Protocol #: MLS-101-201

A Randomized, Double-blind, Placebo-controlled, Doseranging, Multicenter Phase 2 Study to Evaluate the Safety, Efficacy, and Tolerability of MLS-101 in Subjects With Uncontrolled Hypertension

Statistical Analysis Plan

Version 2.0 FINAL

Protocol Number:	MLS-101-201
(Version Date)	Version 7.0, Amendment 6 (07 July 2022)
Name of Test Drug:	MLS-101
[redacted]	2
Methodology:	Randomized, Double-blind, Placebo-controlled, Doseranging, Multicenter study
Sponsor:	Mineralys Therapeutics, Inc. 150 N. Radnor Chester Rd. – Suite F200 Radnor, PA 19087
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Document Version:	Final 2.0

SIGNATURE PAGE

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[redacted]

Principal, Strategic Consulting

[redacted]

Sponsor 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.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:

[redacted]

Mineralys Therapeutics, Inc

[redacted]

MODIFICATION HISTORY

Current Version	Date	Amended by	Summary of Changes from previous version	Reason
2.0	04 October 2022	[redacted]	• Removed "Changes from Protocol" which have been incorporated into the protocol since v1 of the SAP. • Summary of protocol deviations added. • Compliance definition clarified. • Subgroup analyses removed for Part 2. • Clarification on the impact of QC status and addition of Mean Arterial Pressure to ABPM summaries. • Definition of Rescue Medication refined to be derived programmatically. • Handling rules for BLQ laboratory values added. • Definition of concomitant medication updated to exclude medications starting after last dose of study drug. • Visit windowing rules amended to refer to EOT visit rather than EOS visit, and to clarify that for the supplemental Estimand only, windowing for both visits applies. • Clarification of the identification of AESI • Removal of Jessica Ibbitson from the SAP signatories, as she has been unblinded since SAP v1.	• Harmonization to Protocol v7.0 (Amendment 6) • Clarifications noted during programming that should be reflected in the SAP documentation
1.0	07 July 2022	N/A	Original document	N/A

Table of Contents

ABBREVIATIONS

Abbreviation	Description
ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-converting enzyme (ACE) inhibitors
ACTH	Adrenocorticotropic hormone
AE	Adverse events
AESI	Adverse events of special interest
AHA	American heart association
AHT	Anti-Hypertensive Medication
ANP	Atrial Natriuretic Peptide
AOBP	Automated Office Blood Pressure
ARB	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration versus time curve
BID	Twice daily
BNP	Brain/B-type Natriuretic Peptide
BP	Blood pressure
CABG	Coronary Artery Bypass Graft
CI	Confidence interval
CKD	Chronic Kidney Disease
CM	Concomitant medication
Cmax	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture

Abbreviation	Description
EOP2	End of Phase 2
EOT	End of treatment
FDA	Food and Drug Administration
FU	Follow-up
hsCRP	High sensitivity C-reactive protein
ICE	Intercurrent Event
ICF	Informed consent form
ICH	International Council on Harmonization
IMP	Investigational medicinal product
IRB	Institutional review board
IWRS	Interactive web response system
LVH	Left ventricular hypertrophy
MedDRA	Medical Dictionary for Regulatory Activities
MLS-101	A selective aldosterone synthase inhibitor
MMRM	Mixed model repeated measures
ntBNP	N-terminal B-type pro Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	The time from the depolarization of the sinus node to the onset of ventricular depolarization
PT	Preferred Term
QD	Once daily
QRS	The series of deflections in an electrocardiogram that represent electrical activity generated by ventricular depolarization prior to contraction of the ventricles

Abbreviation	Description
QT	Time from the beginning of the QRS complex to the end of the t wave
QTc	QT interval corrected
QTcB	Corrected QT interval by Bazett
QTcF	Corrected QT interval by Fredericia
RR	The time elapsed between two successive R waves of the QRS signal on the electrocardiogram
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	Standard of care
t1/2	Half-life
TEAE	Treatment emergent adverse events
TIA	Transitory Ischemic Attack
TLF	Table Listing Figures
Tmax	Time to maximum plasma concentration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This Statistical Analysis Plan (SAP) is based on Protocol MLS-101-201 version 7.0, Amendment 6 dated 07 July 2022. Mineralys is currently developing MLS-101, a selective aldosterone synthase inhibitor, for the treatment of uncontrolled hypertension in the presence of autonomous aldosterone production.

The protocol for study MLS-101-201 describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such analyses. Table, Listing, and Figure (TLF) shells are provided in a separate, accompanying document. 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 planned in the study protocol. Any deviations from the analysis plan, including any after the time of treatment unblinding, will be documented as such in the study report.

1.2 Objectives

1.2.1 Primary Objective

The protocol lists the following primary objective:

- To characterize the effect of MLS-101 on BP at 5 dosing regimens versus placebo when administered orally for the treatment of uncontrolled hypertension as add-on therapy to stable background treatment

1.2.2 Secondary Objectives

The protocol lists the following secondary objectives:

- To investigate the safety and tolerability of MLS-101 at 5 dosing regimens versus placebo when administered orally for the treatment of uncontrolled hypertension as add-on therapy to stable background treatment
- To investigate the pharmacokinetic (PK) profile of MLS-101 at 5 dosing regimens when administered orally for the treatment of uncontrolled hypertension as add-on therapy to stable background treatment
- To investigate the pharmacodynamic (PD) parameters of MLS-101 at 5 dosing regimens when administered orally for the treatment of uncontrolled hypertension as add-on therapy to stable background treatment.

2 STUDY DESIGN

2.1 Introduction

This is a Phase 2 randomized, double-blind, placebo-controlled, dose-ranging, multicenter study designed to evaluate the effect of orally administered MLS-101 on BP for the treatment of uncontrolled hypertension (hypertensive despite receiving ≥ 2 antihypertensives) when used as add-on therapy to stable background treatment in male and female subjects ≥ 18 years of age.

The study consists of two parts. For enrollment into Part 1 of the study, a subject's value of PRA must be ≤ 1 ng/mL/h based on morning measurement. If the value of PRA > 1 ng/mL/h based on morning measurement, then subjects may be eligible to enter Part 2 of the study.

The initial estimate is that approximately 1100 subjects will undergo up to 2 weeks of pre-Screening for Part 1 and 4 weeks of pre-Screening for Part 2. It is estimated that approximately 270 subjects will have qualifying plasma renin activity (PRA) and serum aldosterone levels to be eligible to enter Screening/start of Placebo Run-in for Part 1 after completing a Screening/main study informed consent form (ICF) that has been approved by the Institutional Review Board (IRB). Assuming a 40% screen-failure rate during Run-in, a total of 160 subjects will meet all eligibility requirements to qualify for enrollment in the study.

For Part 2, it is estimated that approximately 60 subjects will have qualifying PRA and serum aldosterone levels to be eligible to enter Screening/start of Placebo Run-in for Part 2 after completing a Screening/main study ICF that has been approved by the IRB. Assuming an approximately 40% screen failure rate, a total of 36 subjects will meet all eligibility requirements to qualify for enrollment in Part 2 of the study.

In the previous version of the protocol, subjects in Part 1 of the study were randomized into 6 equal treatment groups (1:1:1:1:1:1) to 12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, 100 mg QD, or placebo. After a review of the clinical data at the December 2021 interim analysis, it was decided that the 2 lowest dose levels (12.5 mg QD and 12.5 mg BID) will be dropped due to a lack of consistent meaningful reduction of blood pressure. Effective with Amendment 4, subjects will be randomized into 4 equal treatment groups (1:1:1:1) to 25 mg BID, 50 mg QD, 100 mg QD, or placebo. All 6 treatment groups will be presented in this analysis plan.

