Title Page

A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, 2-WAY, CROSS-OVER PIVOTAL BIOEQUIVALENCE STUDY TO QUALIFY MANUFACTURING SITE TRANSFER FROM VIATRIS TO NEOLPHARMA, FOR SPIRONOLACTONE/HYDROCHLOROTHIAZIDE FILM COATED TABLETS IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITIONS

Study Intervention Number:	PF-06832640
Study Intervention Name:	Spironolactone/Hydrochlorothiazide
US IND Number:	NDA 012616
EudraCT Number:	Not applicable
ClinicalTrials.gov ID:	Not applicable
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	B9531002
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: Pivotal Bioequivalence Study of Spironolactone/Hydrochlorothiazide Film Coated Tablets to Qualify Manufacturing Site Transfer From Viatris to Neolpharma.

Document History

Document	Version Date
Original protocol	28 September 2023

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A single-dose, open-label, randomized, 2-way, cross-over pivotal bioequivalence study to qualify manufacturing site transfer from Viatris to Neolpharma, for Spironolactone/Hydrochlorothiazide film coated tablets in healthy adult participants under fasted conditions.

Brief Title: Pivotal bioequivalence study of Spironolactone/Hydrochlorothiazide film coated tablets to qualify manufacturing site transfer from Viatris to Neolpharma.

Regulatory Agency Identification Number(s):

US IND Number:	NDA 012616
EudraCT Number:	Not applicable
ClinicalTrials.gov ID:	Not applicable
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	B9531002
Phase:	1

Rationale:

The purpose of this study is to assess the bioequivalence (BE) between Spironolactone/Hydrochlorothiazide film coated tablets manufactured at Viatris Pharmaceuticals LLC, Puerto Rico (hereafter referred to as Viatris) and Spironolactone/Hydrochlorothiazide film coated tablets manufactured at Neolpharma, Inc., Puerto Rico (hereafter referred to as Neolpharma).

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To demonstrate bioequivalence between Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the proposed site (Neolpharma) vs Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at current site (Viatris) under fasting conditions in healthy adult participants.	• Maximum observed concentration (C_{max}), area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) (or AUC_{last} if AUC_{inf} cannot be reliably estimated) of Spironolactone and Hydrochlorothiazide.

Objectives	Endpoints
Secondary:	**Secondary:**
• To further characterize pharmacokinetic(s) (PK) of Spironolactone and Hydrochlorothiazide. • To evaluate the safety and tolerability of Spironolactone/Hydrochlorothiazide film coated tablets.	• Terminal elimination half-life ($t_{½}$) (if data permit) and time for C_{max} (T_{max}) of Spironolactone and Hydrochlorothiazide. • Adverse events (AEs), clinical laboratory tests, vital signs, and ECGs.

Overall Design:

This will be an open-label, randomized, single-dose, 2-treatment, 2-period, 2-sequence, crossover study in adult healthy male and/or female participants.

Number of Participants:

Approximately 40 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male and female participants must be 18 to 75 years of age, inclusive, at the time of signing the informed consent document (ICD).

2. Body mass index (BMI) of 16-32 kg/m^2; and a total body weight >50 kg (110 lb).

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

- History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

2. Baseline 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT (QTc) interval >450 msec.

Study Arms and Duration:

Approximately 40 participants will be enrolled in the study (20 in each treatment sequence). Participants will be assigned to 1 of the following 2 sequences according to a computer-generated randomization schedule. There will be a minimum 4-day washout period between successive doses (ie, administration of subsequent doses of study medication will not occur until at least 4 days after the previous dose of study medication).

Study Intervention(s)		
Intervention Name	Spironolactone/Hydrochlorothiazide	Spironolactone/Hydrochlorothiazide
Use	Reference Product	Test Product
IMP or NIMP/AxMP	NIMP	IMP
Dose Formulation	Film coated tablets	Film coated tablets
Unit Dose Strength(s)	25 mg/25 mg	25 mg/25 mg
Route of Administration	Oral	Oral

Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

Study Arm(s)		
Arm Title	Treatment A (Reference)	Treatment B (Test)
Arm Description	Participants will receive Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablet manufactured at Viatris on Day 1 of each treatment period.	Participants will receive Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablet manufactured at Neolpharma on Day 1 of each treatment period.

