Statistical Analysis Plan (SAP)

Protocol Number: **(Version Date)**	MLS-101-206 4.0 (Amendment 3) 28Mar2024
Protocol Title	A RANDOMIZED, CROSSOVER, DOUBLE BLIND, PLACEBO CONTROLLED, PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LORUNDROSTAT IN ADDITION TO SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS, IN ADULTS WITH HYPERTENSION AND CHRONIC KIDNEY DISEASE WITH ALBUMINURIA
Name of Test Drug:	Lorundrostat (MLS-101)
Phase:	2
Methodology:	Randomized, double-blind, placebo controlled, crossover study with a two-period, two-sequence (2x2) design
Sponsor:	Mineralys Therapeutics, Inc., 150 N. Radnor Chester Rd. – Suite F200, Radnor, PA 19087
Sponsor Biostatistical Representative	[redacted] Advisor, Biometrics
Document Date:	29MAY2025
Document Version:	2.0

SIGNATURE PAGE

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Author:
[redacted]
Advisor, Biometrics
Mineralys Therapeutics, Inc

Signature: _____
Date: _____

Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

All changes to the planned analyses will be described in the clinical study report (CSR).

[redacted]
CMO

Signature: _____
Date: _____

VERSION HISTORY

Current Version	Date	Amended by	Summary of changes from previous version	Reason
1.0	03MAR2025		Original document	
2.0	28MAY2025	[redacted]	Run-in safety Analysis Set Introduced	To align with the protocol
			Additional clarifications and definition introduced in Section 5.2 Data Conventions	For clarification purposes
			Windowing of measurements in Section 5.5.2	Additional instructions provided for clarity
			Sample Size justification Section 6.1	Additional computational details provided
			Geometric means introduced for some parameters in section 6.2.1	To clarify summaries for parameters with skewed distributions
			Precision level for summaries introduced in section 6.2	Instructions for TLF production purposes
			Subgroups definitions updated in Section 6.2.6	Redundant subgroups to section 6.6.3.4 removed
			Missing, used and spurious data Section 6.2.7 updated	To avoid redundancy with other sections
			Additional instructions on summary displays provided	To guide layout of summary displays in relation to the crossover design
			Additional details provided for the analysis method used for the primary and exploratory endpoints testing	Competing models for analysis of 2x2 crossover designs are available in the literature. Additional details are provided to select the primary and sensitivity models for analysis.
			Laboratory parameters for summaries using geometric means introduced as Section 6.6.3.3	To use correct method for the parameters with skewed distribution
			Section 6.6.3.5 Adjudication of outlier analysis introduced	To introduce Adjudication Committee review of outliers
			Additional references added to Section 8	References used

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List of Tables

ABBREVIATIONS

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme inhibitors
AESIs	AEs Of Special Interest
AE	Adverse events
AHT	Antihypertensive therapy
ANCOVA	Analysis of covariance
AOBP	Automated office blood pressure
ARB	Angiotensin receptor blockers
ARR	Aldosterone:renin ratio
ASI	Aldosterone synthase inhibitor
AUC	Area Under the Concentration versus time curve
AUC_{0-24}	Area Under the Concentration versus time curve from time 0 to the end of the dosing interval 24 hours later, calculated using linear trapezoid rule
BP	Blood pressure
CKD	Chronic kidney disease
C_{max}	Maximum plasma concentration
C_{min}	Trough plasma concentration, taken 24 hours after dose and prior to subsequent dose
CSR	Clinical study report
DB	Double Blind
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study
EoT	End of treatment
EW	Early withdrawal
FAS	Full analysis set
FDA	Food and drug administration
ICE	Intercurrent event
ICF	Informed consent form
ICH	International council on harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LP	Lorundrostat-Placebo
MAP	Mean arterial blood pressure
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities

MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing Not at Random
OLE	Open-label extension
PL	Placebo-Lorundrostat
PK	Pharmacokinetic
popPK	population pharmacokinetics
PRA	Plasma renin activity
PT	Preferred term
QD	Once daily
RTSM	Randomization and trial supply management
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SOC	System organ class
TEAE	Treatment-emergent AE
TESAE	Treatment-emergent Severe AE
T_{max}	Time to maximum plasma concentration
TP1	Treatment Period 1
TP2	Treatment Period 2
UACR	Urine albumin-creatinine ratio
WHO	World Health Organization

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This statistical analysis plan (SAP) is based on the MLS-101-206 Protocol version 4, amendment 3, dated 28Mar2024. The SAP is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). Analysis sets, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those described in the study protocol, as the SAP provides the definitive data analysis plan.

1.2 History of Protocol Changes That Affect the Statistical Analysis

Protocol amendments and their impact on the overall statistical analysis are summarized below:

- Original Protocol – no impact, as no subjects were enrolled in the study under this version.
- Amendment 1 (25JUL2023) – no impact as the amendment was finalized prior to the enrollment of any subjects in the study.
- Amendment 2 (06NOV2023) – this amendment altered the primary endpoint and patient population, including the objectives and secondary endpoints. Overall design of Part B was also applied. This amendment has minimal impact as only 1 subject was enrolled and randomized into the study (i.e., Part A). This subject will be excluded from the analyses but will be listed in the listings.
- Amendment 3 (28MAR2024) – this amendment updated the study protocol in accordance with clinical site requests to allow for easier enrollment into the study and allowed for expanded use of sodium glucose cotransporter 2 inhibitor (SGLT2i) treatments in accordance with evolving standard of care in kidney disease. The study design was updated to a randomized, double-blind, placebo-controlled, crossover trial. The study enrolled the majority of subjects under this protocol and was completed under this amendment.
- A memo to file (06Aug2024) was issued to rectify a typographical error in the endpoints. This memo altered “Study Week” to “Treatment Week” as appropriate throughout the protocol. This change did not impact study conduct, and its content was included in this SAP.

1.3 Objectives

1.3.1 Primary Objective

To assess the effect of lorundrostat 25 mg once daily (QD), in addition to a sodium-glucose cotransporter 2 inhibitor (SGLT2i), on systolic blood pressure (SBP) in subjects with hypertension and chronic kidney disease (CKD) with albuminuria on stable treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB)

1.3.2 Exploratory Objectives

- [redacted]

1.3.3 Safety Objective

To investigate the safety and tolerability of lorundrostat, in addition to a SGLT2i, in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB

1.3.4 Pharmacokinetic Objective

[redacted]

2 STUDY DESIGN

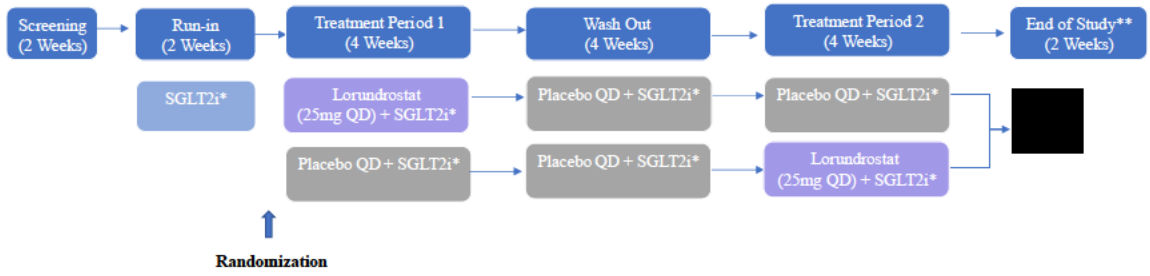
2.1 Introduction

This is a randomized, double-blind (DB), placebo controlled, crossover study with a two-period, two-sequence (2x2) design evaluating the efficacy and safety of 25 mg QD lorundrostat (an aldosterone synthase inhibitor (ASI)) in addition to a SGLT2i for the treatment of hypertension in subjects with CKD and albuminuria despite receiving stable treatment with an ACEi or an ARB. Subjects will be at least 18 years old with hypertension (Automated office blood pressure (AOBP) SBP [redacted] inclusive at Randomization), and mild to severe CKD (eGFR

[redacted] with albuminuria (UACR [redacted] inclusive) at the Screening Visit.

Approximately 60 subjects will be enrolled in approximately 30-40 investigational centers in the US.

The expected duration of the study for each subject from Screening to the End of Study visit is expected to be approximately 18 weeks: consisting of a 2-week screening period, a 2-week run-in period where subjects will either begin study provided dapagliflozin 10 mg or continue on their regularly prescribed SGLT2i, and two double blind (DB) 4-week treatment periods separated by a 4-week washout period:



* Either study provided commercially available dapagliflozin 10mg QD or continue regularly prescribed SGLT2i
**End of Study: Subjects who do not participate in the OLE, will attend a 2week End of Study Safety Follow-up visit.