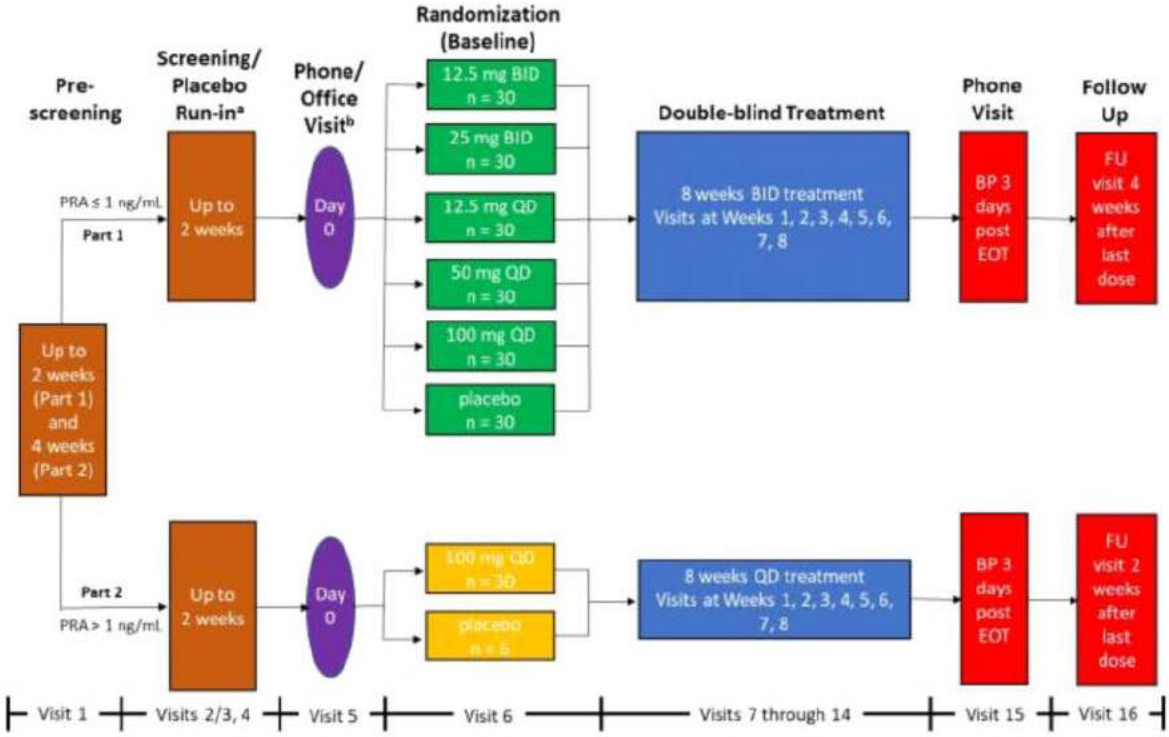
For Part 2, approximately 36 enrolled subjects ≥ 18 years of age will be randomized (6:1) to either 100 mg QD MLS-101 or placebo such that the MLS-101 treatment group will consist of approximately 30 subjects and the placebo treatment group will consist of approximately 6 subjects.

Subjects will orally administer the assigned study drug (MLS-101 or placebo) according to the assigned dosing regimen for 8 weeks beginning on Study Day 1. All subjects in Part 1 (regardless of dosing group) will receive BID dosing to preserve the integrity of the blind; active drug is

administered as the morning dose for all QD dose groups. Subjects will return to the research facility or be seen by the clinical investigator or approved home health care professional at the end of Study Weeks 1, 2, 3, 4, 5, 6, 7, and 8 (± 2 days) for protocol-defined efficacy and safety assessments and procedures, assessment of AEs, and confirmation of compliance with study drug usage. Subjects will also complete a telephone visit and BP check at home approximately 3 days post last dose of study drug. Subjects will attend up to 14 full clinic visits, including a pre-Screening visit, a Screening/start of Placebo Run-in visit, a second visit during Placebo Run-in, a clinic visit to initiate the ABPM procedure, a Randomization visit, 8 weekly visits during double-blind treatment, and an end-of-study visit scheduled 4 weeks after the last study treatment for final efficacy and safety assessments.

A schematic of the study design is shown in Figure 1. A detailed schedule of assessments is provided in Protocol Table 1.

Figure 1 MLS-101-201 Study Schema



ABPM = ambulatory blood pressure monitoring; BP = blood pressure; BID = twice daily; EOT = end of treatment; FU = follow up; PRA = plasma renin activity; QD = once daily

[a] If Screening results are available, inclusion/exclusion evaluation will be performed. If subject is not eligible based on Screening results, they will not continue to Visit 4. If Screening results are not available, subject proceeds to Visit 4. If Screening results are not available at Visit 4, subject should attend Visit 5 to determine final eligibility. If eligible based on Screening results, ABPM assessment can begin at Visit 5.

[b] The ABPM procedure will be initiated at home approximately 24 hours before Randomization (Study Day 1). Alternatively, sites may choose to schedule an office visit on Study Day 0 (Visit 5) to initiate the ABPM procedure. Training for the ABPM procedure can be done at an office visit or via phone.

2.2 Randomization Methodology

In Part 1, all subjects who complete the 2 week placebo run-in period and 24-hour ABPM procedure will be randomized into 6 equal treatment groups (1:1:1:1:1:1) to 12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, 100 mg QD, or placebo; each treatment group will consist of approximately 30 subjects stratified by BP (seated SBP ≤ 160 mm Hg and seated SBP > 160 mm Hg). Randomization numbers and study drug supplies will be assigned using interactive web response system (IWRS). Access to the randomization codes will be controlled and documented.

Following a review of the clinical data at the December 2021 interim analysis, it was decided that the 2 lowest dose levels (12.5 mg QD and 12.5 mg BID) will be dropped due to lack of consistent

meaningful reduction of blood pressure. Effective with Amendment 4, subjects will be randomized into 4 equal treatment groups (1:1:1:1) to 25 mg BID, 50 mg QD, 100 mg QD, or placebo.

In Part 2, subjects will be randomized (6:1) to either 100 mg QD MLS-101 or placebo such that the MLS-101 treatment group will consist of approximately 30 subjects and the placebo treatment group will consist of approximately 6 subjects.

2.2.1 Study Population

The study population consists of male or female subjects ≥ 18 years of age with hypertension on stable background treatment who meet all inclusion criteria and none of the exclusion criteria specified in protocol section 5.

2.3 Stopping Rules

N/A

2.4 Blinding

To support the Interim Analyses and DSMB, a team of statisticians and programmers at Cytel were unblinded. This team is separate from the main (blinded) study delivery team. The list of team members indicates blinded and unblinded status of each person, and Cytel's processes for the control of unblinded data are followed to maintain the integrity of the blind.

Some members of the Sponsor team were also unblinded to support decision making following the Interim Analyses, particularly at End of Part 1. A list of unblinded Sponsor personnel in maintained by the Sponsor. Anyone on this list is not involved in the finalization of the SAP or decisions relating to the analysis of the study, until after final database lock and unblinding of the full team.

2.5 Interim Analyses

2.5.1 Interim Analysis (December 2021)

One interim analysis is planned for this study. A Data Safety Monitoring Board (DSMB) will be setup to review the unblinded interim results. The DSMB will not include any members of the study team. Operations and constitution of the DSMB will be detailed in a separate charter. The interim analyses will focus on key efficacy and safety endpoints and will be carried out after the first 5 to 10 subjects in each dose group (30 to 60 subjects total) complete 4 weeks of treatment.

The following unblinded data displays will be produced for a closed discussion by the DSMB. TLF shells for the interim analysis will be reused for final analysis to the extent possible. Unless stated otherwise, these displays are summary tables that summarize data by treatment groups:

- Subject disposition
- Subject demographics and baseline characteristics
- Change in office-measured SBP and DBP from baseline by scheduled visits
- Summary of concomitant medications
- Overall summary of adverse events
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Adverse events of special interest by SOC and PT
- Change in serum potassium, creatinine and cortisol from baseline by scheduled visits
- Incidence of significant lab abnormalities
- Change in PD parameters from baseline by scheduled visits, to include, at a minimum: ntBNP, BNP, ANP, hsCRP, Leptin, and Adiponectin

At the time of the Interim Analysis, additional exploratory efficacy analyses using the primary efficacy endpoint (in-office SBP) will be conducted within each dose group. The results of these analyses will have limited, pre-specified distribution and will be used for internal decision making and development planning. The analyses will include the evaluation of:

- Change from baseline to Week 8 using a paired t-test within each dose group
- Point-estimate and 90% CI for the difference between each dose group and placebo for the change from baseline to Week 8
- Go/No-Go decision criteria for 80% posterior probability that the true mean change from baseline is >0 mm Hg.

Additional analyses may be performed for the evaluation of safety by the DSMB or for the preparation for the regulatory submissions and planning.

2.5.2 End of Part 1 (July 2022)

When the high renin cohort (PRA > 1 ng/mL/h) was introduced in Protocol v6.0 (Protocol Amendment 5), it increased enrolment and extended the timelines for final database lock. In order to maintain the End of Phase 2 (EOP2) timelines, it was decided to add an interim analysis when all subjects complete Part 1, focusing on the outputs necessary to support EOP2.

A separate team will receive the Part 1 results and prepare for EOP2; the main study team will remain blinded until the end of Part 2.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Endpoint

The primary endpoint is the change in office-measured (mean of last 2 of 5 unattended measurements using an automated oscillometric sphygmomanometer device after approximately 5 minutes of rest in the seated position) systolic blood pressure (SBP) from baseline to the end of Study Week 8.

3.1.2 Secondary Endpoints

The protocol describes as secondary endpoints the following:

- Change in 24-hour ambulatory blood pressure monitoring (ABPM) parameters (systolic and diastolic) from baseline to the end of treatment.
- Change in office-measured SBP from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, and 7.
- Change in office-measured diastolic blood pressure (DBP) from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, 7, and 8.
- Proportion of subjects who achieve office-measured BP of ≤ 130/80 mm Hg by the end of Study Week 8.

3.2 Pharmacodynamics Endpoints

The protocol describes as pharmacodynamics endpoints the following:

- Change in plasma 11-deoxycortisol and PRA from baseline to the end of Study Week 4 and to end of follow up (i.e. end of Study Week 12 for Part 1 and end of Study 10 for Part 2).
- Change in serum aldosterone, cortisol, and 11-deoxycorticosterone concentration from baseline to the end of Study Week 4 and to end of follow-up.

