.017	24.017
	2	9:01	4	0.067	0.817
	1	9:01	2	0.033	0.783
	2	9:30	1	0.017	1.267
	1	9:30	1	0.017	1.267
	1	16:15	1	0.017	8.017
	1	0:15	1	0.017	16.017
	1	11:17	1	0.017	3.017
	2	8:32	1	0.017	0.267
	1	8:32	1	0.017	0.267
	1	11:03	2	0.033	2.783
	1	16:18	2	0.033	8.033

Table No. 14.2.2

Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	0:17	1	0.017	16.017
	1	8:49	1	0.017	0.517
	2	18:19	1	0.017	10.017
	1	9:19	1	0.017	1.017
	1	11:04	1	0.017	2.767
	1	12:19	1	0.017	4.017
	1	13:19	1	0.017	5.017
	1	0:19	1	0.017	16.017
	1	8:35	2	0.033	0.283
	1	12:49	1	0.017	4.517
	1	8:20	2	0.033	24.033
	2	9:21	1	0.017	1.017
	2	11:09	4	0.067	2.817
	2	18:21	1	0.017	10.017
	1	0:21	1	0.017	16.017
	2	8:36	1	0.017	0.267
	2	10:36	1	0.017	2.267
	1	10:23	1	0.017	2.017
	2	11:09	2	0.033	2.783
	2	11:53	1	0.017	3.517
	2	12:53	1	0.017	4.517
	2	9:38	1	0.017	1.267
	1	14:23	1	0.017	6.017
	2	8:23	1	0.017	24.017
	1	10:25	1	0.017	2.017
	2	11:10	1	0.017	2.767
	2	11:55	1	0.017	3.517
	1	9:55	1	0.017	1.517
	1	0:26	2	0.033	16.033
	1	8:25	1	0.017	24.017
	2	8:25	1	0.017	24.017
	1	11:55	1	0.017	3.517
	2	9:40	1	0.017	1.267
	1	8:57	1	0.017	0.517

