

2.7.6 Synopses of Individual Studies

The synopsis of the single bioequivalence study: “A Single Centre, Single-Dose, Open-Label, Randomised, Four-Period Crossover Study to assess the Bioequivalence of an Oral Spironolactone Suspension 10 mg/ mL (KayraasTM) and an Oral spironolactone Tablet 100 mg (Aldactone®, Pfizer Healthcare, Ireland) in a Replicate Design in Healthy Males and Females under Fed Conditions” ([INV684](#)) is presented on the following pages.

2 SYNOPSIS

Title of Study	A SINGLE CENTER, SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, FOUR PERIOD CROSSOVER STUDY TO ASSESS THE BIOEQUIVALENCE OF AN ORAL SPIRONOLACTONE SUSPENSION 10 MG/ML (KAYRAAS™) AND AN ORAL SPIRONOLACTONE TABLET 100 MG (ALDACTONE®, PFIZER HEALTHCARE, IRELAND) IN A REPLICATE DESIGN IN HEALTHY MALES AND FEMALES UNDER FED CONDITIONS	
Study Numbers	<div style="background-color: black; width: 150px; height: 1.2em; display: inline-block;"></div> <div style="background-color: black; width: 80px; height: 1.2em; display: inline-block;"></div> Sponsor Study No.: INV684	
Investigational Medicinal Products	Reference Product:	Aldactone® 100 mg Tablet
	Test Product:	Spironolactone Oral Suspension 10 mg/mL (Kayraas™)
Development Phase	Phase 1 (Bioequivalence Study)	
Sponsor	<div style="background-color: black; width: 100%; height: 100px;"></div>	
Principal Investigator	<div style="background-color: black; width: 100%; height: 20px;"></div>	
Study Center	<div style="background-color: black; width: 100%; height: 20px;"></div>	
Publication	None	
Studied Period	First subject first visit:	11 August 2020 (<i>first signing of Informed Consent</i>)
	Last subject last visit:	19 October 2020 (<i>last sample drawn for repeated investigations of safety data</i>)
Study Objectives Primary Objective To determine whether the test product, spironolactone oral suspension 10 mg/mL (Kayraas™) and the reference product, Aldactone® 100 mg tablets are bioequivalent. For this purpose, the PK profile of spironolactone were compared after administration of a single dose of 100 mg spironolactone of each of the two formulations, under fed conditions. Secondary Objectives <ul style="list-style-type: none"> To evaluate the taste acceptability of the test product (spironolactone oral suspension 10 mg/mL). To evaluate the safety and tolerability of spironolactone oral suspension 10 mg/mL and Aldactone® 100 mg tablets in healthy males and females. 		
Study Design This was a single-dose, open-label, laboratory-blind, randomized, four period crossover, replicate study with orally administered spironolactone 100 mg conducted under fed conditions in at least 30 healthy males and females at a single study center. In order to evaluate the taste acceptability of the test product, subjects completed a palatability questionnaire after administration of the second dose of the test product (spironolactone oral suspension 10 mg/mL).		

The study comprised:

- a screening period of maximum 21 days,
- four treatment periods (each of which included a profile period of 24 hours) separated by a wash out period of 7 calendar days between consecutive administrations of the investigational medicinal product (IMP),
- interim safety evaluations that were performed within 72 hours before the commencement of Treatment Periods 2, 3 and 4, and
- a post-study visit within 72 hours of completion of the last treatment period of the study.

Procedures listed for the post-study visit were performed in the event of early withdrawal from the study.

Subjects were assigned randomly to treatment sequence, before the first administration of IMP.

Study Subjects

Planned for inclusion	36 subjects, to complete the study with 30 evaluable subjects
Enrolled and randomized	36 subjects (18 males and 18 females)
Drop-outs	None
Discontinuers	1 subject (female)
Completed as per protocol	35 subjects (18 males and 17 females)
Analyzed	36 subjects

Main Inclusion Criteria

The study included healthy male and female subjects aged 18 to 60 years (both inclusive) at the time of signing of informed consent, who weighed at least 50 kg and had a body mass index (BMI) between 18 and 29 kg/m² (both inclusive).