3.3 Pharmacokinetic Endpoints

The protocol describes as pharmacokinetics endpoints the following:

- PK parameters, including, if feasible, of area under the plasma concentration versus time curve (AUC), maximum plasma concentration (Cmax), time to maximum concentration (Tmax), and half-life (t1/2) will be summarized descriptively for Randomization (baseline) and Study Weeks 1, 4, and 8

3.4 Safety Endpoints

The protocol describes as safety endpoints the following:

- Incidence and severity of all spontaneously reported adverse events (AEs)
- Changes in vital signs (standing SBP, standing DBP, body temperature, heart rate, and respiratory rate)
- Changes in electrocardiogram parameters (including cardiac intervals: PR, QRS, QT, and corrected QT interval using Fridericia's formula)
- Changes in clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis)
- Change in office-measured SBP from Study Week 8 (end-of-treatment period to end of follow up (i.e. end of Study Week 12 for Part 1 and end of Study 10 for Part 2).

4 ANALYSIS SETS

4.1 Analysis Set Definitions

The following analysis sets are defined in this study:

4.1.1 All Randomized Set

The All-Randomized Set includes all randomized subjects. This analysis set will be used for summaries of subject study disposition, with subjects analyzed according to the randomized study treatment group.

4.1.2 Full Analysis Set (FAS)

The FAS includes all randomized subjects who have received at least 1 dose of randomized study treatment (MLS-101 or placebo). The FAS will be the primary set for efficacy analyses. In analyses performed on the FAS, unless otherwise specified, subjects will be analyzed according to the randomized study treatment group.

4.1.3 Per Protocol Set (PPS)

The Per Protocol Set includes all subjects in the FAS who have completed the Study Week 8 visit without any major protocol violations that could influence the validity of the data for the primary efficacy evaluations. In the analyses based on PPS, subjects will be analyzed according to the randomized study treatment group. All criteria to exclude subjects from the PPS will be made based on a blinded review of the data prior to the unblinding of the study.

A subject may be excluded from the Per Protocol Analysis Set if any of the following criteria are met:

- Not meeting Inclusion/Exclusion criteria
- Use of prohibited medications. Subjects using rescue medications will not be excluded from the PPS unless subjects have met other criteria excluding them from the PPS
- Not compliant with the study drug
- Out of window efficacy assessment at study Week 8 visit

Alternate criteria for exclusion from the Per Protocol Analysis Set may be applied to accommodate unforeseen events that occurred during the conduct of the study.

Analyses on Per Protocol Analysis Set will be of supportive purpose and limited to primary endpoint (i.e., "product Estimand").

4.1.4 Safety Analysis Set (SAF)

The Safety Analysis Set includes all enrolled subjects who received at least one dose of study treatment (MLS-101 or placebo). In analyses performed on the Safety Analysis Set, subjects will be analyzed according to their actual treatment received.

4.1.5 PK/PD Analysis Set (PKPD)

PK/PD Analysis Set includes all subjects in the SAF who have sufficient data available for the analysis of pharmacokinetic and pharmacodynamic measurements. In the analyses based on PKPD, subjects will be analyzed according to the actual treatment received.

4.2 Protocol Deviations

All protocol deviations are recorded in the Clinical Trial Management System, InfoLink2, and will be included in a data listing of deviations.

5 DATA HANDLING

5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded using MedDRA version 24.0. Concomitant medications will be coded using World Health Organization (WHO) Drug version September 2021.

5.2 Data Conventions

For any events on or after the first IMP administration, study day is calculated as:

event date – date of first administration of IMP + 1.

As such, the first dose date is study day 1. For any events before the first administration date, study day is calculated as:

event date – date of first administration of IMP.

5.3 Methods of Pooling Data

Unless otherwise noted, summaries will be provided on the data from Part 1 and Part 2 separately, with no pooling of dose groups for tabulations. Analyses will be performed within each part separately.

5.4 Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdraw from treatment will still be followed until End of Study, unless they withdraw from study also. Withdrawals will not be replaced.

5.5 Visit Windows

No analysis visit windowing will be performed for this study with the exception of early termination visits (specifically the End of Treatment visit, which is recorded on the eCRF as Week 8/EOT). Early termination assessments will be re-numbered to an analysis visit based on their windowed visits defined by actual study day (see table below).

For the supplemental Estimand (defined in Section 6.4.1.5) only, post-treatment visits will also be re-numbered based on their windowed visits defined by actual study day. Specially, this refers to the End of Study visit at Week 12 (Part 1) or Week 10 (Part 2). This is because the supplemental

Estimand uses all observed data, regardless of whether they are on treatment or not. As the supplemental Estimand is only defined for SBP, this is the only variable for which the EOS visit windowing needs to be applied.

The following analysis visit windows will apply to early termination visits:

Visit	Target Study Day	Analysis Window
Baseline	Day 1	≤ Day of first dose in Double-blind treatment period
Week 1 – Visit 7	Day 7 (± 2)	Day 2 – Day 10
Week 2 – Visit 8	Day 14 (± 2)	Day 11 – Day 17
Week 3 – Visit 9	Day 21 (± 2)	Day 18 – Day 24
Week 4 – Visit 10	Day 28 (± 2)	Day 25 – Day 31
Week 5 – Visit 11	Day 35 (± 2)	Day 32 – Day 38
Week 6 – Visit 12	Day 42 (± 2)	Day 39 – Day 45
Week 7 – Visit 13	Day 49 (± 2)	Day 46 – Day 52
Week 8 – Visit 14	Day 56 (± 2)	≥ Day 53
Week 9 – Visit 15	3 days post EOS	N/A
Week 12 – Visit 16	Day 84 (± 2)	N/A

If more than one assessment occurs within a single visit window, the analysis will take the nominal visit assessment if there is a nominal visit or the later assessment if there is no nominal visit assessment.

For by-visit summaries, endpoints will be analyzed according to the nominal visits (i.e. assigned visit). 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.

5.6 Visit Attendance and COVID-19 Impact Assessment

Due to the outbreak of COVID-19 pandemic, visit attendance and how the participation was impacted by COVID-19 will be summarized by treatment group and all subjects pooled together. The summary will contain the number of subjects who attended or missed each scheduled visit and if the visit was affected by the COVID-19 including the specific cause.

Early study discontinuation due to Covid-19 will be summarized in the disposition table as specified in section 6.3.1.

6 STATISTICAL METHODS

6.1 Sample Size Justification

[redacted]

6.2 General Statistical Methods

6.2.1 General Methods

Data are recorded on electronic case report forms (eCRFs). Central laboratory data, PK, at home BP data, and protocol deviation results will be provided via electronic data transfers.

As the primary intent of this study is to provide a preliminary assessment of the relative efficacy of the doses studied, the use of descriptive summary statistics and graphical methods rather than formal statistical tests of significance will be emphasized. Confidence intervals (90% 2-sided) will be used to guide these assessments.

6.2.1.1 Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in the following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject.

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections. Unless specified otherwise, different columns of a summary table will display the statistics for the different treatment groups. The placebo group statistics will be displayed to the left of the MLS-101 group statistics.

Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of nonmissing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized with the number of nonmissing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding analysis set, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

6.2.2 Definition of Baseline

Baseline is defined as the last available observed value of the parameter of interest prior to the first administration of the investigational medicinal product (IMP) for the double-blinded treatment period.

For AOBP measurements and any other clinical or laboratory variable for which there are replicate evaluations at the screening and baseline visits, baseline is defined as the mean of the last two non-missing values prior to first administration of the IMP for the double-blinded treatment period.

Change from baseline is calculated as: post-baseline result – baseline result.

Percentage change from baseline is calculated as: (change from baseline / baseline result) x 100%.

6.2.3 Adjustments for Covariates

Efficacy models with continuous variables based on SBP as the response variable (e.g. change from baseline in office-measured SBP, mean daytime SBP) will have the corresponding baseline value as a continuous covariate.

Similarly, models based on DBP will include the corresponding baseline DBP value as a continuous covariate.

6.2.4 Multiple Comparisons/Multiplicity

Given the preliminary nature of this study, no adjustment for multiplicity will be implemented.

6.2.5 Subgroups

Prespecified subgroup analyses will be conducted for the following subgroups defined at baseline:

- Sex (Male, Female)
- Age (<65, 65-79, 80+)
- Race (African-American vs Non)

- BMI (<25, 25-30, >30 kg/m^2)
- Seated SBP (low tertile, middle tertile, high tertile)
- PRA level at Randomization (1 – 5, > 5 ng/mL/h) [Part 2 only]
- Number of concomitant antihypertensive medications at baseline (2 vs 3 or more)
- Use of Thiazide diuretics (yes/no)
- Use of ACEi/ARB (yes/no)

6.2.6 Missing, Unused, and Spurious Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

Partial dates are allowed on the CRF for adverse events and concomitant medications. Only the day may be entered as unknown for the Adverse Event form while month and day may be entered as unknown for the Concomitant Medications (CM) form. Dates from these forms will be reported in listings as collected. Every effort will be made to query missing dates.