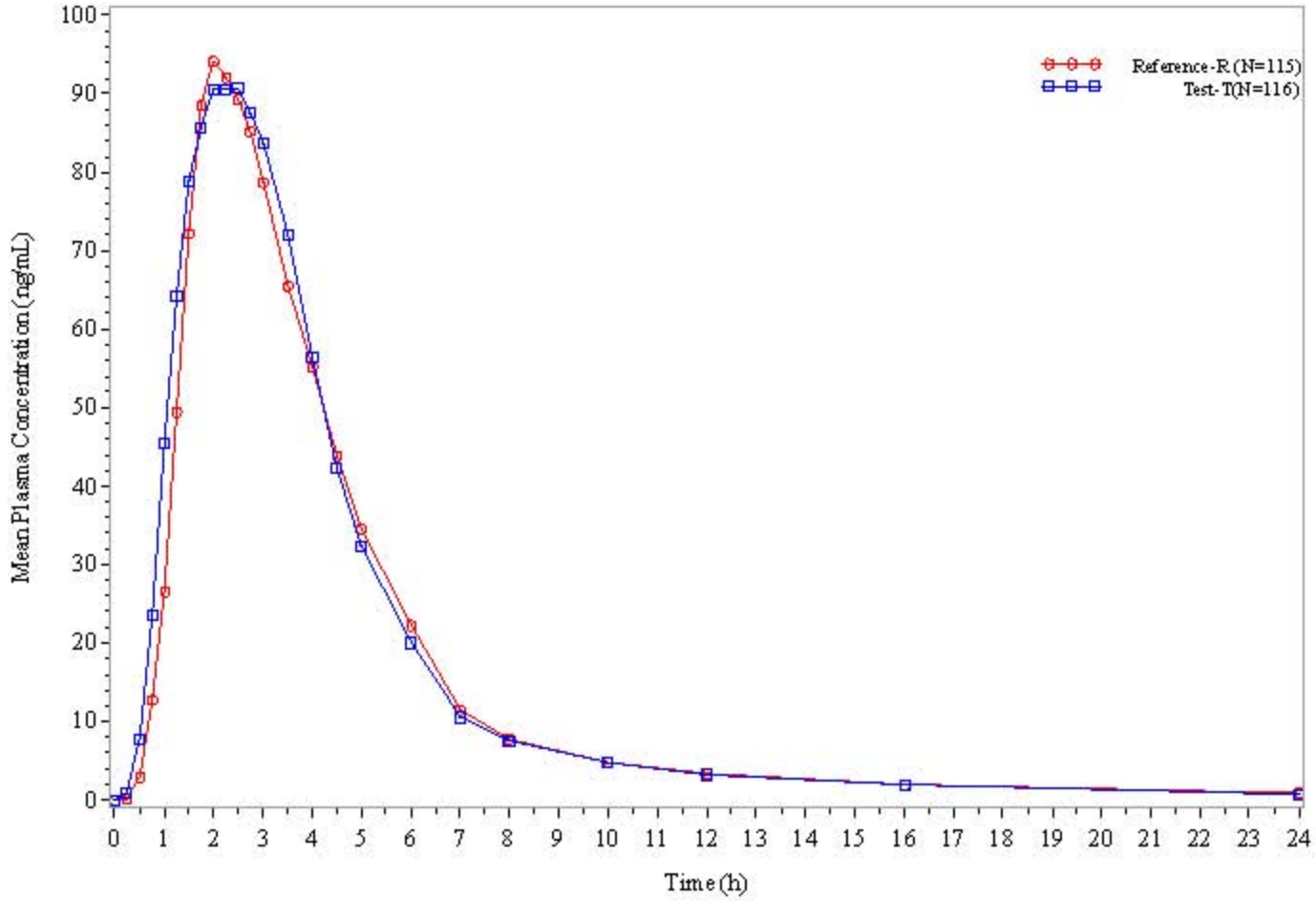
Table No. 14.2.2

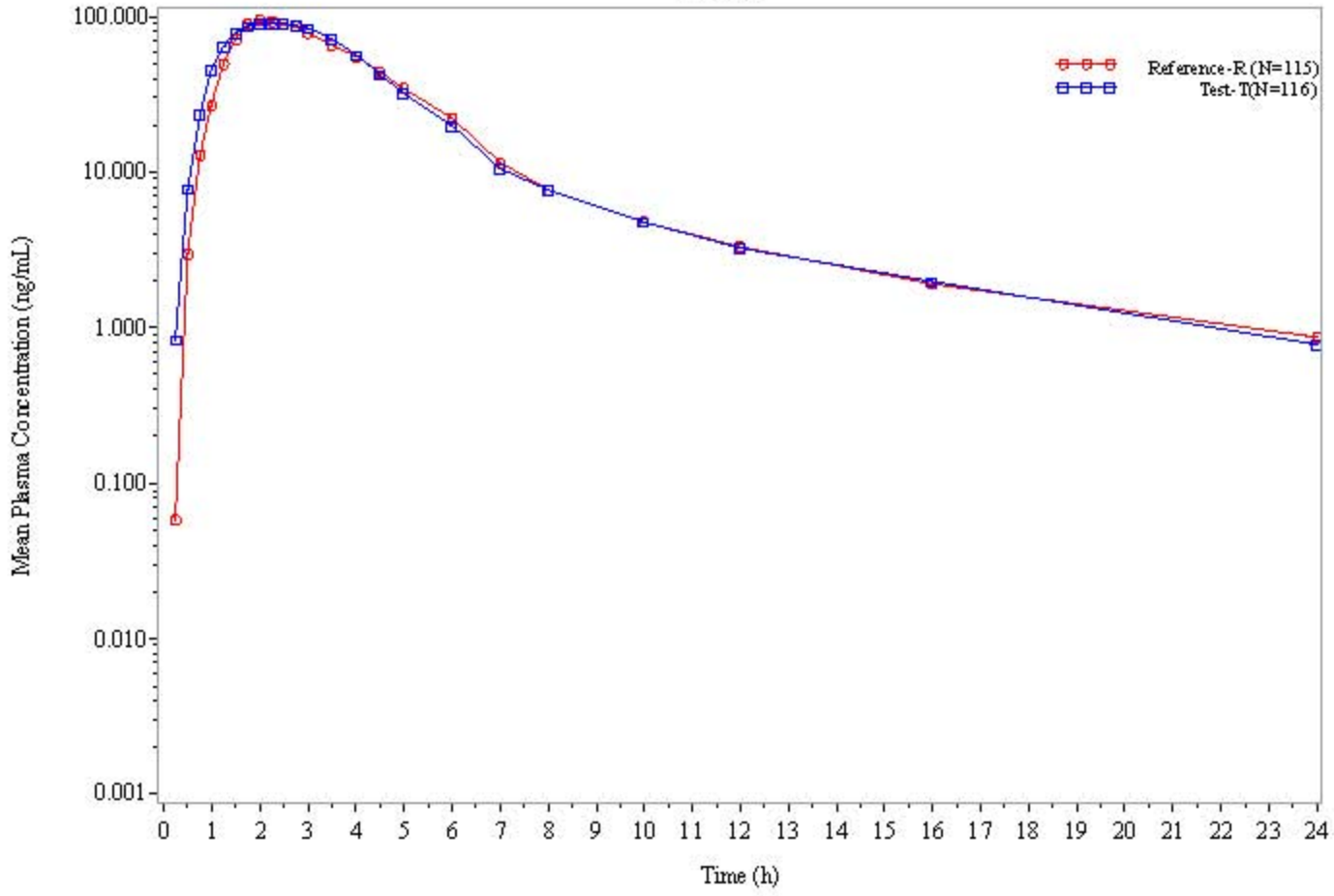
Sampling time point deviations used for pharmacokinetic evaluation