Statistical Methods:

A sample size of 38 evaluable participants will provide ≥99.9% and 91.0% power that the 90% confidence interval (CI) for the ratio of Test to Reference treatment for C_{max} and AUC_{inf}

(or AUC_{last} if AUC_{inf} cannot be reliably estimated) of spironolactone, respectively, will lie within the acceptance region of (80%, 125%). Additionally, it will provide ≥99.6% and ≥99.0% power that the 90% CIs for the ratios of Test to Reference treatment for AUC_{inf} and C_{max} of Hydrochlorothiazide (HCTZ) will lie within the acceptance region of (80%, 125%). Consequently, this study will have approximately 90% overall power to demonstrate BE of the Test treatment to the Reference treatment (ie, equivalence for both AUC_{inf} and C_{max}) of both spironalactone and HCTZ, where overall power for the study is based on the product of the individual powers of the parameters of interest.

Bioequivalence of the Test treatment to Reference treatment will be concluded if the 90% CIs for the ratios of adjusted geometric means for both spironolactone and hydrochlorothiazide AUC_{inf} and C_{max} fall entirely within the acceptance region of (80%, 125%).

Ethical Considerations:

Spironolactone/Hydrochlorothiazide film coated tablets are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate pharmacokinetic and tolerability data of spironolactone and hydrochlorothiazide to support regulatory registration of Spironolactone/Hydrochlorothiazide film coated tablets at 25 mg/25 mg strength manufactured at Neolpharma.

1.2. Schema

Treatment Sequence

Sequence	Number of Participants	Period 1	Washout Period	Period 2
1	20	Treatment A	At least 4 days	Treatment B
2	20	Treatment B		Treatment A

Treatment A: Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the current site (Viatris) under fasting conditions.
Treatment B: Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the proposed site (Neolpharma) under fasting conditions.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1				Period 2			F/U	Early Discontinuation	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • A washout period of at least 4 days (96 hours) will be required between the 2 doses. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose			**0**	**24**	**48**	**0**	**24**	**48**			
Informed consent	X										• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	→	→	X			• Participants will enter CRU on Day -1 and stay in CRU until completion of Period 2 PK blood sampling.
Inclusion/exclusion criteria	X	X									

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Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1				Period 2			F/U	Early Discontinuation	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • A washout period of at least 4 days (96 hours) will be required between the 2 doses. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose			**0**	**24**	**48**	**0**	**24**	**48**			
Medical/medication history	X	X									
Physical examinations	X	X								X	
Safety laboratory	X	X								X	• Safety laboratory includes hematology, chemistry, and urinalysis, which are listed in Appendix 2. • Laboratory safety tests will be obtained after fasting for at least 8 hours.
Demography, age, weight and height	X										
Illegal drug/tobacco/alcohol use	X	X									• For confirmation of no drug/tobacco/alcohol use.
Urine alcohol test or alcohol breath test	X	X									
Urine Pregnancy test (WOCBP only)	X	X								X	• See Section 8.3.5 for additional information.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1				Period 2			F/U	Early Discontinuation	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • A washout period of at least 4 days (96 hours) will be required between the 2 doses. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose			**0**	**24**	**48**	**0**	**24**	**48**			
Contraception check	X	X							X	X	• For confirmation of appropriate use only. • See Section 5.3.1 for additional information.
FSH (Post menopausal women only)	X										
Urine drug testing	X										
Single supine 12-Lead ECG	X									X	• See Section 8.3.3 for additional information.
Blood pressure, pulse rate	X									X	• See Section 8.3.2.1 for additional information.
HIV, HBsAg, HBcAb, HCVAb	X										
Study intervention administration			X			X					• A washout period of at least 4 days (96 hours) will be required between the 2 doses. • The 1st dose will be administered on Study Day 1 (Period 1 Day 1) and the 2nd dose will be administered on Study Day 5 (Period 2 Day 1).
Pharmacokinetic blood sampling			X	X	X	X	X	X		X	• Refer to PK sampling times table (Table 2).