AEs will be flagged as on-treatment treatment emergent AEs (TEAEs) if the CRF question "Did this AE start prior to Randomization?" on the AE form is "No" regardless of whether or not the AE onset date is complete. AEs that cannot be definitively determined as occurring prior to study drug administration will be counted as TEAEs unless either the partial start date or a partial or complete end date indicates the AE as occurring prior to treatment. Partial dates entered in the AE form will be imputed for the purposes of determining whether the record is a treatment emergent adverse event or not based on the following:

- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the month and year of first dosing of study drug (including placebo run-in period), in which case the date will be imputed using the date of first dosing of study drug.
- AE onset dates with missing day and month will be assumed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the year of first dosing of the study drug (including placebo run-in period), in which case the date will be imputed using the date of the first dosing of study drug.
- Partial or missing AE resolution dates will not be imputed.

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 not be imputed.

6.3 Study Population

6.3.1 Subject Disposition

A summary of subjects in the Pre-Screened Analysis Set will display the numbers (and percentages of the population) of:

- Pre-Screened. All subjects who signed the pre-screening informed consent/assent.
- Pre-screen failures
- Reason for pre-screen failure
- Screened. All subjects who signed the main study informed consent/assent
- Main study screen failures.
- Reason for main study screen failure

The following categories will be tabulated in the disposition table among all Pre-Screened subjects as the starting population:

- Number pre-screened
  - Reason for pre-screen failure
- Number screened
  - Reason for screen failure
- Number entering Placebo Run-In
  - Number completing Placebo Run-In
  - Reason for not completing Placebo Run-In
- Randomized
- Analysis Sets
  - FAS
  - Safety Analysis Set
  - PPS
  - PK/PD Analysis Set
- Completed the study treatment. Categories: Yes, No.
- Reason for treatment discontinuation. Categories:
  - Adverse Event
  - Physician Decision
  - Pregnancy
  - Study Terminated by Sponsor
  - Subject Non-Compliance/Protocol Violation(s)
  - Withdrawal of Consent
  - Other
- Completed the study.
  - Categories: Yes, No.
  - Duration (weeks) in the study
- Reason for study discontinuation. Categories:

- Adverse Event
- Death
- Lost to Follow-Up
- Physician Decision
- Pregnancy
- Study Terminated by Sponsor
- Subject Non-Compliance / Protocol Violation(s)
- Withdrawal of Consent
- Other

- Was early discontinuation impacted by COVID-19? Categories: Yes, No.

Protocol deviations will be summarized by treatment group. An additional summary will present the protocol deviations leading to exclusion from PPS.

The disposition and population inclusion data mentioned above will be listed for all subjects. The reasons for being excluded from the PPS will also be provided in the listings.

6.3.2 Demographic and Baseline Characteristics

Subject characteristics defined below will be presented in summary tables and data listings for subjects in the FAS and PP Analysis Sets. No statistical comparisons will be performed.

Demography

- Age (years): Age at time of consent, calculated as the difference between birth year and the year of main study informed consent date.
- Age (categories): <65, 65-79, 80+
- Sex: Male, Female
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Multiple Races.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported.

Baseline Characteristics assessed at Randomization

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI Categories: <25, 25-30, >30 kg/m^2
- Seated AOBP SBP (mmHg)
- Seated AOBP SBP Category (≤ 160 mmHg, > 160 mmHg)
- Seated AOBP DBP (mmHg)
- Standing AOBP SBP and DBP (mmHg)
- For women, of childbearing potential, post-menopausal, Premenarchal, Sterilized)

Cardiovascular History

- Family history of hypertension (Yes, No)
- Obesity (Yes, No)
- Dyslipidemia (Yes, No)
- Diabetes mellitus (Yes [overall and by type], No)
- History of heart failure (Yes [overall and by NYHA classification], No)
- Number of hospitalizations in past year of cardiovascular reasons (*only for subjects who answered "Yes" to history of heart failure*)
- Previous history of carotid artery disease (Yes, No)
- Previous history of myocardial infarction (Yes, No)
- Previous history of Coronary Artery Bypass Graft (CABG) (Yes, No)
- Previous history of Percutaneous Coronary Intervention (PCI) (Yes, No)
- Previous history of atrial fibrillation (Yes [overall and by arterial fibrillation type], No)
- Previous history of stroke or Transitory Ischemic Attack (TIA) (Yes, No)
- Previous history of peripheral vascular disease (Yes, No)
- Previous history of any other arrythmias (Yes, No)
- Number of AHT meds
    - Categories: 2, 3 or more
    - Use of Thiazide Diuretics (Yes, No)
    - Use of ACEi/ARB (Yes, No)

Lifestyle

- 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)
- Sedentarism (Yes, No)
- Following 2016 NY Heart Association Guidelines (Yes, No)

6.3.3 Medical History

Medical history will be coded using MedDRA version 24.0 or higher. Medical Histories will be summarized for the FAS using system organ class (SOC) and preferred term (PT) with frequencies and proportions of subjects experience each.

6.3.4 Prior Medication

Prior medications will be coded using the World Health Organization Drug Dictionary version B3 Global March 2021.

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

6.3.5 Exposure and Compliance

Exposure and compliance to MLS-101 or placebo will be summarized using the following parameters based on the data collected in the EDC:

- Treatment Duration, calculated as the number of days subject received randomized study drug: the date of last dose minus the date of the first randomized dose + 1.
- Total # of Capsules Taken (during the 8-week treatment period), calculated as total # of capsules dispensed minus total # of capsules returned
- Percent compliance (during the 8-week treatment period), calculated as:

$$\frac{Total\ \#\ of\ capsules\ dispensed - Total\ \#\ of\ capsules\ returned}{Treatment\ Duration\ (days) * Planned\ \#\ capsules/day} \times 100$$

For Part 1, the planned number of capsules per day is 5/day. For Part 2, it is 1/day initially (dose: 100 mg QD). If a dose reduction occurs, 2 capsules/day will be taken (50 mg QD). If a second dose reduction occurs, then 1 capsule/day will be taken (25 mg QD).

If a bottle of capsules is not returned at any visit, such that the total number of capsules taken by that subject cannot be calculated, then the percent compliance for that subject will be set to missing.

The above parameters will be summarized for each treatment group and all active treatment groups pooled together.

The number and percentage of subjects with dose modification and the number and percentage of subjects with IMP withdrawal will be summarized for each visit by treatment group and pooled active treatment group.

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

6.4 Efficacy Evaluation

All efficacy analyses will be performed using the FAS.

6.4.1 Primary Efficacy Outcome Analysis

The primary efficacy endpoint is the change in office-measured (mean of last 2 of 5 unattended measurements using an automated oscillometric sphygmomanometer device after approximately 5

minutes of rest in the seated position) SBP from baseline to the end of Study Week 8. The AOBP mean measure recorded in the external data (denoted 'average') will be used for analysis.

6.4.1.1 Primary Estimand

The Primary Estimand is designed to answer the research question on the treatment effect of investigational therapy in addition to standard of care (SOC) vs. placebo in addition to SOC on the change in office blood pressure from baseline to Week 8.

This Estimand is constructed in line with ICH E9 (R1) addendum. The five components that define the Estimand of interest are:

- Treatment is 5 MLS-101 dose levels (12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, or 100mg QD) vs placebo, regardless of compliance.
- Population: Patients with uncontrolled hypertension (hypertensive despite receiving ≥ 2 antihypertensives) as defined by the inclusion/exclusion criteria in the protocol.
- Patient-level outcome / variable: Change in office-measured SBP from baseline to Week 8.
- Population-level summary: Mean (SD) change in office SBP from baseline to Week 8.
- Inter-current events:
  The following Intercurrent Events (ICE) have been identified which could prevent measurement of the primary outcome or change the interpretation of the measured primary outcome:
  1. Initiation of rescue medications
  2. Death before the completion of 8 weeks period (except #5)
  3. Patient withdrawal from treatment before the completion of 8 weeks period for treatment-related reason or worsening (defined as reason for treatment withdrawal being "Adverse Event" or "Physician Decision").
  4. Patient withdrawal from treatment before the completion of 8 weeks period for non-treatment related reason
  5. Death due to COVID-19 / Accidental death

Event 1 will be treated as treatment failure. The observed SBP that triggered rescue medication will be imputed.

Events 2 and 3 will be handled as treatment failure. The baseline value will be imputed.

Events 4 and 5 will be handled using a hypothetical strategy assuming that the clinical course for either treatment group follows their own group with the estimate of the endpoint value obtained using MMRM in the primary analysis.

6.4.1.2 Primary Efficacy Analysis

The primary efficacy endpoint is the Week 8 change from baseline in SBP. The primary efficacy analysis will be performed using a mixed model repeated measures (MMRM) approach with fixed effects of categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous covariate. In this model, the subject is considered as a random effect, where an unstructured variance/covariance matrix is assumed for describing the correlation of repeated measurements over time.

In case of non-convergence of the model estimates under the unstructured covariance, alternative covariance structures will be considered in the following order: Toeplitz, AR(1), CS.