Abbreviations: OLE, open label extension; QD, once daily SGLT2i, sodium glucose cotransporter-2 inhibitor

Subjects will be randomized (1:1) to two treatment sequences: lorundrostat-placebo (LP) and placebo-lorundrostat (PL).

Treatment allocation will be organized as follows:

- Treatment Period 1 (DB Study Week 0 to Study Week 4): Subjects will receive a lorundrostat 25 mg (sequence LP) or one matching lorundrostat-placebo tablet (sequence PL) dosed orally QD.
- Washout (Study Week 4 to Study Week 8): All subjects will receive matching placebo dosed orally QD.
- Treatment Period 2 (DB Study Week 8 to Study Week 12): Subjects will receive one matching lorundrostat-placebo tablet (sequence LP) or a lorundrostat 25 mg (sequence PL) dosed orally QD.

During the DB and Washout periods, subjects will continue their background therapy including ACEi/ARB and SGLT2i.

If at any time during the DB periods, eGFR drops by ≥30% from Randomization, a decision on dose reduction, dose hold or dose withdrawal/discontinuation will be made in consultation between the Investigator and the Medical Monitor.

Following the completion of the study, subjects will be offered the opportunity to participate in a separate open label extension (OLE) study. If subjects do not enter the OLE, a final End-of-Study (EoS) safety visit will take place 2 weeks after the last dose of study drug.

2.2 Randomization Methodology

Approximately 60 subjects will be randomized to receive treatment sequences LP or PL in a 1:1 ratio using a randomization and trial supply management (RTSM) system.

The randomization will not be stratified.

2.3 Stopping Rules

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Sponsor may issue a protocol amendment or discontinue the study entirely, based on regulatory authority or Institutional Review Board/Independent Ethics Committee (IRB/IEC) recommendations, drug safety or availability concerns, discontinuation of the development program for lorundrostat, or at the Sponsor's discretion with at least 30 days' notice. The data monitoring committee (DMC) may also recommend study termination based on a review of the safety data.

2.4 Data Monitoring Committee

A DMC will meet periodically to monitor the study. The primary function of this committee is safety monitoring. As part of these reviews, the DMC will receive summaries of study conduct measures as well as unblinded safety and efficacy data. The DMC may recommend discontinuing enrollment for safety. The full scope and responsibilities of the DMC will be described in the DMC charter per the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees.

2.5 Blinding

The identity of study drug assignments (lorundrostat or placebo) during the DB treatment periods will be concealed from the Investigator, the subject, research center staff, and all personnel involved in the conduct of the study, with the exception of the unblinded Sponsor drug management staff who will oversee the study drug allocations and RTSM/dispensing compliance at the study centers.

Except when it is essential for the medical management of the subject, unblinding the treatment assignment will be considered a protocol deviation. If possible, the Investigator should contact the Sponsor before unblinding any subject's treatment assignment. If this is not possible, the Sponsor should be notified within 24 hours after the unblinding event. Emergency treatment allocation information will be available by secured access to the RTSM system. After unblinding, the subject will be discontinued from study drug treatment, but will continue participation in the study, including participation in all remaining visits and assessments, until the EoS visit. The reason for unblinding must be documented in the electronic case report form (eCRF).

2.6 Interim Analyses

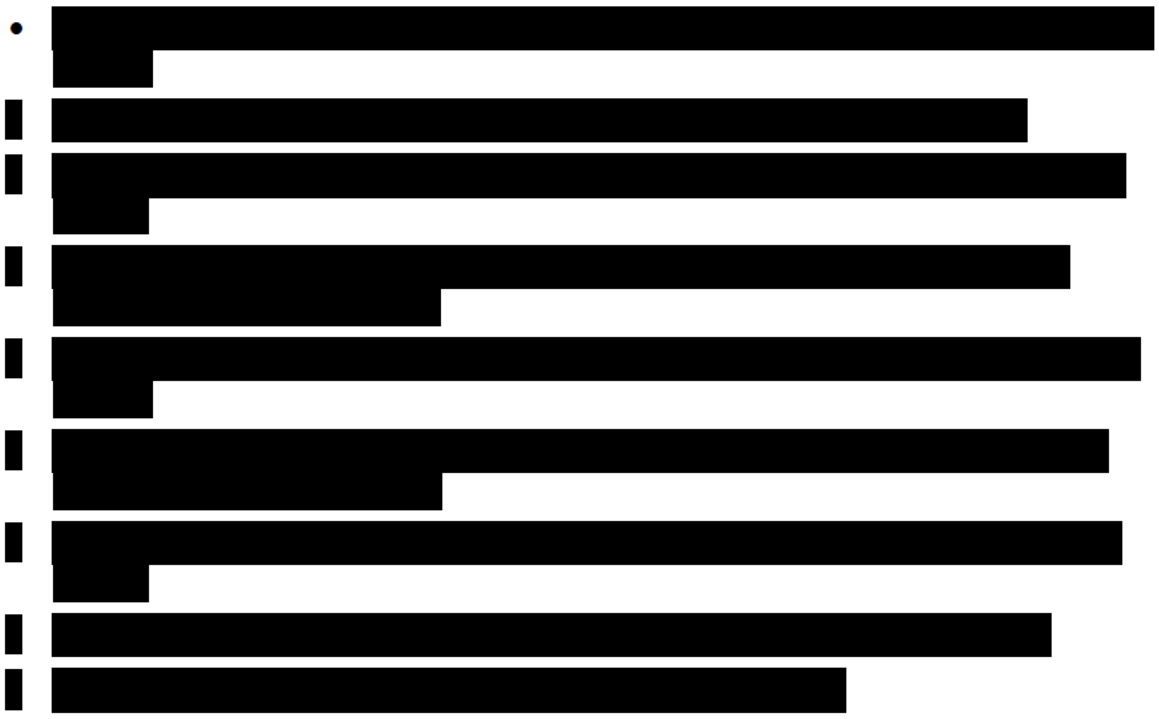
No other interim analysis is planned.

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

Placebo-adjusted change from baseline in AOBP SBP at Treatment Week 4

3.2 Exploratory Efficacy Endpoints



3.3 Safety Endpoints

- Incidence and severity of adverse events (AEs)
- Clinically significant changes in physical examination and electrocardiogram (ECG) parameters
- Clinically significant changes in clinical laboratory assessments (hematology, chemistry, and urinalysis)
- Incidence of AEs of Special Interest (AESI)
    - Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
    - Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
    - Severely elevated BP (AOBP SBP >180 mmHg or AOBP DBP >110 mmHg)
    - Modification of study drug dose due to hypercortisolism (morning serum cortisol [redacted] confirmed by 24-hour urinary free cortisol)
    - Discontinuation of study drug due to hypocortisolism confirmed by ACTH stimulation test
    - Overdose of study drug
    - Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation)

3.4 Pharmacokinetic endpoint

[redacted]

4 ANALYSIS SETS

4.1 Analysis Set Definitions

The following Analysis sets will be evaluated and used for presentation and analysis of the data for the subjects screened starting with Protocol Amendment 3. Subjects screened and enrolled prior to the protocol amendment 3 will be only listed and do not participate in the Analyses sets defined below.

4.1.1 Screened Set (SCR)

The screened set includes all subjects who have signed the informed consent document.

4.1.2 Run-in Safety Analysis Set (RINSAF)

The Run-In Safety Analysis Set will include all subjects who attended the Run-in Visit and were eligible to proceed.

4.1.3 Intent-to-Treat Set (ITT)

The intent-to-treat (ITT) analysis set will include all randomized subjects, regardless of whether treatment was received. This analysis set will be used for demographics and baseline disease characteristics summaries and any analysis of subjects according to the randomized study treatment group.

4.1.4 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all randomized subjects who receive at least one dose of investigational study drug (lorundrostat or placebo). Subjects will be categorized according to the treatment assignment. Efficacy outcomes will be analyzed using the FAS, unless otherwise specified.

4.1.5 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will include all randomized subjects who receive at least one dose of investigational drug (placebo or lorundrostat) during the double-blind treatment period. Subjects will be assigned according to the treatment received.

4.1.6 PK Analysis Set (popPK)

The popPK will include all randomized subjects who received at least one dose of lorundrostat and have at least one evaluable popPK sample taken. The popPK set will be the primary set for the analysis of pharmacokinetic parameters.

4.2 Protocol Deviations

All protocol deviations are recorded in the Clinical Trial Management System, Sitero, and will be reviewed and final classification will be made prior to database lock for the planned analyses. Important protocol deviations (PDs) will be listed and summarized by category for the FAS. Both IPD and non-important protocol deviations (NIPDs) will be listed.