Subject	Period	Actual Time (hh:mm)	Difference in Minutes	Difference in Hour	Actual Time of Collection (h)
[redacted]	1	10:57	1	0.017	2.517
	1	8:27	1	0.017	24.017
	2	11:27	1	0.017	3.017
	2	11:57	1	0.017	3.517
	1	14:27	1	0.017	6.017
	1	0:27	1	0.017	16.017
	1	15:27	1	0.017	7.017
	1	0:27	1	0.017	16.017
	1	8:27	1	0.017	24.017
	2	13:27	1	0.017	5.017
	1	11:29	1	0.017	3.017
	1	8:29	1	0.017	24.017
	2	0:29	1	0.017	16.017
	1	8:44	1	0.017	0.267
	1	0:29	1	0.017	16.017
	2	13:29	1	0.017	5.017
	2	16:29	1	0.017	8.017
	1	10:44	1	0.017	2.267
	1	12:59	1	0.017	4.517
	1	18:29	1	0.017	10.017
	2	8:29	1	0.017	24.017
	1	8:58	1	0.017	0.767
	1	9:13	1	0.017	1.017
	1	9:29	2	0.033	1.283
	1	11:43	1	0.017	3.517
	1	16:13	1	0.017	8.017
	1	18:13	1	0.017	10.017

14.2.3.1

Mean plasma concentration vs. time curve for Spironolactone
(Upper panel : linear plot; Lower panel : semilog plot)