A least-square estimate, along with the 90% CI, of the mean difference between each dose group and the placebo group will be provided for Week 8. P-values corresponding to the pairwise tests, not adjusted for multiplicity, of the difference between each dose group vs placebo will also be provided.

6.4.1.3 Primary Efficacy Analysis for Part 2

To evaluate the impact of PRA levels at baseline, change from baseline to Week 4 and Week 8 in office-measured SBP will be analyzed using an ANCOVA model with binary PRA (< 1 ng/mL/h versus ≥ 1 ng/mL/h) as a factor and baseline SBP as a covariate, in the subset of subjects randomized to receive 100 mg QD.

A least-square estimate for the mean difference between the PRA groups, along with the 90% CI and associated p-value, will be provided.

The observed value and change from baseline in office-measured SBP at each visit will be summarized using descriptive statistics for the following three treatment groups:

- Part 1 100 mg QD
- Part 2 100 mg QD
- Pooled Placebo from Parts 1 and 2.

6.4.1.4 Sensitivity analysis

To test the robustness of the primary efficacy analysis, the following sensitivity analyses will be performed in the FAS:

An analysis where missing endpoint data resulting from ICEs of type 4 and 5 will be handled assuming that the clinical course for either treatment group follows that of the placebo group. The jump-to-reference method (Carpenter et al., 2013) is used, with placebo as the reference group.

Missing data as a result of an ICE are imputed as the mean of the placebo group for that visit, regardless of the treatment group the subject was in.

6.4.1.5 Supplementary analyses

An additional Estimand will be considered for analyzing the primary efficacy endpoint, regardless of intercurrent events post-baseline, defined by the following attributes:

Attribute	Description
Treatment	5 MLS-101 dose levels (12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, or 100mg QD) vs placebo
Population	Subjects with uncontrolled hypertension (hypertensive despite receiving ≥ 2 antihypertensives) as defined by the inclusion/exclusion criteria in the protocol
Endpoint	Change in office-measured SBP from baseline at Study Week 8
Intercurrent events	The occurrence of intercurrent events is considered irrelevant in defining treatment effect; the values of the endpoint will be used regardless of whether subject experiences an intercurrent event. This corresponds to a *treatment policy strategy*.
Population-level summary	Mean change in SBP from baseline at Study Week 8

Under the alternative Estimand, the same analyses above will be repeated as for the primary efficacy analysis

The primary efficacy analysis will also be repeated on the per-protocol analysis set.

6.4.1.6 Subgroup Analyses for Primary Efficacy

The change in office-measured SBP from baseline at Study Week 8 in Part 1, along with corresponding 90% confidence intervals will be calculated by treatment group for each of the subgroups of the FAS defined in Section 6.2.5 for both the primary Estimand described in Section 6.4.1.1 and the supplemental Estimand described in Section 6.4.1.5. These results will be considered exploratory.

Subgroup analyses will not be performed for Part 2, due to the small sample sizes, though the primary efficacy endpoint in Part 2 will be summarized by subgroup.

6.4.2 Secondary Efficacy Outcome Analyses

All secondary efficacy endpoints analyses will be considered supportive and any inferential statistics will be considered descriptive in nature. No adjustment for multiplicity will be performed. Unless otherwise stated, all secondary efficacy endpoints analyses will be based on the FAS.

6.4.2.1 24-hour ABPM

The ABPM will be measured in the clinic at baseline and end of treatment (EOT). If, for any reason, the ABPM procedure is deemed a failure, it can be repeated, and therefore no imputation will be employed regardless of use of rescue medications. The last available post-baseline ABPM assessment will be considered as EOT.

Additionally, ABPM is also collected at the end of Study Week 4 in Part 2. If a repeat test is performed, it supersedes the original test results for Week 4. Tests denoted as Week 4 cannot be flagged as EOT, even if no later post-baseline assessment exists.

The ABPM measurements will be included regardless of the QC Status of individual readings or the derived variables. QC statuses of 'Failed' will be noted in the listings.

Specific derived variables based on ABPM measurements include mean 24-hour, mean Daytime, and mean Nighttime of SBP, DBP, and heart rate. Mean 24-hour Mean Arterial Pressure is derived as

$$(\text{mean 24-hour SBP} + \text{mean 24-hour DBP})/2$$

Each of these derived variables will be summarized by treatment group and visit using descriptive statistics.

Change from baseline to EOT in 24-hour mean SBP (and DBP) based on ABPM will be analyzed using an ANCOVA with a term for treatment group and a baseline mean 24-hour value as a covariate.

The nighttime dip is defined as

$$100\% \times (\text{mean daytime SBP} - \text{mean nighttime SBP})/\text{mean daytime SBP}$$

It is expressed as a percentage and will be summarized by treatment group and visit using descriptive statistics. In addition, the number and percentage of subjects with nighttime dip in each of the dipper categories (Bloomfield & Park, 2015) will be presented by treatment group and visit. The categories are:

- < 10%
- 10-20% inclusive
- > 20%

All ABPM variables will be listed.

6.4.2.2 Change from Baseline in SBP by Week

Change from Baseline in SBP at each visit will be analyzed as per the primary efficacy analysis described in Section 6.4.1.2.

In addition, this analysis will be repeated by subgroup, for each of the subgroups listed in Section 6.2.5.

6.4.2.3 Change from Baseline in DBP by Week

Change from Baseline in DBP at each visit will be analyzed as per the primary efficacy analysis described in Section 6.4.1.2, with the exception that baseline DBP will replace baseline SBP as a fixed covariate in the model.

In addition, this analysis will be repeated by subgroup, for each of the subgroups listed in Section 6.2.5.

6.4.2.4 Proportion with BP <130/80 mmHg

Each subject will be assessed as a success if the Week 8 value for SBP is ≤ 130 mm Hg *and* DBP ≤ 80 mm Hg; a subject will be assessed as a failure otherwise. The number and proportion of subjects will be provided by treatment group.

Number and proportion of subjects who achieve only the SBP or BDP goal (but not both) will be provided as well. Subjects missing an assessment at Week 8 or who have received rescue medications will also be considered as failures.

Relationship between success (as defined above) and SBP levels at baseline (mm Hg) will be evaluated graphically using by-treatment scattered boxplots of baseline SBP with success/failure marked for each subject.

6.4.2.5 Time to first occurrence of BP <130/80 mmHg

The time to first in-office-measured BP of ≤130/80 mmHg up to Week 8/EOT will be analyzed using the Kaplan-Meier method. For subjects who achieve a BP of ≤ 130/80 mmHg, time to first BP of ≤ 130/80 mmHg will be calculated as: date of first in office-measured BP of ≤ 130/80 mmHg minus date of first dose of randomized study drug plus 1.

Subjects who fail to achieve a BP of ≤ 130/80 mmHg prior to Week 8/EOT will be censored at the Week 8/EOT and will be calculated as: Week 8/EOT – date of first dose of randomized study drug + 1.

Subjects who are lost to follow-up prior to Week 8/EOT will be censored at the date of the last known BP assessment and will be calculated as: date of last known BP assessment – date of first dose of randomized study drug + 1.

Subjects who took rescue medications will be censored on the date he/she initiated the rescue medication.

A cumulative incidence plot for time from first dose of randomized study drug to BP ≤ 130/80 will also be provided, with each treatment group represented by a different line.

6.4.3 Other Efficacy-related Summaries

The following are additional efficacy analyses to be performed.

Select summaries and tabulations of efficacy endpoints, including subgroup analyses, will be also presented using boxplots with raw data points indicated on the plots.

6.4.3.1 Change in SBP from End of Treatment to End of Study

Analysis of change in office-measured SBP from End of Treatment (Study Week 8 or last measurement prior to starting the rescue medication) to End of Study (Study Week 12 for Part 1 and Study Week 10 for Part 2) will be analyzed using an ANCOVA model with treatment group as a factor and SBP at EOT as a covariate.

A least-square estimate, along with the 90% CI, of the mean difference between each dose group and the placebo group will be provided for each time point. P-values corresponding to the pairwise tests, not adjusted for multiplicity, of the difference between each dose group vs placebo will also be provided.

6.4.3.2 Comparison between 100mg QD and 25mg BID in Change from Baseline to Week 8 in SBP

Subjects randomized to 100mg QD in Part 1 and 2 and 25 BID dose in Part 1 will be included in this analysis.

The two dose levels, 100mg QD and 25mg BID will be tested for the equality of distributions using Kolmogorov-Smirnov test. If the distributions of responses are considered comparable across dose

and PRA levels at baseline, the dose groups will be pooled. This dataset will be used to repeat efficacy analyses, including the primary and select subset analyses.

6.4.3.3 Correlation between SBP and Aldosterone

The correlation between SBP and aldosterone and will be explored by plotting change in office-measured SBP from baseline to Week 4 against 24hr urinalysis aldosterone levels at baseline for subjects randomized to 100 mg QD in Part 2 (the 'high-renin' cohort). Subjects will be grouped by race (African-American vs Non), with both race groups presented on the same plot.

The plot will be repeated for change in office-measured SBP from baseline to Week 4 against change in 24hr urinalysis aldosterone levels from baseline to Week 4, by race, for the same subjects.