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	Screening	Period 1				Period 2			F/U	Early Discontinuation	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**28-35 Days**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • A washout period of at least 4 days (96 hours) will be required between the 2 doses. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Hours After Dose			**0**	**24**	**48**	**0**	**24**	**48**			
Retained Research Sample for Genetics (Prep D1)		X									• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
CRU discharge								X			
Concomitant medications	X	X	X	X	X	X	X	X			
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. Pharmacokinetic Sampling Times (Period 1 and Period 2)

Visit Identifier	**Period 1 and Period 2**																**Notes**
Study Day	**1**													**2**		**3**	
Hours Before/After Dose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**10**	**12**	**24**	**36**	**48**	Hour 0 = predose sample collection
Study intervention administration	X																
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Predose PK sample to be collected prior to dosing

2. INTRODUCTION

Spironolactone/Hydrochlorothiazide film coated tablets are a combination of 2 diuretic agents spironolactone and hydrochlorothiazide indicated for treatment of essential hypertension, congestive heart failure, liver cirrhosis, nephrotic syndrome and other edematous conditions. Spironolactone and hydrochlorothiazide have different but complementary mechanisms and sites of action, thereby providing additive diuretic and antihypertensive effects.

2.1. Study Rationale

Pfizer Inc. is a marketing authorization holder for Spironolactone/Hydrochlorothiazide film coated tablets. It is currently marketed in the United States as 25 mg/25 mg (Spironolactone/Hydrochlorothiazide) film coated tablets.

Currently Spironolactone/Hydrochlorothiazide film coated tablets are manufactured at Viatris Pharmaceuticals LLC, Puerto Rico (hereafter referred to as Viatris). PGS intends to transfer drug product manufacturing operations for Spironolactone/Hydrochlorothiazide film coated tablets from the currently registered Viatris manufacturing site to the proposed Neolpharma, Inc., Puerto Rico (hereafter referred to as Neolpharma) manufacturing site. The f2 could not be calculated due to high %RSD values (high variability). Bootstrap f2 analysis was performed, and the similarity factor calculated was outside of acceptable range. The comparative dissolution profile data between existing site and proposed new site when tested in release media failed as the similarity factor (f2) calculated did not pass the criterion (f2 value being <50) for both spironolactone and hydrochlorothiazide in release media tested. Therefore, this BE study is being conducted to qualify the manufacturing site transfer, and the associated process changes, by demonstrating BE between Spironolactone/Hydrochlorothiazide film coated tablets manufactured at the proposed site (Neolpharma) versus existing site (Viatris).

The primary objective of this study is to assess the BE between Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at Viatris and Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at Neolpharma.

2.2. Background

The current Spironolactone/Hydrochlorothiazide film coated tablets manufacturing needs to be transferred from Viatris to Neolpharma. The f2 could not be calculated due to high %RSD values (high variability). Bootstrap f2 analysis was performed, and the similarity factor calculated was outside of acceptable range. The comparative dissolution profile data between existing site and proposed new site when tested in release media failed as the similarity factor (f2) calculated did not pass the criterion (f2 value being <50) for both spironolactone and hydrochlorothiazide in release media tested. Hence, this BE study is being conducted to qualify the manufacturing site transfer from Viatris to Neolpharma.

2.2.1. Clinical Overview

Spironolactone/Hydrochlorothiazide film coated tablets are a combination of 2 diuretic agents, spironolactone and hydrochlorothiazide, indicated for treatment of essential hypertension, congestive heart failure, liver cirrhosis, nephrotic syndrome and other edematous conditions. Spironolactone and HCTZ have different but complementary mechanisms and sites of action, thereby providing additive diuretic and antihypertensive effects. The spironolactone component of Spironolactone/Hydrochlorothiazide film coated tablets helps to minimize the potassium loss characteristically induced by the HCTZ component.

The diuretic effect of spironolactone is mediated through its action as a specific pharmacologic antagonist of aldosterone, primarily by competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. HCTZ promotes the excretion of sodium and water primarily by inhibiting their reabsorption in the cortical diluting segment of the distal renal tubule.

Spironolactone/Hydrochlorothiazide is effective in significantly lowering the systolic and diastolic blood pressure in many patients with essential hypertension, even when aldosterone secretion is within normal limits.

Both spironolactone and HCTZ reduce exchangeable sodium, plasma volume, body weight, and blood pressure. The diuretic and antihypertensive effects of the individual components are potentiated when spironolactone and HCTZ are given concurrently.