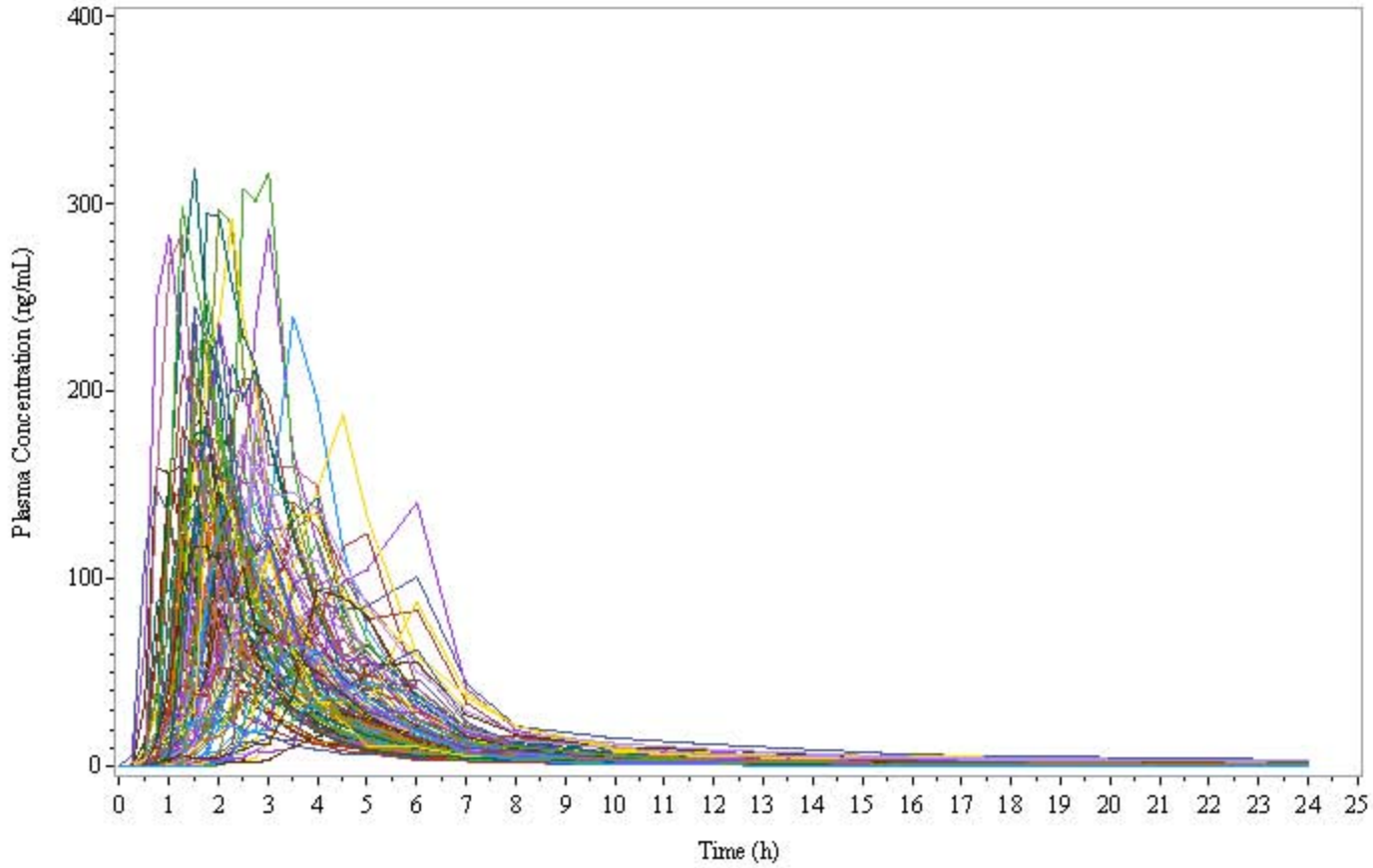




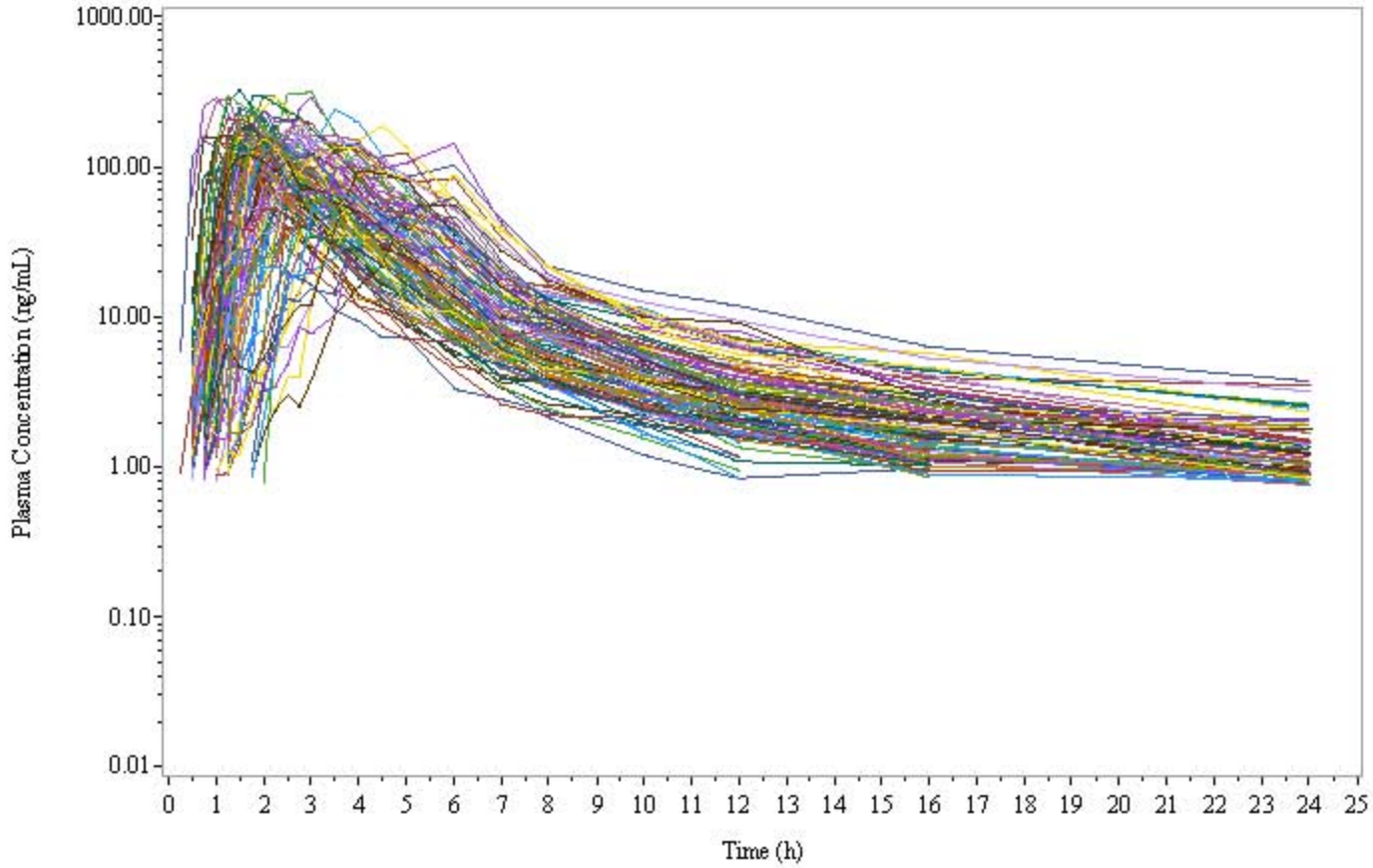
14.2.3.2

Summary plot of individual plasma concentration vs. time curve for Spironolactone
(Upper panel: Linear plot; Lower panel: Semilog plot)