6.5 Pharmacodynamics Evaluations

PD parameters (plasma 11-deoxycortisol, PRA, serum aldosterone, cortisol, and 11-deoxycorticosterone concentration) will be summarized descriptively in summary tables using observed values and change from baseline by treatment groups and scheduled visits. PD analyses will be performed using the PK/PD Analysis Set. A listing specifying PD samples not included in the summaries and reasons for exclusion will be provided.

6.6 Pharmacokinetic Evaluations

The analyses for the pharmacokinetic data will be described in a separate analysis plan.

6.7 Safety Evaluations

Safety analyses will use data from the Safety Analysis Set.

6.7.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs that occur at any point after the initiation of study drug (including placebo run-in period), or medical conditions present prior to the start of treatment but increase in severity or frequency following the initiation of the study drug up until 14 days following last dose of study drug.

On-treatment TEAEs during the double-blind treatment period will be further identified as those occurring or worsening after the initiation of randomized study drug.

AE marked as "Possibly Related" or "Definitely Related" will be summarized as being related to the study drug; otherwise, the AE will be considered unrelated to the study drug. If the relationship to

the study drug is missing, the event will be assigned as related to study drug. Missing severity will be summarized as separate category.

An overall AE summary will be presented by the number and percent of subjects in each treatment group and pooled active treatment group with the following:

- All AEs
- All TEAEs
- On-treatment TEAEs (during double-blind period)
- On-treatment Treatment-related TEAEs
- On-treatment TEAEs by worst severity (mild/moderate/severe)
- Serious TEAEs
- On-treatment Treatment-related serious TEAEs
- On-treatment Adverse Event of Special Interest (AESIs)
- On-treatment TEAE Leading to Withdrawal from Study Drug
- On-treatment TEAE Leading to Dose modification
- TEAEs leading to death

The following AE summaries will be produced by SOC and PT with the number and percent of subjects with the following:

- On-treatment TEAEs
- On-treatment TEAEs by severity
- On-treatment Treatment-related TEAEs
- Serious TEAEs
- On-treatment TEAEs leading to permanent withdrawal of study drug
- Fatal TEAEs
- On-treatment AESIs

The tables will display the counts and percentages of subjects who reported at least one AE in each SOC by treatment groups and pooled active treatment groups. Within each SOC, the tables will display the counts and percentages of subjects reporting at least one AE as designated by the PT. The outputs will be presented by descending frequency across all subjects for a given SOC and PT. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity and relationship to the study drug will be summarized in a similar manner. For example, if a subject reports multiple AEs of the same type, the subject will be represented in the most severe category or maximum relationship to the study drug.

The following AE listings will be prepared:

- All AEs
- On-treatment Treatment-related TEAEs
- Serious TEAEs
- On-treatment AESIs

- On-treatment TEAEs leading to permanent withdrawal of study drug
- On-treatment TEAEs leading to death
- All AEs reported during the run-in period

6.7.1.1 Adverse Events of Special Interest (AESI)

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

- Hyperkalemia with dose modification (dose reduction, dose hold, or permanent dose withdrawal),
- Hypotension with symptoms (eg, light-headedness, dizziness, presyncope, or syncope),
- Adrenal Insufficiency.

If AESI are reported in the eCRF these will be prioritized and used for all analyses. Otherwise, the above definition of AESI will be used.

6.7.2 Laboratory Data

Laboratory test results (including hematology, serum chemistry, coagulation, urinalysis, cortisol, and ACTH) and abnormal laboratory values will be presented in data listings. Summaries of observed values and changes from baseline will be presented by treatment group for each post-baseline visit.

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

In addition, spot urine results will be summarized similarly to the laboratory test results.

ACTH simulation test/24-hour urine results (K+, Na+, creatinine, aldosterone) and pregnancy test results will be listed but not summarized.

Laboratory values quantified as below the quantitative limit (noted as < X.XX units) will be imputed as the half of limit (i.e., X.XX/2) in the quantitative analyses.

6.7.2.1 Analysis of Select Laboratory Values of Interest

The following laboratory test results will be further examined as follows:

- A shift table summarizing serum potassium level, with categories defined as:
  - ≤ 5.2 mmol/L,
  - > 5.2 and ≤ 5.5 mmol /L,
  - > 5.5 and ≤ 6 mmol /L,
  - > 6 mmol /L,
  - missing.

- Plot of mean change (with SEM) from baseline in serum potassium by study visit
- Boxplot of mean change (with SEM) from baseline in serum potassium at Week 8
- Plot of mean change (with SEM) from baseline in serum creatinine by study visit
- Plot of mean change (with SEM) from baseline in serum sodium and urine sodium by study visit
- Plot of mean change (with SEM) from baseline in urine sodium/potassium ratio by study visit
- Listing of individual changes in urine protein in subjects with urine protein detected prior to initiation of study treatment.
- Descriptive statistics on ntBNP, performed on samples for further analysis taken at Weeks 1, 4, 8.

6.7.3 Vital Signs and Physical Examinations

Height from the screening visit, weight, BMI, and vital sign results (temperature, pulse, and respiratory rate) and change from baseline values will be presented in data listings by subject.

Height, weight, BMI and vital sign summaries of observed values and changes from baseline will be presented by treatment group and each applicable visit/at scheduled timepoint.

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.

6.7.4 12-Lead Electrocardiogram (ECG)

ECG parameters (PR, RR, QRS, QT, QTcB, and QTcF intervals) will be summarized descriptively in summary tables using observed values and change from baseline by treatment groups and scheduled visits. In addition, shift from baseline of investigator's overall ECG evaluation (i.e., normal, abnormal not clinically significant, abnormal clinically significant) at the Study Week 8 visit will be summarized using counts and percentages of subjects.

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.

6.7.5 Standing BP

Standing BP will be measured at Screening, Randomization, Study Week 1, Study Week 8 with the AOBP device. In addition, standing BP will be measured if a subject reports symptom of hypotension and will be assessed weekly until symptoms resolve.

Standing BP will be summarized descriptively in summary tables using observed values and change from baseline by treatment groups and scheduled visits. In addition, the number and percentage of subjects who experienced a decrease in SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg from sitting to standing position within 3 minutes of standing will be summarized.

A listing of all standing BP data will be provided.

6.7.6 Concomitant Medications

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

Concomitant medications are defined as any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) with a start date on or after the first study drug administration (following randomization) or medications with a start date prior to first study drug administration but ongoing or with stop dates on or after first study drug administration. Medications that stop during the placebo run-in period will be considered prior medications. Medications with a start date after 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 4 (ATC4) classification and PT by treatment group and the combined active treatment groups pooled together. The summary table will display counts and percentages of subjects who reported using at least 1 concomitant mediations in any of the treatment groups. Subjects may have more than 1 medication per ATC4 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 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 8, whichever occurs later. Time from baseline to initiation of rescue medication will be analyzed by treatment group using Kaplan-Meier methods. Subjects without rescue medication by Week 8/EOT will be censored at this date. A cumulative incidence plot of the proportion of subjects initiating rescue medication at each Study Visit will also be presented by treatment group.

Only concomitant and rescue medication data will be summarized but a listing of all prior, concomitant, and post-treatment medication data will be provided. This listing will also include an indicator column specifying whether the medication is an AHT or thiazide diuretic.

7 CHANGES TO PLANNED ANALYSES

The following are changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

- **No pooling of data from Parts 1 and 2 for main analyses (some exploratory analyses will pool)**

In order to present the final results for the Part 1 data at the time of the Part 1 IA, no pooling of treatment groups or models with the Part 2 data will be done.

- **Timing of ABPM analysis**

ABPM was collected at Week 8 until Protocol v4 (Amendment 3) and then changed to Week 7 in Protocol v5 (Amendment 4), 10 Jan 2022. Though the current protocol (v6) states that ABPM is collected at Week 7, the data collected is a mix of both Week 8 and Week 7. As such, the wording of the ABPM endpoints has been changed in this SAP to reflect that it is the "end of treatment" value that is to be presented. The Study Week that corresponds to the EOT for ABPM will vary depending on which protocol the subject was enrolled under.