5 DATA HANDLING

5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or higher), unless otherwise noted. Medical history and AEs will be coded using Medical Dictionary for Regulatory Authorities (MedDRA) version 28. Concomitant medications (CMs) will be coded using World Health Organization (WHO) Drug version Global B3.

5.2 Data Conventions

Subjects

Screened subject is any subject who signs informed consent.

Screen Failure is any subject that does not get randomized, regardless of inclusion/exclusion criteria status.

Randomized Subject is any subject that receives Randomization ID in eCRF.

Study Arms

Randomized Sequence refers to the sequence to which the subject was randomized. There are two randomized sequences (Lorundrostat-Placebo and Placebo-Lorundrostat). If the reference is made to the as Randomized Arm, it is the same as sequence.

Treatment Arm refers to lorundrostat and placebo. Each subject is planned to receive both lorundrostat and placebo treatment, in prespecified order as defined by the sequence.

Study day

Efficacy analysis will consider study day relative to the date of the first exposure to the treatment. Any events and observations on or after the date of the first exposure to the treatment will be calculated as: assessment date – date of the first exposure to the treatment + 1. As such, the date of the first exposure to the treatment is study day 1. For any events before the date of the first exposure to the treatment, study day will be calculated as: assessment date – date of the first exposure to the treatment

Period and date definitions

Screening Period: Period prior to Run-in Period (Week -2). The screening period starts on the day of enrollment (signing of the informed consent).

Run-In: The period from enrollment into Run-in Period to Randomization Visit (Week 0)

Last Run-In dose date will be the last dose date of administered Dapagliflozin or their regularly prescribed SGLT2i prior to randomization.

Treatment Period 1 (TP1): A double-blind period from Randomization to last dose (study treatment) date of TP1 or Study Week 4 Date, whichever is later.

Washout Period: A single-blind placebo period from after the end of TP1 to before first investigational administration of Treatment Period 2 (TP2) or Study week 8 visit, whichever is later.

First Washout dose date will be the first dose date of placebo after last investigational drug administration during TP1.

Last Washout dose date will be the last dose date of placebo prior to first investigational drug administration during TP2.

Treatment Period 2 (TP2): A double-blind period from first investigational drug administration during TP2 or Study Week 8 visit, whichever is later, to last investigational drug administration or Study week 12 / EoT visit, whichever is later.

First investigational drug administration during TP1 will be selected from the "Investigational Drug Administration" CRF page for the Randomization Visit or vendor AiCure's Dosing Diary data (selecting the first [Lorundrostat or Placebo] record following randomization) – the earlier available from each source.

Last investigational drug administration during TP1 will be selected from the "Investigational Drug Administration" CRF page for the Study Week 4 visit if the drug was administered at the Week 4 visit or, vendor AiCure's Dosing Diary data (selecting the last [Lorundrostat or Placebo] record on or prior to Week 4 Study Visit Date, the latest available from each source.

First investigational drug administration during the Washout Period will be selected for the subjects who were dispensed placebo after the TP1 from the vendor AiCure's Dosing Diary data (selecting the first [Placebo] record following Week 4 Visit. If that is not available, the first dose will be imputed as Week 4 Visit Date +1 day at 08:00 AM if the subject was dispensed placebo.

First investigational drug administration during TP2 will be selected from the "Investigational Drug Administration" CRF page for Study Week 8 visit if the administration occurred on Week 8 visit date or, vendor AiCure's Dosing Diary data (selecting the first [Lorundrostat or Placebo] record on or after Week 8 visit ["Investigational Drug Administration" or "Date of Visit" CRF pages]) – the earlier available from each source. Only subjects who were dispensed drug on Week 8 visit record can have this information.

Last investigational drug administration during TP2. Only subjects with the First investigational dose administration in TP1 may have the last investigational drug administration in TP2. The last administration will be selected from the "Investigational Drug Administration" CRF page for Week12 / EoT visit (when study drug was administered at the visit) or vendor AiCure's Dosing Diary data (selecting the last [Lorundrostat or Placebo] record following Week 12 visit ["Investigational Drug Administration" or "Date of Visit" CRF pages]) – the latest available from each source.

Safety Follow-up Period: All observations and measurements following End of Treatment Period 2 are considered safety Follow-up Period, including the EoS (Week 14/EoS) visit. [redacted]. Subjects who were [redacted] may have Safety Follow up period after the Run-In. Subjects who have discontinued the study early may have an EoS prior to Study Week 14.

Derivations

Numerical results for the laboratory results that have observations reported as "<xx" and ">xx" will be calculated as follows. The laboratory data file contains numerical result precision variables for the results in conventional (CNVRESNP, Conventional Numeric Results Precision) and the SI units (SIRESNP, SI Numeric Results Precision). The numerical result will be calculated by subtracting (for the results with "<") or adding (for the results with ">") the (CNVRESNP-8) for the conventional units and (SIRESNP-8) for the SI units. By a way of example, the result that is <3.4 in the SI units and the SIRESNP=8.1, the numerical result will be calculated as: [redacted]

Derivation of Automated Office Blood Pressure (AOBP) parameters: There are 12 derived AOBP parameters five for the measurements obtained in the sitting position, 5 for the measurements obtained in the standing position, and two comparing standing and sitting SBP and DBP. The parameters are derived from the raw AOBP measurements according to the specifications provided in Sponsor document titled "Derivation of AOBP parameters" from 07 Nov 2024.

The number of antihypertensive (AHT) medications will be derived as follows. The AHT medications will be selected form the Concomitant Medications coded by using the Anatomical Therapeutic Chemical (ATC) Classification 2nd level code. The following ATC 2nd level are considered AHT medications (Table 1). For combination medications each medication counts as a separate medication. For example, a combination of beta blocking agent and a thiazide diuretic (ATC4 Code "C07B") counts as 2 medications.

Table 1 Anatomical Therapeutic Chemical codes for antihypertensive medications

ATC 2nd Level Code	Description
C02	**Antihypertensives**
C03	**Diuretics**
C07	**Beta Blocking Agents**
C08	**Calcium Channel Blockers**
C09	**Agents Acting on the Renin-Angiotensin System**

Corrected Serum Sodium will be calculated as follows. If serum glucose [redacted] then corrected sodium = Measured sodium + [redacted] Serum glucose - 100); otherwise Corrected Sodium = Measured sodium; where sodium is in mmol/L and glucose in mg/dL. Corrected sodium will be rounded to the nearest integer.

Body Mass Index (BMI): weight (kg) / height(m)^2. Round to one decimal place precision (xx.x). Height is obtained only at the screening and it will be used for all BMI derivations.

eGFR (Cystatin C) (PARAMCD = "GFRE2012") will be calculated using the CKD-EPI Cystatin C Equation (2012) available at: CKD-EPI Cystatin C Equation (2012) | National Kidney Foundation.
eGFR = [redacted] (Scys/[redacted] 0.499 x max (Scys/[redacted])-[redacted] 96Age x 0.932 [if female]
where,
eGFR (estimated glomerular filtration rate) = mL/min/[redacted]
Scys (standardized serum cystatin C) = mg/L,
min = indicates the minimum of Scys/[redacted]
max = indicates the maximum of Scys/[redacted]
age = years
Round to the nearest integer.

ARR (Aldosterone to Renin Ratio) (PARAMCD = "ARR") as Serum Aldosterone (ng/dL) / Renin (ng/mL/hr). Round to 2 decimal places precision (x.xx).

Urine Albumin-to-Creatinine Ratio (UACR1) as (Spot Urine Albumin (mg/dL) to Spot Urine Creatinine (mg/dL))[redacted] The result's PARAMCD="UACR" and PARAM is "Urine Albumin to Creatinine Ratio (mg/g) (Spot Urine)". Round to two decimal places precision (x.xx). This parameter is already calculated in the original central laboratory data but is expressed as g/g. It needs to be multiplied by [redacted] to obtain the result in mg/g. No new calculation should occur except for the multiplication by [redacted]

Urine Albumin-to-Creatinine Ratio (UACR2) as 24-h Urine Albumin (mg/day) to 24-h Urine Creatinine (mg/day))[redacted] The result's PARAMCD="UACR" and PARAM is "Urine Albumin to Creatinine Ratio (mg/g) (24-h Urine)". Round to two decimal places precision (x.xx).

Urine Protein-to-Creatinine Ratio (UPCR1) as (Spot Urine Protein (mg/dL) to Spot Urine Creatinine (mg/dL))[redacted]. The result's PARAMCD="UPCR1" and PARAM is "Urine Protein to Creatinine Ratio (mg/g) (Spot Urine)". Round to two decimal places precision (x.xx). This parameter is already calculated in the original central laboratory data but is expressed as g/g. It needs to be multiplied by [redacted] obtain the result in mg/g. No new calculation should occur except for the multiplication by [redacted]

Urine Protein-to-Creatinine Ratio (UPCR2) as 24-h Urine Protein (mg/day) to 24-h Urine Creatinine (mg/day))*[redacted] The result's PARAMCD="UPCR2" and PARAM is "Urine Protein to Creatinine Ratio (mg/g) (24-h Urine)". Round to two decimal places precision (x.xx).