Formulation=R

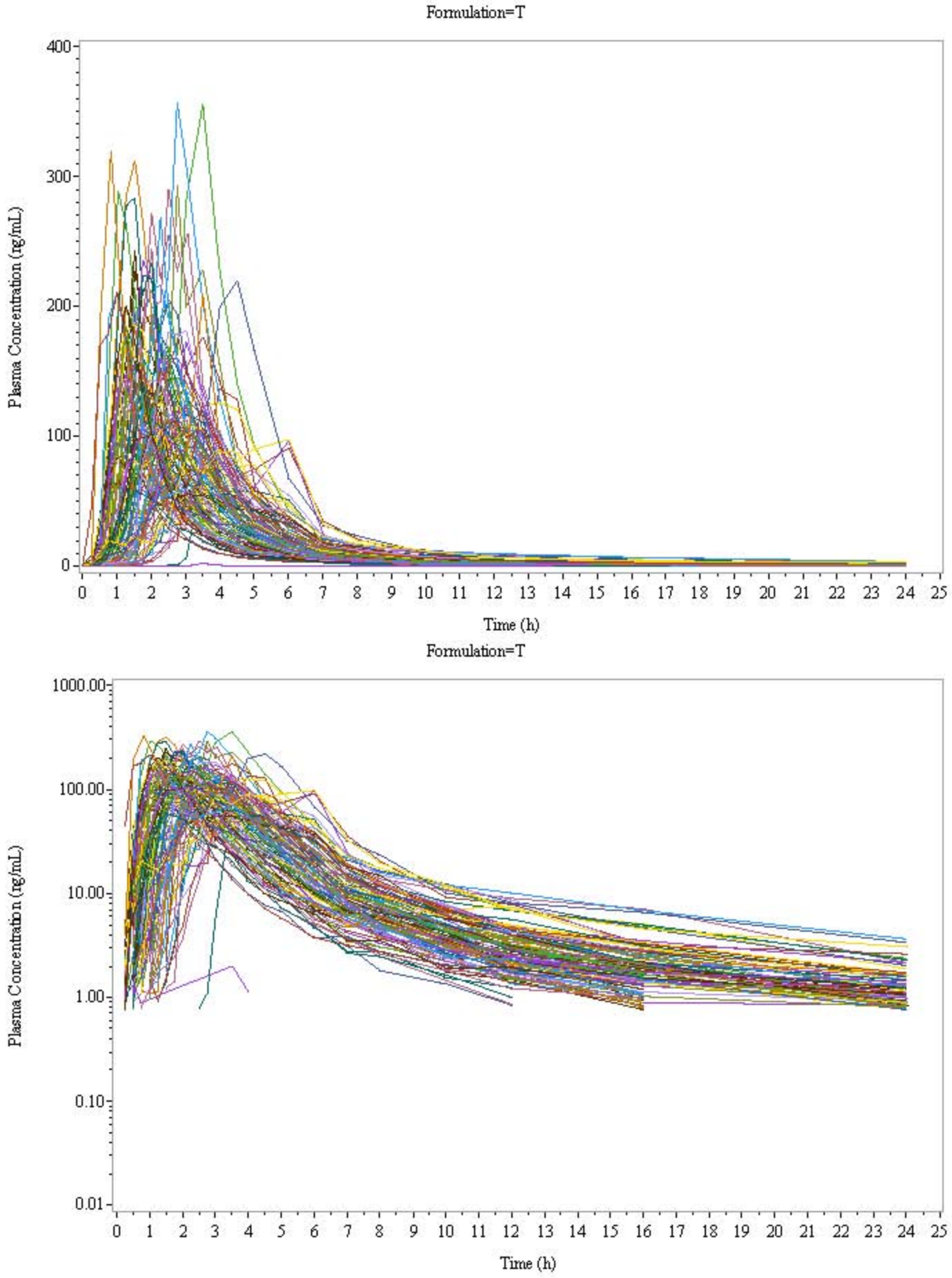


Formulation=R



14.2.3.2

Summary plot of individual plasma concentration vs. time curve for Spironolactone
(Upper panel: Linear plot; Lower panel: Semilog plot)



14.3.1 Displays of Adverse Events

Test Product-T (N=122)									
Adverse event (Preferred Term)	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	R	**NR**	**R**	**NR**	**R**	**NR**	**R**	**NR**	**R+NR**
General disorders and administration site conditions									
Pyrexia	1 (0.82%)	1 (0.82%)	0	0	0	0	1 (0.82%)	1 (0.82%)	2
Subject Nos.	[redacted]	[redacted]							
Nervous system disorders									
Headache	1 (0.82%)	1 (0.82%)	0	0	0	0	1 (0.82%)	1 (0.82%)	2
Subject Nos.	[redacted]	[redacted]							
Vascular disorders									
Thrombophlebitis superficial	0	1 (0.82%)	0	0	0	0	0	1 (0.82%)	1
Subject No.		[redacted]							
Investigations									
Alanine aminotransferase increased	1 (0.82%)	0	0	0	0	0	1 (0.82%)	0	1
Subject No.	[redacted]								
Aspartate aminotransferase increased	1 (0.82%)	0	0	0	0	0	1 (0.82%)	0	1
Subject No.	[redacted]								
Reference Product-R (N=124)									
Adverse event (Preferred Term)	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	R	**NR**	**R**	**NR**	**R**	**NR**	**R**	**NR**	**R+NR**
General disorders and administration site conditions									
Pyrexia	3 (2.42%)	1 (0.81%)	0	0	0	0	3 (2.42%)	1 (0.81%)	4
Subject Nos.	[redacted]	[redacted]							
Nervous system disorders									
Headache	2 (1.61%)	1 (0.81%)	0	0	0	0	2 (1.61%)	1 (0.81%)	3
Subject Nos.	[redacted]	[redacted]							

Continued....

Refer Appendix No. 16.2.7 for MedDRA version used for adverse event coding.