8 REFERENCES

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9 APPENDICES

9.1 Schedule of Assessments

Table 1: Schedule of Assessments for Part 1

Study Periods	Pre-Screen	Screening/Start of Placebo Run-in Week 1	Single-blind Placebo Run-in Week 2	Phone or Office Visit	Random-ization[a]	Double-blind Treatment								Phone Visit	Follow Up
Study Visit (V)	V1	V2/V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Study Week	-4 to -2	-2	-1	0	0	1	2	3	4	5	6	7	8	9	12
Study Day	-28 to -14	-14±2	-7±2	0	1	7±2	14±2	21±2	28±2	35±2	42±2	49±2	56±2	59+2	84±3
Test/Procedure															
Informed Consent[b]	X	X													
Inclusion/Exclusion Assessment		X	X[c]	X[d]	X										
Medical History	X	X													
Physical Examination		X			X								X		
Vital Signs[e]	X	X	X		X	X	X	X	X	X	X	X	X		X
AOBP[f]	X	X	X		X	X	X	X	X	X	X	X	X		X
Home BP check[g]														X	
Standing BP[h]		X			X	X							X		
24-hour ABPM[i]				X								X			
12-lead ECG[j]		X			X								X		
Pregnancy Test[k]		X			X				X				X		
PD Sample Collection[l]	X[m]	X			X				X						X
Safety Labs (hematology, chemistry, coags, cortisol, ACTH)[n]		X			X	X	X	X	X	X	X	X	X		X
Safety Labs (ACTH stimulation test)[o]		X											X		
Safety Labs (urinalysis)[p]		X			X	X	X	X	X	X	X	X	X		X
Spot Urine Collection[q]					X								X		
PK Sample Collection[r]					X	X			X				X		
Adverse Events[s]		X	X		X	X	X	X	X	X	X	X	X		X
Concomitant Medications		X	X		X	X	X	X	X	X	X	X	X		X
Study Drug Compliance		X	X		X	X	X	X	X	X	X	X	X		
IP Administration[t]		X[u]	X[u]		X	X	X	X	X	X	X	X	X		

ABPM = ambulatory blood pressure monitoring; ACTH = adrenocorticotropic hormone; AOBP = automated office blood pressure; BID = twice daily; BP = blood pressure; coags = coagulation tests; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; ICF = informed consent form; IP = investigational product; PD = pharmacodynamic; PK = pharmacokinetic; PRA = plasma renin activity

a Subjects who continue to meet all eligibility requirements will be randomized to receive MLS-101 or placebo.
b A pre-Screening ICF must be signed before entering pre-Screening period. A Screening/main study ICF must be signed before entering Screening period.
c If Screening results are available, inclusion/exclusion evaluation will be performed. If subject is not eligible based on Screening results, they will not continue to Visit 4. If Screening results are not available, subject proceeds to Visit 4.
d If Screening results are not available at Visit 4, subject should attend Visit 5 to determine final eligibility. If eligible based on Screening results, ABPM assessment can begin at Visit 5.
e Body temperature, heart rate, and respiratory rate will be measured.
f AOBP measurement is defined as the average of the last 2 of 5 unattended measurements using an automated oscillometric sphygmomanometer device after approximately 5 minutes of rest in the seated position.
g Blood pressure measurement to be performed at home.
h In addition to sitting measurements, standing BP will be measured at Screening/start of Placebo Run-in, Randomization, Study Week 1, and Study Week 8 with the AOBP device according to the procedure described in Appendix 12.5. In addition, standing blood pressure measurements will be measured if a subject reports symptoms of hypotension (eg, light-headedness, dizziness, presyncope, or syncope); the standing BP measurement will be assessed weekly for these subjects until symptoms resolve.
i Subjects will be given the ABPM device on the second visit of the placebo-run in period (Visit 4; Study Day -7 ± 2). The ABPM procedure will be initiated at home approximately 24 hours before Randomization (Study Day 1) and again in the clinic at the end of Study Week 7 (ie, Visit 13; Study Day 49 ± 2). Alternatively, sites may choose to schedule an abbreviated office visit on Study Day 0 (Visit 5) to initiate the ABPM procedure. At the end of Study Week 7, the ABPM procedure can be initiated at home in extraordinary circumstances, such as site closure due to COVID-19, subject exposure to COVID-19, or subject testing positive for COVID-19. Training for the ABPM procedure can be done at an office visit or via phone. If, for any reason, the ABPM procedure is deemed a failure at the end of Study Week 7, it can be repeated at the end of Study Week 8.
j ECG changes consistent with hyperkalemia will require confirmation of potassium levels at a local laboratory.
k Women of childbearing potential only. A sample for serum pregnancy test will be collected at Screening/start of the single-blind, Placebo Run-in, ie, Study Day -14 ± 2, and a sample for urine pregnancy test will be collected on Study Day 1, Study Day 28 ± 2 (Study Week 4), and at the end-of-treatment visit, Study Day 56 ± 2. Follicle stimulating hormone must be used to confirm postmenopausal status in all postmenopausal women at Screening/start of Placebo Run-in.
l Blood samples for aldosterone, cortisol, 11-deoxycorticosterone, 11-deoxycortisol, and PRA will be collected. Cortisol assessment should occur before 10 am on the morning of the study visit.
m Pre-Screening labs include blood samples for aldosterone and PRA **only** and should be collected in the morning after at least 8 hours of fasting.
n Blood samples for hematology, chemistry, and coags will be collected, including hemoglobin A1c concentration, cortisol, and ACTH (see Table 6). Cortisol assessment should occur before 10 am on the morning of the study visit.
o ACTH stimulation test should be performed as described in Appendix 12.7 at Screening/start of Placebo Run-in, Study Week 8, and whenever low cortisol levels are noted as per Section 6.5.3. ACTH stimulation test may be waived with sponsor's approval.
p Urine will be collected for urinalysis (see Table 6).
q Subjects will be given a urine collection kit on the second visit of the placebo-run in period (Visit 4; Study Day -7 ± 2). First morning urine will be collected prior to morning dose of study drug on Study Day 1 and again at the end of Study Week 8 (ie, Study Day 56 ± 2 or end-of-treatment period) for determination of potassium, sodium, and creatinine levels.
r Single blood samples for determination of MLS-101 will be collected at baseline (predose) and at Study Weeks 1, 4, and 8 (trough levels). Additional blood samples for long-term storage for metabolites, drug-drug interaction profiles of background therapy, or other exploratory analyses will also be collected at baseline (predose) and at Study Weeks 1, 4, and 8. In addition, blood samples for determination of MLS-101 (and metabolites) will be collected predose, and 1, 2, 3, and 4 hours postdose on Study Days 1 (Randomization) and 28 (Study Week 4).
s Adverse events and serious adverse events will be collected from the signing of the Screening/main study ICF to 30 days post last dose of study drug.
t On site visit days, subjects should be instructed to take their morning dose of study drug at the site.
u Single-blind, 2-week run-in period of BID oral treatment with placebo.

Table 2: Schedule of Assessments for Part 2

Study Periods	Pre-Screen	Screening/Start of Placebo Run-in Week 1	Single-blind Placebo Run-in Week 2	Phone or Office Visit	Randomization[a]	Double-blind Treatment								Phone Visit	Follow Up
Study Visit (V)	V1	V2/V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Study Week	-6 to -2	-2	-1	0	0	1	2	3	4	5	6	7	8	9	10
Study Day	-42 to -14	-14±2	-7±2	0	1	7±2	14±2	21±2	28±2	35±2	42±2	49±2	56±2	59+2	70±3
Test/Procedure															
Informed Consent[b]	X	X													
Inclusion/Exclusion Assessment		X	X[c]	X[d]	X										
Medical History	X	X													
Physical Examination		X			X								X		
Vital Signs[e]	X	X	X		X	X	X	X	X	X	X	X	X		X
AOBP[f]	X	X	X		X	X	X	X	X	X	X	X	X		X
Home BP check[g]														X	
Standing BP[h]		X			X	X							X		
24-hour ABPM[i]				X					X			X			
12-lead ECG[j]		X			X								X		
Pregnancy Test[k]		X			X				X				X		
PD Sample Collection[l]	X[m]	X			X				X						X
Safety Labs (hematology, chemistry, coags, cortisol, ACTH)[n]		X			X	X	X	X	X	X	X	X	X		X
Safety Labs (ACTH stimulation test)[o]		X											X		
Safety Labs (urinalysis)[p]		X			X	X	X	X	X	X	X	X	X		X
24-Hour Urine Collection[q]					X				X						
PK Sample Collection[r]					X	X			X				X		
Adverse Events[s]		X	X		X	X	X	X	X	X	X	X	X		X
Concomitant Medications		X	X		X	X	X	X	X	X	X	X	X		X
Study Drug Compliance		X	X		X	X	X	X	X	X	X	X	X		
IP Administration[t]		X[u]	X[u]		X	X	X	X	X	X	X	X	X		