Spironolactone/Hydrochlorothiazide is contraindicated in patients with acute renal insufficiency, significant renal compromise, anuria, Addison's disease; significant hypercalcemia; hyperkalemia, or hypersensitivity to spironolactone, thiazide diuretics, or to other sulfonamide-derived drugs.

Spironolactone/Hydrochlorothiazide film coated tablets formulations are available in strengths of 25 mg/25 mg (Spironolactone/Hydrochlorothiazide).

Following oral administration, spironolactone rapidly gets absorbed with peak plasma concentrations reached within 1 hour post dosing. Following oral administration of a single 100 mg dose of spironolactone, the mean AUC_{inf} of spironolactone was approximately 154 ng•hr/mL, mean C_{max} was 48.3 ng/mL and elimination half-life of 2 to 3 hours (Xu et al, 2008). Food increased the bioavailability of unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known (USPI, 09 January 2023).

Spironolactone is rapidly and extensively metabolized by both the kidneys and liver. Following deacetylation and S-methylation, spironolactone is converted to 7-α-thiomethylspironolactone, a sulfur-containing active metabolite that is considered the major metabolite of spironolactone in serum. Sulfur-containing products are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the drug. Approximately 25% to 30% of spironolactone is also converted to canrenone by dethioacetylation (non-sulfur-containing active metabolite) (CDS, 14 April 2022).

Spironolactone and its metabolites are more than 90% bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.

In a PK study in 5 healthy male volunteers receiving spironolactone 500 mg, 47% to 57% of the dose was excreted in the urine within 6 days and the remaining amount could be detected in the feces (total recovery 90%). In another study in 5 healthy men, after a single 200 mg (with radioactive tracer) dose of spironolactone administration, over 5 days, 31.6% ± 5.87% of the radioactivity was excreted in the urine mainly as metabolites and 22.7% ± 14.1% in the feces (CDS, 14 April 2022).

HCTZ is rapidly absorbed following oral administration. HCTZ peak plasma concentrations reached within 1 to 2 hours. Concurrent administration of HCTZ with food has resulted in significant decreases in plasma drug levels as compared to the administration of HCTZ in a fasted state (USPI, 09 January 2023). Following oral administration of a single 50 mg dose of hydrochlorthiazide, the mean AUC_{inf} of hydrochlorthiazide was approximately 1730 ng•hr/mL, mean C_{max} was 281 ng/mL and elimination half-life of approximately 10 hours (Fierro Humberto, 2016).

HCTZ is approximately 40% protein bound and accumulates in erythrocytes by an unknown mechanism. The ratio between red blood corpuscles and plasma is 3.5:1. The volume of distribution of HCTZ is approximately 3 L/kg to 4 L/kg (CDS, 14 April 2022).

HCTZ undergoes only slight metabolic alteration and is excreted unchanged in urine. Following oral administration of 4 different doses (12.5 mg, 25 mg, 50 mg and 75 mg) of HCTZ to 8 healthy volunteers, renal clearance ranged between 319 mL/min and 345 mL/min. HCTZ is excreted unchanged in the urine and appears in the urine within 1 hour of dosing. Approximately 50% to 70% was recovered in the urine within 24 hours after the oral administration of 25 mg to 65 mg of HCTZ.

Spironolactone has been shown to be tumorigenic in chronic toxicity studies in rats, thus unnecessary use of this drug should be avoided.

2.3. Benefit/Risk Assessment

Spironolactone/Hydrochlorothiazide film coated tablets are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Spironolactone/Hydrochlorothiazide film coated tablets may be found in the package insert, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Spironolactone/Hydrochlorothiazide Film Coated Tablets		
Tumorigenic	The potential risk is based on pre-clinical toxicology findings for Spironolactone and HCTZ.	Eligibility criteria have been selected to ensure only appropriate participants are included in the study and study procedures are in place to evaluate this risk ie, physical examination. AEs will be closely monitored.

2.3.2. Benefit Assessment

Spironolactone/Hydrochlorothiazide film coated tablets are not expected to provide any clinical benefit to healthy participants.