14.3.1 Displays of Adverse Events

Adverse event (Preferred Term)	Mild		Moderate		Severe		Total		Total
	R	NR	R	NR	R	NR	R	NR	R+NR
Musculoskeletal and connective tissue disorders									
Pain in Jaw	0	1 (0.81%)	0	0	0	0	0	1 (0.81%)	1
Subject No.		[redacted]							
Gastrointestinal disorders									
Vomiting	1 (0.81%)	0	0	0	0	0	1 (0.81%)	0	1
Subject No.	[redacted]								
Investigations									
Alanine aminotransferase increased	1 (0.81%)	0	0	0	0	0	1 (0.81%)	0	1
Subject No.	[redacted]								

R=Related; NR=Not Related

Calculation of % of AEs = Total number of AEs*100 / Total number of subjects who have consumed the particular study drug (Reference Product-R or Test Product-T) during the conduct of the study.

Refer Appendix No. 16.2.7 for MedDRA version used for adverse event coding.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

There were no deaths or serious adverse events during the conduct of the study. However, eight (08) significant AEs were reported during the conduct of the study.

Test Product-T (N=122)									
Adverse event (Preferred Term)	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	R	**NR**	**R**	**NR**	**R**	**NR**	**R**	**NR**	**R+NR**
General disorders and administration site conditions									
Pyrexia	1 (0.82%)	1 (0.82%)	0	0	0	0	1 (0.82%)	1 (0.82%)	2
Subject Nos.	[redacted]	[redacted]							
Nervous system disorders									
Headache	1 (0.82%)	1 (0.82%)	0	0	0	0	1 (0.82%)	1 (0.82%)	2
Subject Nos.	[redacted]	[redacted]							
Vascular disorders									
Thrombophlebitis superficial	0	1 (0.82%)	0	0	0	0	0	1 (0.82%)	1
Subject No.		[redacted]							
Reference Product-R (N=124)									
Adverse event (Preferred Term)	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	R	**NR**	**R**	**NR**	**R**	**NR**	**R**	**NR**	**R+NR**
General disorders and administration site conditions									
Pyrexia	0	1 (0.81%)	0	0	0	0	0	1 (0.81%)	1
Subject No.		[redacted]							
Nervous system disorders									
Headache	0	1 (0.81%)	0	0	0	0	0	1 (0.81%)	1
Subject No.		[redacted]							
Musculoskeletal and connective tissue disorders									
Pain in Jaw	0	1 (0.81%)	0	0	0	0	0	1 (0.81%)	1
Subject No.		[redacted]							

R=Related; NR=Not Related

Calculation of % of AEs = Total number of AEs*100 / Total number of subjects who have consumed the particular study drug (Reference Product-R or Test Product-T) during the conduct of the study.

Refer Appendix No. 16.2.7 for MedDRA version used for adverse event coding.

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

There were no deaths or serious adverse events during the conduct of the study. However, eight (08) significant AEs were reported during the conduct of the study.

Period-I

Subject No.	Age (years)	Gender	Adverse Event (Preferred Term)	Last IMP administered		Last IMP Administered	Medication Required	Severity of Adverse Event	Relationship to the Study Drug
				Time (hh:mm)	Date				
[redacted]	[redacted]	Male	Pyrexia Headache	[redacted]	[redacted]	Test Product-T	Yes	Mild	Unlikely Related

Summary and Management of the Significant Adverse Events

[redacted]

Contents of concomitant medication:

[redacted]

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

Period-I

Subject No.	Age (years)	Gender	Adverse Event (Preferred Term)	Last IMP administered		Last IMP Administered	Medication Required	Severity of Adverse Event	Relationship to the Study Drug
				Time (hh:mm)	Date				
[redacted]	[redacted]	Male	Pyrexia Headache	[redacted]	[redacted]	Test Product-T	Yes	Mild	Possibly Related

Summary and Management of the Significant Adverse Events

[redacted]

Contents of concomitant medication:

[redacted]

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

Period-I

Subject No.	Age (years)	Gender	Adverse Event (Preferred Term)	Last IMP administered		Last IMP Administered	Medication Required	Severity of Adverse Event	Relationship to the Study Drug
				Time (hh:mm)	Date				
[redacted]	[redacted]	Male	Thrombophlebitis superficial	[redacted]	[redacted]	Test Product-T	Yes	Mild	Not Related