Urinary Aldosterone-to-Creatinine Ratio (24-h Urine) is calculated as a ratio of urine aldosterone excretion (ng) and the simultaneous urine creatinine excretion (mg). The PARAMCD will be "U24ALDCR" and the PARAM "24-h Urine Aldosterone (ng) to Creatinine (mg) Ratio". Round to two decimal places precision (x.xx).

Identifying ARB and ACEi medications will be as follows. The ARB and ACEi medications will be selected from the Concomitant Medications coded by using the Anatomical Therapeutic Chemical (ATC) Classification 3rd level code. The following ATC 3rd level are considered ARB and ACEi medications (Table 2).

Table 2 Anatomical Therapeutic Chemical codes for ACEi and ARB medications

Medications	**ATC 3rd Level Code**	**Description**
ARB	C09C	Angiotensin II receptor blockers (ARBs), plain
ARB	C09D	Angiotensin II receptor blockers (ARBs), combinations
ACEi	C09A	ACE inhibitors, plain
ACEi	C09D	ACE inhibitors, combinations

Identifying SGLT2i medications will be as follows. The SGLT2i medications will be selected from the Concomitant Medications coded by using the Anatomical Therapeutic Chemical (ATC) Classification 4th level code. The following ATC 4th level will be considered for SGLT2i medications (Table 3).

Table 3 Anatomical Therapeutic Chemical codes for SGLT2i medications

ATC 4th Level Code	**Description**
A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors

5.3 Methods of Pooling Data

Clinical sites follow a common protocol, are monitored for compliance with the protocol, and report data collected via a central electronic database. These factors allow the data to be pooled and analyzed jointly across sites (Meinert, 1986).

5.4 Withdrawals and Loss to Follow-up

Subjects have the right to withdraw participation in the study at any time and for any reason or for no reason and will be removed from the study upon request. At the time of withdrawal from the study, if possible, an EoS visit should be conducted to complete all assessments scheduled for a safety follow-up visit in either study part as shown in the schedule of assessments. Subjects who withdraw prematurely from the study for any reason will not be eligible to participate in the OLE study. Details regarding subjects who choose to discontinue study participation will be recorded on the appropriate page(s) of the eCRF.

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

5.5 Analysis Visit Windows

5.5.1 Windowing of the AOBP and the Laboratory Measurements

All efficacy analyses of the AOBP and laboratory measurements will use analysis visits assigned by study day ranges relative to DB treatment start or TP2 first dose (TP2 visits only). Scheduled, unscheduled, EoT, or EoS/early withdrawal (EW) efficacy assessments will be mapped to an analysis visit. In cases where a subject has multiple assessments windowed to the same analysis visit, the assessment closest to the protocol-specific target day will be selected for analysis. Screening will not be windowed; nominal visits will be used. In the case of multiple screening visits, the visit closest to the start of the Run-in Period Visit will be used. Visits during the safety follow-up period will not be windowed.

The Study Baseline is the measurement with the datetime of the measurement that is closest to the before the datetime of first dose in TP1 (ADTM <= Treatment date/time in the TP1). For AOBP, the measurements with the AOBP AOQC=1 will be excluded from baseline determination. If the subject was randomized but has not received the treatment, the Randomization datetime will be used to establish the baseline.

The windowing will be performed by matching the date of the measurement with the date of the visit as reported in the eCRF. For example, if there is a measurement that is obtained on the Week 4 site visit date, that measurement will be used for the Week 4 observation. The measurement for Week 8 will be the one obtained on the Week 8 site visit date as obtained from the raw.sv file and so on. In case there is no measurement that matches the site visit date then the measurement obtained *prior* to the site visit and with the date closest to the site visit date will be used. If there are two competing measurements (e.g. two measurements obtained on the same date), the later measurement on the date will be used.

This procedure will allocate measurements into Study weeks Baseline, Week 2, Week 4, Week 8, Week 10 and Week 12, as applicable. Subjects who do not participate in [redacted] may have Week 14/EoS visit. Week 14/EoS visit is Safety Follow-up. Subject is not on the study investigational medications during the Safety Follow-up Period. If there is an EoS Visit Date on the same date of the Study Visit Date, and the subject is on study medications, then the measurement maps into the Study Visit. All measurements that do not map into these visits will be listed but will not contribute to the summaries and analyses.

Next, for the analysis purposes, the measurements need to be organized into the cross-over design pattern, with two baselines corresponding to Study Week 0 and 8 and two treatment visits (Treatment Visit 2 and 4). This is in addition to the above windowing. The ADaM level data set will have data organized both by Study flow (above) and the data organized by Cross-Over design flow.

5.5.2 Windowing of vitals and other safety measurements

Vitals will be analyzed according to the nominal visits as reported in the eCRF. They may need to be organized by cross-over design as well or analysis visits (i.e., as reported on the eCRF).

Unscheduled measurements will not be included in by-visit summaries but will contribute to the Baseline timepoint and/or minimum/maximum/worst value (e.g., shift table), if applicable.

Listings will include all visit data, including unscheduled visits, in chronological order based on visit date.

Actual dates and times will be used for pharmacokinetic analyses rather than nominal days and times.

6 STATISTICAL METHODS

6.1 Sample Size Justification

Approximately 60 subjects randomized in a 1:1 ratio to the two sequences (LP and PL) will provide 85% power to detect a placebo-adjusted change in AOBP SBP of at least 5.5 mmHg at Treatment Period Week 4 (pooling both Treatment Periods in a joint longitudinal analysis), assuming 14 mmHg as a standard deviation of change, and 1-sided alpha of 0.05.

Power for a joint analysis is a function of the alternative (assumed 5.5 mmHg), the standard deviation (assumed 14 mmHg), and both the within-treatment-period correlation denoted ρ_1, and the between-treatment-period correlation denoted ρ_2. We consider a simple exchangeable correlation model where $\rho_2 = \rho_1$, and a time decay model where $\rho_2 = \rho_1^2$. The following table shows power as a function of the correlation model using analytical expressions for standard errors obtained from the primary linear mixed model analysis:

Correlation (ρ_1)	**Power assuming Exchangeable model ($\rho_2 = \rho_1$)**	**Power assuming Time decay model ($\rho_2 = \rho_1^2$)**
0.50	0.819	0.756
0.55	0.850	0.785
0.60	0.882	0.819
0.65	0.915	0.858
0.70	0.945	0.900
0.75	0.971	0.941
0.80	0.988	0.975

Crossover trials generally find a correlation model that closely approximates an exchangeable model since this corresponds to a common magnitude of between subject variation that would be induced from a simple random intercepts model (see Jemielita, Putt and Mehrotra 2016 for examples). Under the exchangeable correlation model, the study has ≥ 85% power provided the correlation is ≥ 0.55.

6.2 General Statistical Methods

6.2.1 General Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, standard deviation, median, Q1, Q3, minimum and maximum values will be presented. For some parameters with skewed distributions geometric means, geometric standard deviations and geometric confidence intervals will be presented as specified in the Section 6.6.3.3.

Statistical hypothesis testing will be performed for the primary efficacy endpoint, as described in this document. The alpha value used for specific statistical hypothesis is described in Section 6.2.5. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below. Statistical testing using nominal p-values will be provided for exploratory endpoints using the alpha value from Section 6.2.5.

Means and medians will be presented with one more decimal place compared to the raw data. Standard deviation will be shown with two more decimal places. Minimum and maximum values will retain the same number of decimal places as in the raw data. Percentages will be displayed with one decimal place.

6.2.2 Definition of Baseline

The baseline for the efficacy measurement is defined in the Section 5.5.1.

Baseline for non-efficacy observations is defined as the last valid assessment on or before the first treatment dosing in TP1 or, for the subjects that are not dosed as the last valid assessment prior to the randomization datetime. If the endpoint refers to the change related to the cross-over design, then the baselines (TP1 and TP2) will be determined in the same fashion as described in the section 5.5.1.

6.2.3 Adjustments for Covariates

No adjustment will be made except as provided in the specific analysis model.

6.2.4 Alpha Value

The overall alpha (α) value is set to one-sided 0.05. The primary and all exploratory endpoints will be tested on the same one-sided alpha of 0.05. The confidence intervals for all analyses will be 90%.