Subjects who met all the inclusion criteria and none of the exclusion criteria were considered eligible to participate in the study.

Reference Product (Treatment A), Dose and Mode of Administration, Batch Number

Generic name:	Spironolactone
Trade name:	Aldactone®
Manufacturer:	Pfizer Healthcare
Country of origin:	Ireland
Dosage form and strength:	100 mg tablets
Study dose:	100 mg (1 tablet)
Route of administration:	Oral
Packaging number:	NOVPh113
Expiry date:	31 December 2023
Assayed product content:	Not available

Test Product (Treatment B), Dose and Mode of Administration, Batch Number

Generic name:	Spironolactone
Product Name:	Kayraas™
Manufacturer:	Nova Laboratories Ltd.
Country of origin:	United Kingdom
Dosage form and strength:	Oral Suspension containing 10 mg/mL spironolactone
Study dose:	10 mL of spironolactone 10 mg/mL oral suspension (100 mg)
Route of administration:	Oral

Packaging number:	
Expiry date:	25 May 2021
Assayed product content:	10.1 mg/mL
Duration of Treatment Subjects received a single 100 mg oral dose of spironolactone, either as a tablet or oral suspension, in each of the four treatment periods, separated by a wash-out period of 7 calendar days.	
Administration of Investigational Medicinal Products After an overnight fast of at least 10 hours, subjects received a standardized high fat, high calorie breakfast 30 minutes before administration of IMP. The entire meal was consumed within 30 minutes. Subjects received either the reference or the test product (according to the randomization schedule) with 240 mL water, 30 minutes after the start of the meal. The tablet of spironolactone was swallowed whole with water. In the case of the test oral suspension (Kayraas™), 10 mL (100 mg) of the suspension was prepared by drawing up into a syringe for oral administration. The syringe was placed directly into the mouth of the subject and the contents gently released. The syringe was then rinsed with 10 mL water immediately after dosing, which the subject swallowed. Subjects were then asked to drink an additional 230 mL of water.	
Treatment Compliance To ensure treatment compliance, the IMP was self-administered by the subjects under supervision of the principal investigator or designee. A mouth check was performed after each dosing by the principal investigator or designee to ensure that the subjects had swallowed the IMP.	
Protocol Deviations The final version of the clinical study protocol and amendment were adhered to except for the following deviations: <ul style="list-style-type: none">• Twenty-eight blood samples were collected outside of the agreed time window during the study. As actual blood sampling times were used during pharmacokinetic (PK) analysis, these deviations did not influence the PK analysis.• One blood sample (Subject 032: Treatment Period 3; 10 minutes post-dose) was reported as a “missed assessment”. The deviations were all classified as “minor”. In the opinion of the investigator, these deviations were not likely to have influenced the outcome of the study.	
Pharmacokinetic Parameters <i>Primary Pharmacokinetic Parameters for Spironolactone:</i> <ul style="list-style-type: none">• Maximum observed plasma concentration (C_{max})• Area under the plasma concentration versus time curve, from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$) <i>Secondary Pharmacokinetic Parameters for Spironolactone:</i> <ul style="list-style-type: none">• Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)• Time to maximum observed plasma concentration (t_{max})• Terminal elimination rate constant (λ_z)• Apparent terminal elimination half-life ($t_{1/2}$) Safety Variables Safety variables included reporting of adverse events (AEs), vital signs, physical examination, 12-lead electrocardiogram (ECG), and laboratory investigations (hematology, clinical chemistry, urinalysis, and pregnancy tests). Prior and concomitant medication was also recorded.	
Statistical Methods Pharmacokinetic Analysis <i>Pharmacokinetic population:</i> All subjects for whom primary PK parameters could be calculated for at least two treatment periods, and who had no major protocol deviations thought to impact the analysis of the PK data were	

included in the statistical PK analysis for the study.