2.3.3. Overall Benefit/Risk Conclusion

Spironolactone/Hydrochlorothiazide film coated tablets are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK, safety and tolerability data of spironolactone and hydrochlorothiazide to support regulatory registration of Spironolactone/Hydrochlorothiazide 25 mg/25 mg strength film coated tablets manufactured at Neolpharma.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To demonstrate bioequivalence between Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the proposed site (Neolpharma) vs Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at current site (Viatris) under fasting conditions in healthy adult participants.	• C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) of Spironolactone and Hydrochlorothiazide.
Secondary:	**Secondary:**
• To further characterize PK of Spironolactone and Hydrochlorothiazide. • To evaluate the safety and tolerability of Spironolactone/Hydrochlorothiazide film coated tablets.	• $t_{½}$ (if data permit) and T_{max} of Spironolactone and Hydrochlorothiazide. • AEs, clinical laboratory tests, vital signs, and ECGs.

4. STUDY DESIGN

4.1. Overall Design

This will be an open-label, randomized, single-dose, 2-treatment, 2-period, 2-sequence, crossover study in adult healthy male and/or female participants. Approximately 40 participants will be enrolled in the study (20 in each treatment sequence). Dropouts for non-safety reasons or non-evaluable participants may be replaced at the discretion of the sponsor and investigator. Screening evaluation will occur within 28 days prior to the first dose of study medication. Participants will be assigned to 1 of the following 2 sequences according to a computer-generated randomization schedule.

Table 3. Treatment Sequence

Sequence	Number of Participants	Period 1	Washout Period	Period 2
1	20	Treatment A	At least 4 days	Treatment B
2	20	Treatment B		Treatment A

Treatment A: Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the current site (Viatris) under fasting conditions.
Treatment B: Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablets manufactured at the proposed site (Neolpharma) under fasting conditions.

There will be a minimum 4-day washout period between successive doses (ie, administration of subsequent doses of study medication will not occur until at least 4 days after the previous dose of study medication).

Screening evaluation will occur within 28 days prior to the first dose of study medication. Day -1 is defined as the day prior to the first day of dosing (Day 1) in each period.

Participants will be admitted to the CRU on Day -1 and will remain confined in the CRU from Period 1 through Period 2 until the collection of the 48-hour PK sample making it a total of 8 days and 7 nights including Day -1. The washout period between the 2 successive dosing's will be at least 4 days (96 hours).

On Day 1 of each period, participants will receive a single dose of investigational product as per randomization schedule. Study treatments will be administered with 240 mL of ambient temperature water under fasted conditions (overnight fast and no food until 4 hours after dosing). Water will be allowed without restriction until 1 hour prior to dosing and may be consumed without restriction beginning 1 hour after dosing.

Blood samples for the analysis of spironolactone and HCTZ in plasma will be obtained predose (immediately prior to dosing) and postdose as outlined in the Schedule of Activities.

Tolerability and safety will be assessed for all treatments by monitoring AEs.

4.2. Scientific Rationale for Study Design

Currently Spironolactone/Hydrochlorothiazide film coated tablets are manufactured at Viatris. PGS intends to transfer drug product manufacturing operations for Spironolactone/Hydrochlorothiazide film coated tablets from the currently registered Viatris manufacturing site to the proposed Neolpharma manufacturing site. The f2 could not be calculated due to high %RSD values (high variability). Bootstrap f2 analysis was performed, and the similarity factor calculated was outside of acceptable range. The comparative dissolution profile data between existing site and proposed new site when tested in release media failed as the similarity factor (f2) calculated did not pass the criterion (f2 value being <50) for both Spironolactone and hydrochlorothiazide in release media tested. Therefore, this BE study is being conducted to qualify the manufacturing site transfer, and the associated process changes, by demonstrating BE between Spironolactone/Hydrochlorothiazide film coated tablets manufactured at the proposed site (Neolpharma) versus existing site (Viatris).

4.2.1. Choice of Contraception/Barrier Requirements

Spironolactone/Hydrochlorothiazide is known to cause risk for severe manifestations of developmental toxicity in humans or suspected on the basis of the nonclinical studies. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for Spironolactone/Hydrochlorothiazide. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

Studies to evaluate the developmental toxicity of Spironolactone/Hydrochlorothiazide have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.3. Justification for Dose

Spironolactone/Hydrochlorothiazide film coated tablets have a dose strength equivalent to 25 mg/25 mg respectively. Since this is the only dose that will be transferred from Viatris to Neolpharma for spironolactone and hydrochlorothiazide, a BE study will be conducted for the 25 mg/25 mg strength.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male and female participants must be 18 to 75 years of age, inclusive, at the time of signing the ICD.

   Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Other Inclusion Criteria:

2. BMI of 16-32 kg/m^2; and a total body weight >50 kg (110 lb).

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

   - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

   - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

2. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

3. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study

intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

4. Current use of any prohibited concomitant medication(s) or participant unwilling or unable to use a required concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

5. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.

Diagnostic Assessments:

6. A positive urine drug test. A single repeat for positive drug screen may be allowed.

7. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If systolic BP is ≥ 140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

8. Hepatic dysfunction defined as:

   - Total bilirubin ≥1.5 × ULN (For Gilbert's syndrome, direct bilirubin >ULN is exclusionary)
   - AST ≥1.5 × ULN
   - ALT ≥1.5 × ULN

9. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms). If QTcF exceeds 450 ms, the ECG should be repeated twice and the average of the 3 QTcF values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

10. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

12. History of sensitivity to heparin or heparin induced thrombocytopenia.

13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

14. History of hypersensitivity to spironolactone or HCTZ or any of the components in the formulation of the study products, or allergic to thiazide diuretics or to other sulfonamide-derived drugs.

15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior or as specified above for red wine to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

- Smoking may be allowed according to CRU practices. Smoking will not be permitted during frequent sampling procedures, and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Smoking will also not be permitted 2 hours before and 2 hours following any dose of study intervention.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to Spironolactone/Hydrochlorothiazide film coated tablets.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	Spironolactone/Hydrochlorothiazide	Spironolactone/Hydrochlorothiazide
Type	Drug	Drug
Use	Reference Product	Test Product
IMP or NIMP/AxMP	NIMP	IMP
Dose Formulation	Film Coated Tablets	Film Coated Tablets
Unit Dose Strength(s)	25 mg/25 mg	25 mg/25 mg
Dosage Level(s)	Single dose	Single dose
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in unit dose containers as unblinded. Each container will be labeled as required per country requirement.	Study intervention will be provided in unit dose containers as unblinded. Each container will be labeled as required per country requirement.
SRSD	Package Insert	Package Insert
Current Name(s)	Spironolactone/Hydrochlorothiazide	Spironolactone/Hydrochlorothiazide

Study Arm(s)		
Arm Title	Treatment A (Reference)	Treatment B (Test)
Arm Description	Participants will receive Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablet manufactured at Viatris on Day 1 of each treatment period.	Participants will receive Spironolactone/Hydrochlorothiazide 25 mg/25 mg film coated tablet manufactured at Neolpharma on Day 1 of each treatment period.

Pivotal BA/BE study film coated tablets will be supplied to the CRU in multidose labeled containers (in sufficient number to allow unopened containers to be kept as retains).

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL.

Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for 4 hours by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled

storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. All pivotal BA/BE retains should be stored by the investigator site or with a third-party vendor. Sample retention is the responsibility of the entity performing the BA/BE study.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider,

participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is an open-label study.

As this is an open-label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Dose modification is not allowed in this single dose study.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of Spironolactone/Hydrochlorothiazide greater than 25 mg/25 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:

(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR

(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.1.2. ECG Changes

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms and QTcF >450 ms.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Pregnancy

In the case of a positive confirmed pregnancy, the participant will be withdrawn from the study.

7.1.4. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following: safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1 for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether

the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the

investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 290 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the

definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 calendar days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Not applicable.

8.3.5. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to

starting the Spironolactone/Hydrochlorothiazide film coated tablet. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and

obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 4 days that is at least 5 terminal half-lives after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures

for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of

whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOP.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of HCTZ and Spironolactone as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of spironolactone and HCTZ. Samples collected for analyses of spironolactone and HCTZ plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of spironolactone and HCTZ will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

The alternative hypothesis of BE (H_1: $\theta_L <= \mu_T - \mu_R <= \theta_U$), and the null hypothesis of inequivalence (H_o: $\mu_T - \mu_R < \theta_L$ or $\mu_T - \mu_R > \theta_U$) can be expressed as the following 2 separate 1-sided hypotheses:

H_{oA}: $\mu_T - \mu_R < \theta_L$
H_{1A}: $\theta_L <= \mu_T - \mu_R$

H_{oB}: $\mu_T - \mu_R > \theta_U$
H_{1B}: $\mu_T - \mu_R <= \theta_U$

Where μ_T and μ_R represent the average BA on a log scale for the Test and Reference products respectively and $[\theta_L, \theta_U]$ defines the BE range.