6.2.5 Multiple Comparisons/Multiplicity

Only the primary endpoint will be tested. There will be no adjustment for multiplicity for the exploratory endpoints.

6.2.6 Subgroups

[redacted]

6.2.7 Missing, Unused, and Spurious Data

Unless stated otherwise, missing data will not be replaced with imputed values.

The handling of intercurrent events (ICEs) and sensitivity analyses, including planned handling of missing observations for primary endpoint, are described in Section 6.4.1.2, the rules below will apply unless otherwise specified.

Partial and missing AE or concomitant medication dates will be imputed as described in Section 6.6.

6.3 Study Population

6.3.1 Subject Disposition

Subject disposition will be presented by Randomized Sequence and overall, including the number of subjects screened, screen failed, entered run-in period, completed run-in period and not randomized, randomized, dosed in TP1, dosed in TP2, the number of subjects that withdrew from study treatment and from the study after the randomization in TP1 and TP2 along with the reasons, the number that completed DB Treatment in TP1, TP2 and overall, the number that entered Safety Follow-up Period, and the number that completed the Safety Follow-up Period. The denominator for percentages will be the total number of subjects randomized in each Randomized Sequence, when applicable.

The number of subjects that screen fail at Screening or Randomization and reasons (inclusion/exclusion criteria or other) will be presented by the total number of screen failures.

The following by-subject listings will be presented.

- Study completion information, including the reason for premature study withdrawal, overall and by Treatment period
- Screen failure with inclusion/exclusion criteria
- Randomized patient inclusion in study Analysis Sets or reasons for exclusion.
- Protocol deviations

6.3.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the total sample. The data will be also listed. The tables will include only Total. The listing will indicate the Randomized Sequence. The characteristics will be presented per baseline definition (e.g. BMI at Baseline).

- Age (years): Age at time of consent
- Age (categories): (< 65, 65-74 and >=75)
- Sex: Male, Female; For women, of childbearing potential, post-menopausal, sterilized

- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, and Not Reported.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported.
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI (kg/m^2); Categories: (< 30 kg/m^2 and ≥ 30 kg/m^2)
- Hip circumference (cm)
- Waist circumference (cm)
- Waist to Hip Ratio
- Waist to Hip Ratio (WHR): Healthy: < 0.90 [men] and <0.85 [female], Obese: ≥ 0.9 [men] and ≥ 0.85 [women], High Risk: > 1.0 (both men and women).
- AHT regimen (listing only)
- Prescribed AHT regimen (≤2 and 3 or more) as randomized
- AHT Therapy Class (ACT Level
- SGLT2i status at screening (naïve or not)
- Seated AOBP SBP and DBP (mmHg)
- Seated AOBP SBP Category (<130 mmHg, 130- < 140 mmHg, ≥140 mmHg - <160 mmHg and ≥160 mmHg)
- Standing AOBP SBP and DBP (mmHg)
- Smoking Status (Current, Former, Never)
- History of alcohol abuse (Yes, No)
- History of illicit drug use (Yes, No)
- History of any other tobacco use (Yes, No)
- eGFR (ml/min/1.73m2) (2021 CKD-Epi formula using serum creatinine)
- Baseline eGFR (< 30 mL/min/1.73m2, 30-44 mL/min/1.73m2, 45-59 mL/min/1.73m2, 60-89 mL/min/1.73m2, 90 mL/min/1.73m2 and more) (2021 CKD-Epi formula using serum creatinine)
- eGFR (ml/min/1.73m2) (2012 CKD-Epi formula using serum Cystatin-C)
- Baseline eGFR (< 30 mL/min/1.73m2, 30-44 mL/min/1.73m2, 45-59 mL/min/1.73m2, 60-89 mL/min/1.73m2, 90 mL/min/1.73m2 and more) (2012 CKD-Epi formula using serum Cystatin-C)
- UACR (<30 mg/g, 30-<300 mg/g, >=300 mg/g)

6.3.3 Medical History

Medical Histories will be summarized for the ITT by Treatment Sequence and overall by using system organ class (SOC) and preferred term (PT) with frequencies and proportions of subjects that experienced each level. Medical Histories will be provided in a data listing.

6.3.4 Exposure and Adherence

The proportion of subjects who permanently discontinued blinded investigational drug, overall and by reasons for discontinuation, will be summarized overall and by Treatment Group within Randomized Sequence.

The proportion of subjects who experienced at least one temporary holding of blinded investigational drug, overall and by reasons for holding, will be summarized by treatment arm. Descriptive statistics of the duration of exposure to investigational drug in total and adjusted for temporary holds will be summarized by the treatment arm. Treatment duration, calculated as the number of days the subject received randomized investigational drug will be calculated as the date of the last dose minus the date of the first randomized dose + 1. The duration will be adjusted for temporary holds by subtracting days the investigational drug was temporarily held.

Treatment adherence will be defined by the treatment adherence ratio: the number of doses taken by the subject divided by the number of doses assigned.

Adjusted treatment adherence will be defined by the treatment adherence ratio: the number of doses taken by the subject divided by the number of doses assigned adjusting for the treatment holds.

A listing of the exposure and adherence parameters will be provided, including reasons for modification, if they occur.

6.3.5 Prescribed AHT

A listing of each patient prescribed AHT therapy will be provided.

6.4 Efficacy Evaluation

All efficacy analyses will be performed using the FAS unless stated otherwise.

The efficacy analyses of primary and exploratory endpoints will provide the observed values at each Baseline (TP1 baseline and TP2 baseline), the end of each treatment period (TP1 Treatment Week 4 and TP2 Treatment Week 4), and the change from baseline by each treatment arm in addition to model estimates.

Analyses including repeated visits / time points will include each repeated visit/time point considered in the model. Parameter estimates that include multiple repeated visits / time points may be presented if specified for analysis.

A summary table of each assessment will provide the observed value and change from baseline for each scheduled visit by Randomized Sequence and treatment period and totals by treatment group, unless otherwise specified.

Line plots of blood pressure mean value over time and change from baseline over time with 95% CIs will be provided by treatment arm and treatment period. Endpoints estimated with analysis models will also plot LS Means and their 95% CIs for each time point.

Box-and-whiskers plots of observed data distributions will be provided for primary endpoint for treatment arm and treatment period. A box-and-whiskers for model analysis estimates of LS Means will plot Standard Error of the Mean (instead of Q1/Q3) and 95% CIs (instead of Min/Max). A waterfall plot of the change in systolic blood pressure will be provided overall and separately for treatment period.

Categorical analysis will display the number and proportion of patients that meet the endpoint at baseline and for the time point of interest. Proportions at the endpoint's time point will only consider those that did not meet criteria at baseline.

Categorical endpoints will be presented with Bar Charts of proportion and 95% CIs.

6.4.1 Primary Efficacy Endpoint Analysis

Endpoint: Placebo-adjusted change in AOBP SBP from TP baseline to TP Week 4

6.4.1.1 Estimand Question

The Primary Efficacy Endpoint estimand is designed to answer the question of the effect of lorundrostat in a dose of 25 mg QD for 4 weeks on blood pressure in subjects with uncontrolled hypertension and CKD with albuminuria on treatment with SGLT2i and a prescribed AHT medication regimen including ACEi or an ARB.

6.4.1.2 Estimand Definition

This estimand is constructed in line with ICH E9 (R1) addendum and described below.

Table 4 Definition of the estimand for the primary efficacy endpoint

Population:	Patients aged 18 years and older with a history of medically treated hypertension and CKD with albuminuria whose blood pressure prior to initiation of study treatment is uncontrolled based on blood pressure measured by AOBP despite being prescribed antihypertensive therapy including a stable dose of ACEi or ARB. In addition, subjects are on a treatment with SGLT2i. Additional inclusion and exclusion criteria as specified in protocol apply. Only patients who receive at least one dose of the study treatment (lorundrostat or placebo) are included.

Treatment	Treatment is lorundrostat 25 mg QD for 4 weeks on a background of the prescribed AHT medication regimen including a stable dose of ACEi or ARB and SGLT2i. The treatment is administered in the cross-over randomized sequence (Lorundrostat/Placebo or Placebo/Lorundrostat) with a 4-week washout in between.
Variable	AOBP SBP at Treatment Week 4 (TP1 Week 4 and TP2 Week 4)
Population-level summary	Mean placebo-adjusted change in AOBP SBP from Treatment Period baseline to Treatment Period Week 4
Handling of ICE events	Is described in the Table 5.