The test product was compared to the reference product by means of statistical analysis with respect to the primary PK parameters for spironolactone using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Upon antilog transformation of the difference estimates of "test – reference" the geometric means ratio of the test and reference product ("test/reference"), as well as the corresponding 90% confidence interval (CI) for the geometric mean ratio of the test and reference products ("test/reference") and the intra-subject Coefficient of variation percentage (CV%) were provided.

Bioequivalence of the test and reference products was assessed on the basis of the 90% CIs for estimates of the geometric mean ratios between the primary PK parameters for spironolactone in relation to the conventional acceptance range of 70.00% to 143.00% for C_{max} and 80.00% to 125.00% for $AUC_{(0-t)}$. Analysis of spironolactone was the principal determinant of product bioequivalence.

In addition, for exploratory purposes, the intra-subject (within-subject) variability between treatment periods were analyzed separately for both the test and reference products. This variation was expressed with CV% derived from a similar model used to test for bioequivalence but selecting only data for one product at a time.

Safety Analysis

Safety population: All subjects who received at least one dose of IMP were included in the safety analysis for the study.

AEs were coded, listed, and summarized by treatment using the safety population. Adverse events were coded and summarized by System Organ Class (SOC), preferred term and treatment. Separate listings of AEs leading to death, serious AEs (SAEs) and AEs leading to treatment discontinuation were provided.

Laboratory parameters (serum chemistry and hematology) were summarized by treatment, using descriptive statistics at study Baseline and 72 hours prior to admission for Treatment Periods 2, 3 and 4. Changes from study Baseline were also summarized for Treatment Periods 2, 3 and 4. Urinalysis and pregnancy test results were not summarized but were provided in a data listing. All laboratory data were listed for all subjects in the safety population. A separate listing of abnormal laboratory measurements recorded throughout the study were provided.

Vital signs were summarized using descriptive statistics at each period Baseline and at each post baseline time point, by treatment group. Changes from Baseline were also summarized at each post-baseline assessment. Vital signs were listed for all subjects in the safety population.

12-Lead electrocardiogram and physical examination results at screening were listed for all subjects in the safety population.

Prior and concomitant medication were listed separately in the safety population.

The palatability questionnaire results were summarized using descriptive statistics for the test product by category (taste, smell, texture, and ease of use) and treatment. The variable of interest was the grading scale in millimeter as measured by the clinician on the questionnaire. All results were listed for each subject in the safety population, where applicable.

Pharmacokinetic Results and Conclusions

This bioequivalence study was conducted to compare plasma concentrations of spironolactone of the reference product, Aldactone® 100 mg tablets with the test product, spironolactone oral suspension 10 mg/mL (Kayraas™). The study design was a single-dose, open-label, laboratory blind, randomized, four period crossover, replicate study with a 7-day wash-out period between doses of spironolactone. Data from 36 evaluable subjects were analyzed. There was no carry-over effect of spironolactone between the treatment periods with all pre-dose spironolactone values in Treatment Periods 2, 3 and 4 recorded as below the lower limit of quantification (BLQ).

Bioequivalence was based on the primary PK parameters of spironolactone, C_{max} and $AUC_{(0-t)}$. Statistical analyses of plasma spironolactone primary PK parameters are summarized below in [Table 2-1](#).

Table 2-1 Summary of Statistical Analyses of Plasma Spironolactone Primary Pharmacokinetic Parameters

			LS Means		Test / Reference Geometric Mean Ratio (%)		
Parameter (Unit)	n / N (Test)	n / N (Reference)	Treatment B (Test)	Treatment A (Reference)	Estimate	90% CI	Model Intra CV%
C _{max} (ng/mL)	72 / 36	71 / 36	142.24	215.03	66.15	(61.62 ; 71.01)	25.95
AUC _{0-t} (h*ng/mL)	72 / 36	71 / 36	417.56	411.36	101.51	(98.11 ; 105.02)	12.30

CI = confidence interval; CV% = coefficient of variation percentage; n = number of samples; N = number of subjects
Estimates were obtained using an ANOVA with sequence, period, product and subject within sequence as fixed effects, after logarithmic transformation of the data.