BE of the Test treatment to Reference treatment will be concluded if the 90% CIs for the ratios of adjusted geometric means for both spironolactone and hydrochlorothiazide AUC_{inf} and C_{max} fall entirely within the acceptance region of (80%, 125%).

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization.
Full analysis set	Example: All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

PK parameters will be derived from the concentration-time profiles as shown in Table 4. Actual PK sampling times will be used in the derivation of PK parameters.

Table 4. PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Ln(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.

a. If data permits.

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

9.3.1. General Considerations

Not applicable.

9.3.2. Primary Endpoint(s) Analysis

Pharmacokinetic and statistical analysis will be performed for spironolactone and hydrochlorothiazide.

Natural log transformed PK parameters (C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated)) will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test/ Reference) and the corresponding 90% CIs will be obtained from the model. The adjusted mean differences and the 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/ Reference) and the 90% CIs for the ratios.

For bioequivalence assement of Spironolactone/Hydrochlorothiazide 25/25 mg film coated tablets between proposed site (Neolpharma) and current site (Viatris), bioequivalence of the Test treatment (Treatment B) relative to Reference treatment (Treatment A) will be concluded if the 90% confidence intervals for the ratio of adjusted geometric means of Test treatment (Treatment B) relative to Reference treatment (Treatment A) for C_{max}, AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) fall wholly within (80%, 125%).

9.3.3. Secondary Endpoint(s) Analysis

The secondary PK parameters like T_{max} and $t_{½}$ would be derived from the concentration-time profiles. AUC_{inf}, area under the plasma concentration-time profile from time 0 extrapolated to infinite time is calculated from $AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. C_{max} is the maximum plasma concentration observed directly from the data. $t_{½}$ is the terminal elimination half-life calculated from $Ln(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.

The PK parameters AUC_{last}, AUC_{inf}, C_{max}, T_{max}, and $t_{½}$ will be summarized descriptively by analyte and treatment. For AUC_{inf}, AUC_{last}, and C_{max} parameters, individual data and geometric mean will be plotted with box plots by analyte and treatment for each parameter. Plasma concentration data will be listed and summarized descriptively by analyte, PK sampling time and treatment. Individual participant and summary profiles (mean and median) of the plasma concentration-time data will be plotted against analyte by treatment. Mean and median profiles will be presented on both linear-linear and log-linear scales. For summary statistics and summary (mean and median) plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

9.3.4. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.5. Other Analyses

Not applicable.

9.4. Interim Analyses

No interim analysis will be conducted for this study.

9.5. Sample Size Determination

A sample size of 38 evaluable participants will provide ≥99.9% and 91.0% power that the 90% CI for the ratio of Test to Reference treatment for C_{max} and AUC_{inf} (or AUC_{last} if AUC_{inf} cannot be reliably estimated) of spironolactone, respectively, will lie within the acceptance region of (80%, 125%). Additionally, it will provide ≥99.6% and ≥99.0% power that the 90% CIs for the ratios of Test to Reference treatment for AUC_{inf} and C_{max} of HCTZ will lie within the acceptance region of (80%, 125%). Consequently, this study will have approximately 90% overall power to demonstrate BE of the Test treatment to the Reference treatment (ie, equivalence for both AUC and C_{max}) of both spironolactone and HCTZ, where overall power for the study is based on the product of the individual powers of the parameters of interest. These estimates are based on the assumption that the true ratio between Test and Reference treatments for both AUC_{inf} and C_{max} is 0.95 and also assumes within-participant SDs of 0.141 and 0.246 for $\ln(AUC_{inf})$ and $\ln(C_{max})$ of spironolactone and 0.165 and 0.179 for $\ln(AUC_{inf})$ and $\ln(C_{max})$ of hydrochlorothiazide, respectively, as obtained from the literature (Xu et al, 2008; Fierro Humberto, 2016).