Table 5 Handling of ICE for the primary efficacy estimand

ID	Description of ICE	Type of the Event	Observations handling (Strategy)	Rationale
1	Permanent discontinuation[1] of investigational drug (lorundrostat or placebo) due to adverse events, clinically significant laboratory finding or due to medical assessment as described in the protocol	Treatment-modifying event	Treatment Policy Strategy: Observations for subjects with ICE will be used regardless of occurrence of ICE	Permanent discontinuation of the investigational treatment due to AEs, significant laboratory findings and protocol defined medical assessments are anticipated to occur in the clinical practice and the estimate of the treatment effect of intervention needs to incorporate these events.

[1] Temporary discontinuation (“drug holds”) or dose modification do not qualify as ICE. Modification or changes in background prescribed AHT medications do not qualify as ICE.

ID	Description of ICE	Type of the Event	Observations handling (Strategy)	Rationale
2	Death for any cause	Censoring Event	Composite Strategy: The endpoint will be imputed to assign a poor outcome value by applying a distribution of the worst 5% of the observations across all arms	The treatment policy strategy is not applicable as there are no post-event observations.

6.4.1.3 Missing Observations for the AOBP SBP

For general guidance about the missing values, see 6.2.7. Guidance on handling the missing observations is provided below.

Table 6 Missing observations imputation for the primary efficacy estimand

Cause for Missing Observation	**Type of Missingness**	**Imputation Approach**	**Rationale**
Lack of follow-up observation in subject with ICE ID #1.	MNAR	Values for the missing observation will be imputed using the distribution for the subjects with ICE ID#1 who do not miss the value (so called "retrieved dropouts"), within the same randomized sequence, if such approach is possible. In case there are not enough retrieved dropouts within the same sequence, the imputation will be performed by Jump to the Reference Group (Placebo Arm)	Retrieved dropouts' imputation is closest to following a treatment strategy for missing observations. Jump to reference as a last resort is conservative imputation strategy that disfavors treatment effect.
Death for any cause (ICE Event #2)	MNAR	This observation is missing by default. The endpoint will be imputed to assign a poor outcome value by applying a distribution of the worst 5% of the observations across both randomized sequences.	The treatment policy strategy is not applicable as there are no post-event observations. Death, as an unfavorable truncating event prevents observations to be obtained.
Premature study discontinuation in subjects without ICE (e.g. loss to follow-up, withdrawal of consent)	MAR	Values for the missing observations will be imputed using the randomized sequence specific distribution	These observations are assumed to be missing at random and will be imputed as a part of the treatment arm they belong to.

Cause for Missing Observation	Type of Missingness	Imputation Approach	Rationale
Missing observation due to failure to obtain AOBP in subjects without ICE	MAR	Values for the missing observations will be imputed using the randomized sequence specific distribution	AOBP may fail for technical reasons or subject may miss the visit. These observations are assumed to be missing at random and will be imputed as a part of the treatment arm they belong to.

6.4.1.4 Primary Efficacy Estimation

The primary analysis of the primary efficacy estimand will assess the superiority of lorundrostat 25 mg QD dose compared to placebo in mean change in AOBP SBP from TP baseline (TP1 Baseline and TP2 Baseline) to TP Week 4 (TP1 Week 4 and TP2 Week4).

The analysis includes two baselines (TP1 baseline and TP2 baseline). The primary analysis will be based on the work of Mehrotra DV, 2014 and Jemielita, T., et al. 2016. Specifically, the Model IV from Mehrotra DV, 2014 will be used for the primary analysis as the best performing model for pairwise correlation of 0.6 and balanced 2x2 design. Sensitivity analyses will use additional models as specified later.

Example of SAS code for the planned estimation is provided below. The actual code may differ from the example depending on the data, carry-over effect and convergence.

```
proc mixed data = file;
class trtseqp aperiodc trtp usubjid;
model aval = xdiff trtseqp aperiodc xdiff*aperiodc trtp ;
repeated aperiodc/subject=usubjid(trtseqp) type=un;
estimate 'Lorundrostat v placebo' trtp 1 -1 /cl alpha=0.1;
lsmeans trtp /pdiff cl alpha=0.1;
```

where,
trtseqp is a planned treatment sequence (Lorundrostat-Placebo and Placebo-Lorundrostat),
aperiodc is analysis period (TP1 and TP2),
trtp is planned treatment (Lorundrostat and Placebo),
xdiff is a difference between TP1 baseline and TP2 baseline.

The estimate statement depends upon the coding of the variables and needs to be adjusted accordingly.

6.4.1.5 Sensitivity analysis

Sensitivity analyses will be performed as follows:

- Using observed data only,
- Assuming that all missing values are MAR
- Utilizing a longitudinal linear analysis model as described in Cheng X, et al., 2021

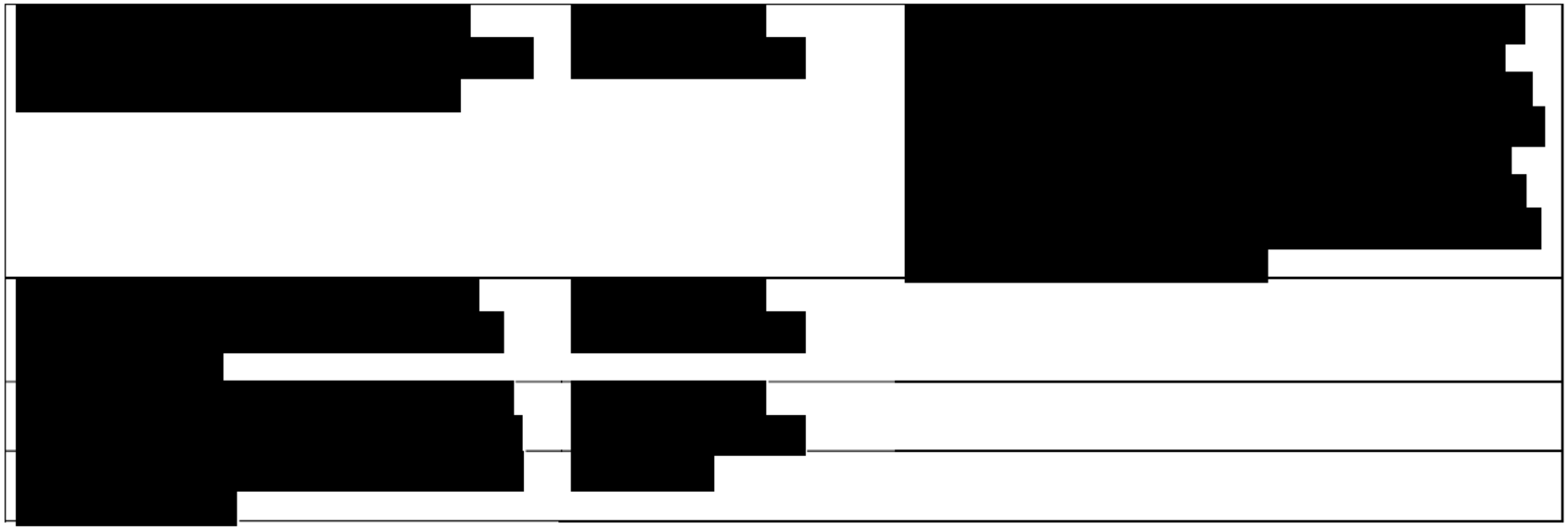
6.4.1.6 Subgroup analyses for Primary Efficacy

[redacted].

6.4.2 Exploratory Efficacy Endpoint Analyses

[redacted]

Table 7 Overview of planned estimations for exploratory endpoints



6.5 Pharmacokinetic Evaluations

[redacted]

6.6 Safety Evaluations

6.6.1 Safety Treatments Displays

Safety analyses will be conducted using the Safety Analysis Set. All safety events starting or worsening of the existing AE between the first dose in the TP1 and the First dose in the TP2 (Week 0 to Week 8, including the washout) will be allocated to the medication received first in the randomized sequence (lorundrostrat or placebo). All AEs starting or worsening of the existing AE from the first dose in the Treatment Period 2 to the End of Treatment / End of Study, whichever is later, will be allocated to the medication starting in the TP2 (lorundrostat or placebo).

All AE Summary displays will present AEs by Treatment Period and Treatment Group within the period and, by Treatment Group Total.

6.6.2 Adverse Events

Adverse events definitions are provided in the protocol.

6.6.2.1 AEs during the Run-In Period

Any AEs occurring after the first dose of SGL2-i medication in the Run in Period and before the first dose of the investigational medication (lorundrostat/placebo) in the DB period are considered AEs in the Run-In period. This definition also includes worsening of the existing AE during the Run-In period.

6.6.2.2 Treatment-emergent AEs

Treatment-emergent AEs (TEAEs) are defined as any AE that occurs or worsens after the first dose of the treatment in TP1. All AEs occurring after the first dose and until the end of the study participation are considered treatment-emergent events, including the adverse events occurring during the washout period in between the two treatment periods. Adverse events occurring during the Safety Follow-up period are considered TEAEs if they occur within 14 days of the start of the Safety Follow-up Period.