Treatment A (reference): Aldactone® 100 mg tablet

Treatment B (test): Kayraas™ 10 mL oral suspension

The geometric mean ratio ("test/reference") of C_{max} was 66.15% with the 90% CI between 61.62% and 71.01%. For AUC_(0-t), the geometric mean ratio was 101.51% with 90% CI between 98.11% and 105.02%.

The lower and upper values of the 90% CIs for the primary PK parameter AUC_(0-t) were within the predefined bioequivalence limits of 80.00% to 125.00%. However, the lower value of the 90% CIs for the primary PK parameter C_{max} extended below the predefined bioequivalence limit of 70.00% indicating that the PK profiles of the test and reference products were not equivalent with respect to the rate of absorption of spironolactone.

Safety Results and Conclusions

In general, an oral dose of 100 mg spironolactone administered as a tablet or oral suspension was well tolerated by healthy subjects in this study.

No deaths or SAEs were reported during the study, and no AE was of severe intensity. One subject presenting with iron deficiency anemia was withdrawn from the study prior to Treatment Period 4. The investigator regarded this AE as unlikely related to the IMP. Fourteen of the 36 subjects reported 27 AEs. Ten of the events were considered by the investigator as possibly related to the IMP. Of these, 2 events were considered of moderate intensity and 8 as mild in intensity. The most common IMP-related AEs were headache (3 events experienced 3 by subjects) and somnolence (2 events experienced by 1 subject on 2 separate occasions). They were rated as possibly related to the IMP, and all were mild in intensity. Other IMP related AEs included single events of dry eye (mild), eye pruritus (mild), nausea (moderate), vomiting (moderate) and hyperkalemia (mild).

12-Lead electrocardiogram evaluations performed at screening only were compatible with expectations for a healthy male and female population.

There was no clinically significant and/or consistent drug-related change in vital signs or physical findings after administration of a total dose of 100 mg spironolactone per treatment period.

Abnormal laboratory findings for one subject were considered by the investigator as clinically significant and were reported as an AE of iron deficiency anemia. However, the AE was regarded as unlikely related to the IMP.

Most of the subjects found the test product to have an aftertaste. The overall mean visual analog scale (VAS) results for taste, smell, texture and ease of use ranged between 63.6 mm and 75.0 mm indicating the test product was considered palatable by subjects in this study.

Discussion and Overall Conclusions

This study in healthy males and females was designed to determine whether the test product, spironolactone oral suspension 10 mg/mL (Kayraas™) and the reference product, Aldactone® 100 mg tablets are bioequivalent. For this purpose, the rate and extent of absorption of spironolactone were compared after administration of a single dose of 100 mg spironolactone of each of the two formulations, under fed conditions.

Thirty-six subjects (18 males and 18 females) were considered eligible and entered into the study. One female subject was withdrawn from the study by the investigator due to an AE that was not related to IMP.

Analytical data generated for the 36 subjects entered into the study, were available for statistical analysis. All 36

subjects who were enrolled and received at least one dose of study medication were included in the safety analysis. Bioequivalence of the test and reference products was based on the CIs for the primary PK parameters C_{\max} and $AUC_{(0-t)}$, for spironolactone in relation to the acceptance range of 70.00% to 143.00% for C_{\max} and the conventional acceptance range of 80.00% to 125.00% for $AUC_{(0-t)}$. The results of this study indicate that the test product is equivalent to the reference product with respect to the extent of absorption of spironolactone, but the test product is not equivalent to the reference product with respect to the rate of absorption of spironolactone. Study medication was well tolerated by all subjects. No deaths or SAEs were reported during the study, and no AE was of severe intensity. No subjects were withdrawn due to any IMP-related AEs. Subjects found the test product palatable.

Date of Report: 24 February 2021, Final 1.0

This study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation, Good Clinical Practice guidelines.