Summary and Management of the Significant Adverse Event

[redacted]

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

Summary and Management of the Significant Adverse Event

[redacted]

Contents of concomitant medications:

[redacted]

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

Period-I

Subject No.	Age (years)	Gender	Adverse Event (Preferred Term)	Last IMP administered		Last IMP Administered	Medication Required	Severity of Adverse Event	Relationship to the Study Drug
				Time (hh:mm)	Date				
[redacted]	[redacted]	Male	Pyrexia Headache	[redacted]	[redacted]	Reference Product-R	Yes	Mild	Unlikely Related

Summary and Management of the Significant Adverse Events

[redacted]

Contents of concomitant medication:

[redacted]

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

Period-II

Subject No.	Age (years)	Gender	Adverse Event (Preferred Term)	Last IMP administered		Last IMP Administered	Medication Required	Severity of Adverse Event	Relationship to the Study Drug
				Time (hh:mm)	Date				
[redacted]	[redacted]	Male	Pain in Jaw	[redacted]	[redacted]	Reference Product-R	Yes	Mild	Unlikely Related

Summary and Management of the Significant Adverse Event

[redacted]

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

Summary and Management of the Significant Adverse Event

[redacted]

Contents of concomitant medications:

[redacted]

14.3.4 Abnormal Laboratory Value Listing (Each Subject)

Refer Appendix No. 16.2.8 (Listing of individual laboratory measurements by subject, when required by regulatory authorities)

15.0 REFERENCE LIST

1. Aldactone® 100 mg tablets, Summary of Product Characteristics (last updated on eMC: 03-May-2018).

   https://www.medicines.org.uk/emc/product/2898/smpchttps://www.medicines.org.uk/emc/medicine/2726

2. Schedule Y (with subsequent amendments) of CDSCO (Central Drugs Standard Control Organization) Ministry of health and family welfare, Government of India.

3. 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants', ICMR [Indian Council of Medical Research (2017)].

4. ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) 'Guideline for Good Clinical Practice' 2016.

5. Declaration of Helsinki (Brazil, October 2013).

6. 'Guidance for Bioanalytical Method Validation' U.S Department of Health and Human Services 21 May 2018.

7. Guideline on Bioanalytical Method Validation adopted on 21 July 2011. European Medicines Agency (EMA). EMEA/CHMP/EWP/192217/2009, Rev. 1.

16.0 APPENDICES

Appendix No.	Title
16.1	STUDY INFORMATION
16.1.1	Protocol and protocol amendments
16.1.2	Sample case report form
16.1.3	List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for subject and sample consent forms
16.1.4	List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
16.1.5	Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement
16.1.6	Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
16.1.7	Randomization scheme and codes (subject identification and treatment assigned)
16.1.8	Audit certificates
16.1.9	Documentation of statistical methods
16.1.9.1	SAS output of ANOVA and BE for Spironolactone [Excluding Subject No. [redacted] Period-I, R)]
16.2.9.2	SAS output of ANOVA and BE for Spironolactone [Including Subject No [redacted] (Period-I, R)]
16.1.10	Documentation of inter-laboratory standardization methods and quality assurance procedures if used
16.1.11	Publications based on the study
16.1.12	Important publications referenced in the report

Appendix No.	Title
16.2	SUBJECT DATA LISTINGS
16.2.1	Discontinued subjects
16.2.2	Protocol deviations
16.2.3	Subjects excluded from the pharmacokinetic analysis
16.2.4	Demographic data
16.2.5	Compliance and/or drug concentration data
16.2.5.1	Pharmacokinetic summary table of Spironolactone
16.2.5.2	Pharmacokinetic final parameters of Spironolactone
16.2.6	Individual pharmacokinetic response data
16.2.6.1	Individual plasma concentration vs. time curve for Spironolactone
16.2.7	Adverse event listings (each subject)
16.2.8	Listing of individual laboratory measurements by subject, when required by regulatory authorities
16.3	CASE REPORT FORMS
16.3.1	CRFs for deaths, other serious adverse events and withdrawals for AE
16.3.2	Other CRFs submitted
16.4	INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)
16.5	BIO-ANALYTICAL PHASE REPORT