6.6.2.3 Adverse Events of Special Interest (AESI)

The AESIs for all study drugs (MLS-101 and placebo) include the following:

- Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
- Severely elevated blood pressure (AOBP SBP >180 mmHg or DBP >110 mmHg)
- Modification of study drug dose due to hypercortisolism (serum cortisol >35 µg/dL, confirmed by 24-hour urinary free cortisol)
- Discontinuation of study drug due to hypocortisolism confirmed by ACTH (Cosyntropin) stimulation test
- Overdose of study drug
- Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, temporary or permanent hold on dosing)

Note: AESIs are reported on the eCRF.

6.6.2.4 Missing or Partial Dates for AEs

Imputation rules for the missing or partially missing AE dates are as follows.

Completely missing Start Date rules in order of application:

- Rule #1. Start date will be imputed as occurring on the first date of the study investigational drug administration, except if complete or partial end date is prior to the study investigational drug administration date.
- Rule # 2. If rule #1 does not apply, then the AE Start Date will be imputed as occurring on the date of the ICF.

Note: If the complete or partial study AE End Date is before the date of the ICF, then the event is not an AE.

Partially missing AE Start Date -missing MONTH and DAY rules in order of application:

- Rule #1. AE Start Day and Month will be imputed as January 1, except if AE Start Year is the same, or earlier, than the year of the first administration of the study investigational drug.
- Rule #2 If rule #1 does not apply, then AE Start date will be imputed as occurring on the first date of the study investigational drug administration, except if AE Start Year is prior to Year of the first study investigational drug administration or complete or partial end date is prior to the study investigational drug first administration date.

- Rule #3. If rules #1 and #2 do not apply, AE Start date will be imputed as occurring on the date of the ICF.

Note: If the complete or partial study AE End Date is before the date of the ICF, or the Month and Year of the AE start Date is prior than Month and Year of the ICF, then the event is not an AE.

Partially missing AE Start Date – missing DAY rules in order of application:

- Rule #1. AE Start Day will be imputed as "1", except if AE Start Month and Year are the same as the Month and Year of the first administration of the study investigational drug or, as the Month and Year of the ICF.
- Rule #2 If rule #1 does not apply, and the AE Start Month and Year are the same as Month and Year of the first study investigational drug administration, then the date will be imputed as the date of the first study investigational drug administration, except if complete end date is prior to the study investigational drug first administration date, in which case the start Day will be imputed as 1.
- Rule #3. If rules #1 and #2 do not apply, Start date will be imputed as occurring on the date of the ICF.

Partial or missing AE resolution dates will not be imputed.

6.6.2.5 AE Relatedness

CRFs have assessment of relatedness to investigational drug (lorundrostat/placebo) and SGLT2i or placebo. Only relatedness to lorundrostat will be used for the determination of relatedness. AEs marked as "Possibly" or "Definitely" related to investigational study treatment (lorundrostat or placebo) will be classified as being related to the study investigational drug ("related"). All other AEs will be classified as not related to investigational study drug. If the relationship to the investigational study treatment (lorundrostat or placebo) is missing, the event will be assigned as related to the study investigational drug.

6.6.2.6 AE Displays

An overall AE summary will be presented by the number and percent of subjects with one or more events of specific type and total number of events of specific type by Treatment Period, Treatment Group within Treatment Period and Treatment Group in Total with the following:

- TEAEs
- TEAEs by worst severity (mild/moderate/severe)
- Treatment-related TEAEs
- Treatment-related TEAEs by worst severity (mild/moderate/severe)
- Serious AEs (SAEs)

- Treatment Emergent SAEs
- Treatment-related Treatment-emergent SAEs
- Adverse Events of Special Interest (AESIs)
- TEAEs leading to permanent discontinuation of study investigational drug
- TEAEs leading to dose modification of the investigational drug
- AEs with death as an outcome
- TEAEs with death as an outcome
- Treatment-related AEs with death as an outcome

The following AE summaries will be produced by MedDRA SOC and PT with the counts and percent of subjects with one or more event and counts of events for each PT and SOC level. The outputs will be presented by the alphabetic order of SOC and PT classes. The summary will be by Treatment Period, Treatment Group within Treatment Period and Treatment Group in Total.

- Any AE
- AEs in Run-In Period
- TEAEs
- TEAEs by worst severity (mild/moderate/severe)
- Treatment-related TEAEs
- Treatment-related TEAEs by worst severity (mild/moderate/severe)
- Serious AEs (SAEs)
- Treatment Emergent SAEs
- Treatment-related Treatment -emergent SAEs
- Adverse Events of Special Interest (AESIs)
- TEAEs leading to permanent discontinuation of study investigational drug
- TEAEs leading to dose modification of the investigational drug
- AEs with death as an outcome
- TEAEs with death as an outcome

The following AE listings will be prepared:

- AEs in Run-In Period
- TEAEs
- TEAEs by worst severity (mild/moderate/severe)

- Treatment-related TEAEs
- Treatment-related TEAEs by worst severity (mild/moderate/severe)
- Serious AEs (SAEs)
- Treatment Emergent SAEs
- Treatment-related Treatment -emergent SAEs
- Adverse Events of Special Interest (AESIs)
- TEAEs leading to permanent discontinuation of study investigational drug
- TEAEs leading to dose modification of the investigational drug
- AEs with death as an outcome
- TEAEs with death as an outcome

6.6.3 Laboratory Data

6.6.3.1 Reference Range for local serum potassium

The reference range for the local laboratory serum potassium for reporting will be established as follows:

ANRLO = [redacted]; ANRLHI = [redacted]. The reference ranges need to be derived according to these reference ranges.

6.6.3.2 General summaries of laboratory data

Laboratory test results (including hematology, serum chemistry, spot urine, urinalysis, 24-hour urine, and ACTH) and abnormal laboratory values will be presented in data listings. Summaries of observed values and changes from baseline will be presented by the Treatment Period and Treatment Group within the period and by Treatment Group in Total for each analysis visit. The SI units will be presented. In addition, the conventional units will be presented for the following tests.

Table 8 Laboratory tests to be presented in conventional units

Laboratory Test Name	Specimen
C Reactive Protein	Serum
Cortisol, ACTH Stimulation, 30 Minute	Serum
Cortisol, ACTH Stimulation, 60 Minute	Serum
Cortisol, ACTH Stimulation, Baseline	Serum
Cortisol, Morning Collection	Serum
Creatinine	Serum
Direct Bilirubin	Serum

Glucose	Serum
Glucose, Random	Serum
Total Bilirubin	Serum
Creatinine	Urine

Note: all laboratory tests will be presented in SI units. The tests presented in this table will also be presented using conventional units.

Shifts from baseline to post-baseline values in abnormality status according to normal range criteria will be provided for applicable lab parameters.

6.6.3.3 Additional summaries

The following laboratory tests will be in addition summarized using geometric mean, geometric standard error and two-sided 90% geometric confidence intervals. Only the analysis value will be summarized, by Treatment Period and Treatment Group within the period and by Treatment Group in Total for each analysis visit.

Table 9 Laboratory tests summarized by geometric means

Laboratory Test Name
Urine Albumin Excretion Rate
Serum Aldosterone
Serum Aldosterone / Renin Ratio
Urine Aldosterone Excretion Rate
Plasma Renin Activity
24-h Urine Aldosterone to Creatinine Ratio
Urine Albumin to Creatinine Ratio (both spot urine and 24-h urine)
Urine Protein Excretion Rate
Urine Albumin
Urine Protein to Creatinine Ratio (both spot and 24-h urine)
Urine Protein

6.6.3.4 Outlier Analysis

The following outlier analysis will be created by Treatment Period and Treatment Group within the period and by Treatment Group in Total.

Table 10 Patients with one or more chemistry analyte values with elevated or low values meeting specified levels for the following parameters

Parameter	Categories
Sodium (low) mEq/L	Level 1 [redacted] Level 2 Level 3

Potassium (high) mEq/L	Level 1 [redacted] Level 2 [redacted]) Level 3 [redacted])

Table 11 Patients with one or more kidney function analyte values exceeding specified levels

Parameter	Categories
Creatinine, high (mg/dL)	Level 1 [redacted] x baseline) Level 2 [redacted] x baseline) Level 3 [redacted] x baseline)
eGFR 2021 (low) mL/min/1.73 m^2	Level 1 ([redacted] decrease) Level 2 ([redacted] decrease) Level 3 ([redacted] decrease)
eGFR 2012 (low) mL/min/1.73 m^2	Level 1 [redacted] decrease) Level 2 ([redacted] decrease) Level 3 (≥75% decrease)

6.6.3.5 Adjudication of outlier analysis

The Adjudication Committee will review the outlier laboratory data based on the locked and unblinded subjects who experienced at least 1 elevated potassium post-randomization, irrespective of period. The committee will review each subject and their associated event(s) assignment and provide documented rationale in the revised listing. Details of the adjudication procedure will be specified in the charter. The adjudicated listing will be used to create adjusted outlier tables using the same layout as in the previous section.