Approximately 40 participants will be enrolled in the study (20 in each treatment sequence) to ensure at least 38 evaluable participants. Participants who withdraw from the study or discontinue treatment, or whose PK samples are considered to be non-evaluable with respect to the primary PK objective may be replaced at the discretion of the investigator upon consultation with the sponsor.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

Not applicable.

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password-protected to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate

with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number,

hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values; for example: calculation of estimated kidney function. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 5. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea Creatinine Cystatin C[a] eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[b]	At screening: • FSH[c] • Urine drug screening[d] • Hepatitis B surface antigen • HBcAb • Hepatitis C antibody • HIV Pregnancy test (β-hCG)[e]

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
c. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
d. The minimum requirement for drug screening includes cocaine, THC, marijuana, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
e. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. See SoA for collection times.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical

records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 4 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 4 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier

method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must

discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to Spironolactone/Hydrochlorothiazide or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

  - Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any

remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat-only based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat-only based equation (see Table in Section 10.7.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat-only based eGFR and combined Screat plus Scys eGFR).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²) (Inker et al, 2021)

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units are used for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for adult participants.

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-seconds duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to reported as AEs/SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with Spironolactone/Hydrochlorothiazide for the period of time at least equal to, the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs) if the overall benefit/risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs	Required Washout Period Requirement
ACE inhibitors	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril	5 days or 5 half-lives whichever is longer
Angiotensin II Receptor antagonists	Losartan, telmisartan, irbesartan, Olmesartan, valsartan	5 days or 5 half-lives whichever is longer
Aldosterone blockers	Eplerenone, Finerenone	3 days or 5 half-lives whichever is longer
Potassium supplements	Potassium iodide, Potassium chloride	5 days or 5 half-lives whichever is longer
Anticoagulants	Heparin, low molecular weight heparin	8 hours or 5 half-lives whichever is longer
Alcohol	Ethyl alcohol	1 day or 5 half-lives whichever is longer
Antidiabetic drugs	Insulin, sulphonylureas, Biguanides, meglitinides, thiazolidinediones, Alpha glucosidase inhibitors	2 weeks or 5 half-lives whichever is longer

Drug Category	Drugs	Required Washout Period Requirement
Corticosteriods, ACTH	Hydrocortisone, Dexamethasone, methylprednisone and prednisone	1 day or 5 half-lives whichever is longer
Pressor amines	Norepinephrine, phenylephrine, ephidrine	1.5 days or 5 half-lives whichever is longer
Skeletal muscle relaxants, nondepolarizing	Tubocuraine	10 hours or 5 half-lives whichever is longer
Antimaniac/Antidepressant	lithium	5 days or 5 half-lives whichever is longer
NSAIDs	Indomethacin, Dyclofenac, Aceclofenac, ibuprofen, naproxen, aspirin, acetylsalicylic acid	1 day or 5 half-lives whichever is longer
Cardiac glycoside	Digoxin	2 weeks or 5 half-lives whichever is longer
Bile acid sequestrant	Cholestyramine	5 hours or 5 half-lives whichever is longer
Androgen biosynthesis inhibitor	Abiraterone	3.5 days or 5 half-lives whichever is longer

Investigators should consult the USPIs for Spironolactone/Hydrochlorothiazide for information regarding medication that is prohibited for concomitant use.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
ACTH	adrenocorticotropic hormone
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
AxMP	auxiliary medicinal product
BA	bioavailability
BE	bioequivalence
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{last}	the last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTIS	Clinical Trial Information System

Abbreviation	Term
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
f2	degree of similarity
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCTZ	Hydrochlorothiazide
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
KDIGO	Kidney Disease Improving Global Outcomes

Abbreviation	Term
k_{el}	first-order elimination rate constant
LBBB	left bundle branch block
LFT	liver function test
MQI	medically qualified individual
NA	not applicable
NDA	New Drug Application
NIMP	noninvestigational medicinal product
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	pharmacodynamic(s)
PGS	Pfizer Global Supply
PR	pulse rate
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
RSD	relative standard deviation
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T bili	total bilirubin
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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