6.6.4 Vital Signs and Physical Examinations

Height from the screening visit, weight, BMI, waist and hip circumference and vital signs (temperature, pulse, and respiratory rate) and change from baseline values in applicable follow-up visits will be presented in data listings by subject.

Summaries of observed height, weight, BMI and vital signs of observed values and changes from baseline will be presented by Randomized Sequence and in total for each applicable follow-up visit.

A table will summarize physical examination results by Randomized Sequence and in total. The summary will include the number and percentage of participants with physical examination outcome (Normal, Abnormal [Not Clinically Significant, Clinically Significant])

In addition, the number and percentage of subjects who experienced a ≥20 bpm increase from baseline in pulse will be summarized. In these summaries, the first occurrence of the event per subject will be summarized. Investigator assessment of body system (Normal, Abnormal) performed during the complete physical examination will be listed but not summarized.

6.6.5 12-Lead Electrocardiogram (ECG)

ECG results (PR, RR, QRS, QT, QTcB, QTcF, and overall ECG evaluation [Normal, Abnormal not Clinically Significant, Abnormal Clinically Significant]) will be presented in data listings by subject and visits.

6.6.6 Prior and Concomitant Medications

Prior medications are defined as any medications taken and stopped prior to the start of the study drug (including prior to run-in period).

Concomitant medications are defined as any medication or vaccine (including over the counter medications, prescription medications, recreational drugs, vitamins, and/or herbal supplements) with a start date on or after the first study investigational drug administration (following randomization) or medications with a start date prior to first study investigational drug administration but ongoing or with stop dates on or after first study drug administration. Medications that stop during the run-in period will be considered prior medications. Medications with a start date after the last study drug administration will not be considered as concomitant medications; these post-treatment medications will be identified in the listing.

The number and percentage of subjects with concomitant medications will be summarized by WHO-DD Anatomical-Therapeutic-Chemical 2 (ATC2) classification and PT by treatment sequence group and treatment period and in total. The summary table will display counts and percentages of subjects who reported using at least 1 concomitant mediations in any of the treatment groups in each treatment period. Subjects may have more than 1 medication per ATC2 classification. At each level of subject summarization, a subject will only be counted once if he/she reports 1 or more medications.

A similar summary table will be created for rescue medication data. Rescue medications are defined as any new anti-hypertensive treatment that starts between the first administration of the double-blind study drug and either the last administration of the double-blind study drug or the AOBP assessment at week 12, whichever occurs later. Replacement of Antihypertensive therapy (AHT) medication in the prescribed AHT regime with equivalent medication from the same class will not be considered a rescue medication. Change in dose will not be considered a rescue medication. Time from baseline to initiation of rescue medication will be analyzed by treatment group using Kaplan-Meier methods. Subjects without rescue medication by Week 12/EoT will be censored on this date.

Only concomitant and rescue medication data will be summarized but a listing of all prior, concomitant, and post-treatment medication data will be provided.

6.6.6.1 Imputation of Missing Data for Concomitant Medications

Partial dates entered in the CM form will be imputed for the purposes of determining whether the record is a concomitant or prior medication based on the following:

- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month.
- Medications that are not ongoing and have a medication stop date with missing day and month will be assumed to occur on the last day of the non-missing year (i.e., December 31).
- Partial or missing CM start dates will be imputed as follows:
    - Missing day will be imputed as the first day of the month.
    - Missing month will be imputed as January.

7 CHANGES TO PLANNED ANALYSES

There were no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

8 REFERENCES

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9 APPENDICES

9.1 Schedule of Assessments

Study Period	Screening[1]	Run-in	Randomization[2]	Treatment Period 1 (4 weeks)		Wash Out (4 weeks)	Treatment Period 2 (4 weeks)		EoS[3]	Unscheduled Visit[4]
Weeks[5]	-4	-2	0	2	4	8	10	EOT 12	14	UNS
Study Visit#	1	2	3	4	5	6	7	8	9	
Informed Consent[6]	X									
Randomization			X							
Demographics	X									
Medical history	X									
Eligibility confirmed	X		X							
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical exam, body weight, height, waist and hip circumference[7]	X		X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
AOBP, seated and standing	X		X	X	X	X	X	X	X	X
12-lead ECG	X		X						X	X
Serum chemistry (including eGFR, excluding potassium) central lab	X		X	X	X	X	X	X	X	X
Cystatin-C (central lab)	X		X	X	X	X	X	X	X	X
Serum potassium (local lab)	X		X[8]	X	X	X	X	X	X	X
HbA_{1C} (central lab)	X				X			X	X	X
Hematology (central lab)			X		X			X	X	X
Urinalysis, spot urine (central lab)	X				X			X	X	X
Dispense kit for first morning urine void	X	X		X			X			X
Subject collects first morning urine void, midstream[9]	X		X		X			X		X
Dispense kit, for 24-hour urine[10]	X	X		X	X		X			X
Subject collects 24-hour urine[11]		X	X		X	X		X		X
Pregnancy test[12]	X		X			X		X	X	X
Adverse events[13]	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X[14]	X		X	X				X
In-clinic dosing			X	X	X	X	X	X		X
Study drug compliance			X	X	X	X	X	X	X	X
Biomarkers (central lab)[15]			X		X	X		X	X	X
Morning serum cortisol[16]	X			X	X		X	X		X
PK (sampling)[17]				X	X		X	X		
ACTH stimulation test[18]										X

1 Screening will be 2 weeks. However, if required, the screening window may be extended to 4 weeks without approval from the Medical Monitor.

2 Only subjects who continue to meet all eligibility criteria will be randomized.

3 Visit for subjects not participating in the open label extension study only. Study visit window is ± 5 days.

4 Assessments performed during an unscheduled visit will be done on an as needed basis.

5 Study visit windows (double blind period and run-in) are ± 3 days.

6 Written informed consent must be obtained prior to conducting any study procedures.

7 At the Screening Visit a physical examination will be performed and should include an evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Height will be measured at Screening only. At other visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be recorded either as medical history or AE accordingly.

8 Serum potassium must be collected 3 days prior to Randomization and values must be reviewed by the Investigator for Randomization eligibility.

9 During Screening, one first morning urine void to be brought in, in the first week after Screening to determine eligibility. An unscheduled visit during Screening period for subjects to return first morning void must take place a minimum of 7 days prior to the Run-in visit so that the result is available for eligibility review. The sample needs to be 200-5000 mg/g inclusive to meet eligibility criteria. Samples will be assessed for albumin, protein, and creatinine.

10 Subjects will be given a 24-hour urine collection kit to take home at preceding visits. An aliquot of urine will be retained for future biomarker assessments.

11 Subjects must start urine collection on Day-1 and return the collected 24-hour urine on Week 0 Randomization visit. 24-hour urine samples will be utilized for assessment of albumin, protein, creatinine, sodium, potassium, cortisol, and aldosterone. An aliquot of urine will be retained for future assessments.

12 Women of childbearing potential only. A sample for serum pregnancy test will be collected at Screening. Follicle stimulating hormone must be used to confirm postmenopausal status in all postmenopausal women at Screening. Urine pregnancy tests will be done at other visits. If urine pregnancy test is positive, a serum pregnancy test will be collected to confirm results at the local lab.

13 All AEs and SAEs will be collected from signing of informed consent form until the subject has completed the EoS visit or transitioned to the open label extension study. All AESIs will be collected upon initiation of treatment until the subject has completed the EoS visit or transitioned to the open label extension study.

14 Only for SGLT2i naïve patient or patient switching to sponsor provided SGLT2i.

15 An aliquot of serum will be retained for future biomarker assessments. A sample of whole blood will be collected at Randomization and retained for future proteomic and genomic assessments. A mid-stream urine sample will also be collected for future biomarker analyses. Blood and urine samples will be processed and stored as described in the laboratory manual.

16 Blood draw for cortisol assessment should occur as close to 8 AM as possible on the morning of the study visit.

17 Subjects should have a blood sample drawn just prior to dosing and another blood sample taken 1-2 hrs. post-dose.

18 ACTH (Cosyntropin) stimulation testing to be performed at unscheduled visits if clinically indicated by signs, including serum cortisol below 3 µg/dL, or below 10 µg/dL accompanied by symptoms of hypocortisolism.