ABPM = ambulatory blood pressure monitoring; ACTH = adrenocorticotropic hormone; AOBP = automated office blood pressure; BP = blood pressure; coags = coagulation tests; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; ICF = informed consent form; IP = investigational product; PD = pharmacodynamic; PK = pharmacokinetic; PRA = plasma renin activity; QD = once daily

a Subjects who continue to meet all eligibility requirements will be randomized to receive MLS-101 or placebo.
b A pre-Screening ICF must be signed before entering pre-Screening period. A Screening/main study ICF must be signed before entering Screening period.
c If Screening results are available, inclusion/exclusion evaluation will be performed. If subject is not eligible based on Screening results, they will not continue to Visit 4. If Screening results are not available, subject proceeds to Visit 4.
d If Screening results are not available at Visit 4, subject should attend Visit 5 to determine final eligibility. If eligible based on Screening results, ABPM assessment can begin at Visit 5.
e Body temperature, heart rate, and respiratory rate will be measured.
f AOBP measurement is defined as the average of the last 2 of 5 unattended measurements using an automated oscillometric sphygmomanometer device after approximately 5 minutes of rest in the seated position.
g Blood pressure measurement to be performed at home.
h In addition to sitting measurements, standing BP will be measured at Screening/start of Placebo Run-in, Randomization, Study Week 1, and Study Week 8 with the AOBP device according to the procedure described in Appendix 12.5. In addition, standing blood pressure measurements will be measured if a subject reports symptoms of hypotension (eg, light-headedness, dizziness, presyncope, or syncope); the standing BP measurement will be assessed weekly for these subjects until symptoms resolve.
i Subjects will be given the ABPM device on the second visit of the placebo-run in period (Visit 4; Study Day -7 ± 2). The ABPM procedure will be initiated at home approximately 24 hours before Randomization (Study Day 1) and again in the clinic at the end of at the end of Study Week 4 (ie, Study Day 28 ± 2) and Study Week 7 (ie, Visit 13; Study Day 49 ± 2). Alternatively, sites may choose to schedule an abbreviated office visit on Study Day 0 (Visit 5) to initiate the ABPM procedure. At the end of Study Week 7, the ABPM procedure can be initiated at home in extraordinary circumstances, such as site closure due to COVID-19, subject exposure to COVID-19, or subject testing positive for COVID-19. Training for the ABPM procedure can be done at an office visit or via phone. If, for any reason, the ABPM procedure is deemed a failure at the end of Study Week 7, it can be repeated at the end of Study Week 8.
j ECG changes consistent with hyperkalemia will require confirmation of potassium levels at a local laboratory.
k Women of childbearing potential only. A sample for serum pregnancy test will be collected at Screening/start of the single-blind, Placebo Run-in, ie, Study Day -14 ± 2, and a sample for urine pregnancy test will be collected on Study Day 1, Study Day 28 ± 2 (Study Week 4), and at the end-of-treatment visit, Study Day 56 ± 2. Follicle stimulating hormone must be used to confirm postmenopausal status in all postmenopausal women at Screening/start of Placebo Run-in.
l Blood samples for aldosterone, cortisol, 11-deoxycorticosterone, 11-deoxycortisol, and PRA will be collected. Cortisol assessment should occur before 10 am on the morning of the study visit. Subjects should be in a fasted state unless there is a medical reason not to fast as determined by the investigator.
m Pre-Screening labs include blood samples for aldosterone and PRA **only** and should be collected in the morning after at least 8 hours of fasting.
n Blood samples for hematology, chemistry, and coags will be collected, including hemoglobin A1c concentration, cortisol, and ACTH (see Table 6). Cortisol assessment should occur before 10 am on the morning of the study visit. Subjects should be in a fasted state unless there is a medical reason not to fast as determined by the investigator.
o ACTH stimulation test should be performed as described in Appendix 12.7 at Screening/start of Placebo Run-in, Study Week 8, and whenever low cortisol levels are noted as per Section 6.5.3. ACTH stimulation test may be waived with sponsor's approval.
p Urine will be collected for urinalysis (see Table 6).
q Subjects will be given a 24-hour urine collection kit on the second visit of the placebo-run in period (Visit 4; Study Day -7 ± 2). First morning urine will be collected prior to morning dose of study drug on Study Day 1 and urine collection continued for 24 hours for determination of potassium, sodium, creatinine, and aldosterone levels. A second 24-hour urine collection will occur at the end of Study Week 4 (ie, Study Day 28 ± 2).
r Single blood samples for determination of MLS-101 will be collected at baseline (predose) and at Study Weeks 1, 4, and 8 (trough levels). Additional blood samples for long-term storage for metabolites, drug-drug interaction profiles of background therapy, or other exploratory analyses will also be collected at baseline (predose) and at Study Weeks 1, 4, and 8. In addition, blood samples for determination of MLS-101 (and metabolites) will be collected predose, and 1, 2, 3, and 4 hours postdose on Study Days 1 (Randomization) and 28 (Study Week 4). Subjects should be in a fasted state unless there is a medical reason not to fast as determined by the investigator.
s Adverse events and serious adverse events will be collected from the signing of the Screening/main study ICF to 15 days post last dose of study drug.
t Subjects should administer study drug QD in the morning. On site visit days, subjects should be instructed to take their dose of study drug at the site.
u Single-blind, 2-week run-in period of QD oral treatment with placebo.

9.2 Estimands

Estimand	Estimator	Treatment	Population	Variable	Strategy for Handling ICEs	Summary Measure	Method of Estimation
Primary Estimand	Main estimator	Comparison between Placebo and 5 MLS-101 dose levels (12.5 mg BID, 25 mg BID, 12.5 mg QD, 50 mg QD, or 100mg QD), regardless of adherence	Patients with uncontrolled hypertension (hypertensive despite receiving ≥ 2 antihypertensives) as defined by the inclusion/exclusion criteria in the protocol. Full Analysis Set	Change in office-measured SBP (AOBP as recorded in EDC) from baseline to the end of Study Week 8.	Rescue medication use: treatment failure; value prior to rescue carried forward to subsequent visits Death (non-Covid/non-accidental) or Treatment discontinuation for treatment-related reason (i.e. lack of efficacy, toxicity): treatment failure; baseline value carried forward to subsequent visits Accidental or covid-related Death, or Treatment discontinuation not related to treatment: hypothetical strategy imputed based on MMRM for each treatment group	Difference between each active dose and placebo in mean change from baseline to Week 8 in office-measured SBP	The primary efficacy analysis will be performed using a mixed model repeated measures (MMRM) approach with fixed effects of categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous covariate. In this model, the subject is considered as a random effect, where an unstructured variance/covariance matrix is assumed for describing the correlation of repeated measurements over time. In case of non-convergence of the model estimates, alternative covariance structures will be considered (in the following order: Toeplitz, AR(1), CS). The first covariance structure that converges will be deemed the main estimator. Missing data for non-treatment related reasons (e.g. accidental or covid-related Death, or Treatment discontinuation not related to treatment) will be imputed from MMRM model directly, which implicitly assumes missing-at-random (MAR).
Primary Estimand	Sensitivity estimator 1	See primary Estimand	See primary Estimand	See primary Estimand	See primary Estimand	See primary Estimand	MMRM with fixed effects of categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous

							covariate. Subject is considered as a random effect, with the covariance structure selected for the main estimator. Missing data for non-treatment related reasons (e.g. accidental or covid-related Death, or Treatment discontinuation not related to treatment) will be imputed using jump-to-reference method with placebo as reference, where the mean of the placebo group at that visit will be imputed as the missing value, regardless of which treatment group the subject was assigned to.
Supplemental Estimand	Supplemental estimator 1	See primary Estimand	Patients with uncontrolled hypertension (hypertensive despite receiving ≥ 2 antihypertensives) as defined by the inclusion/exclusion criteria in the protocol. Per Protocol Set	See primary Estimand	See primary Estimand	See primary Estimand	See primary Estimand / main estimator
Supplemental Estimand	Supplemental estimator 2	See primary Estimand	See primary Estimand	See primary Estimand	The occurrence of intercurrent events is considered irrelevant in defining treatment effect; the values of the endpoint will be used regardless of whether subject experiences an intercurrent event. This	See primary Estimand	MMRM with fixed effects of categorical terms for treatment, week, and treatment by week interaction, and baseline SBP as a fixed continuous covariate. Subject is considered as a random effect, with the covariance structure selected for the main estimator. All observed data will be used,

					corresponds to a treatment policy strategy.		regardless of treatment discontinuation or other ICE. Any remaining missing data will be imputed from MMRM model directly, which implicitly assumes missing-at-random (MAR).
Key Secondary Estimand 1	Main estimator	See primary Estimand	See primary Estimand	Change in 24-hour ABPM parameters (systolic and diastolic) from baseline to the end of Study	No imputation will be employed regardless of use of rescue medications – treatment policy approach	Difference between each active dose and placebo in 24-hour mean, daytime mean, and nighttime mean change from baseline to EOT in ABPM SBP and DBP	ANCOVA with treatment group as a factor and a baseline value as a covariate. Missing ABPM is replaced by repeated test; no other imputation for missing data, regardless of cause.
Key Secondary Estimand 2	Main estimator	See primary Estimand	See primary Estimand	Change in office-measured SBP from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, and 7	See primary Estimand	Difference between each active dose and placebo in mean change from baseline to Study Weeks 1, 2, 3, 4, 5, 6, and 7 in office-measured SBP	See primary Estimand / main estimator
Key Secondary Estimand 3	Main estimator	See primary Estimand	See primary Estimand	Change in office-measured DBP from baseline to the end of Study Weeks 1, 2, 3, 4, 5, 6, 7, and 8	See primary Estimand	Difference between each active dose and placebo in mean change from baseline to Study Weeks 1, 2, 3, 4, 5, 6,	See primary Estimand / main estimator

						7, and 8 in office-measured DBP	
Key Secondary Estimand 4	Main estimator	See primary Estimand	See primary Estimand	Proportion of subjects who achieve in office-measured BP of ≤ 130/80 mm Hg by the end of Study Week 8	Rescue medication use, Death (non-Covid/non-accidental) or Treatment discontinuation for treatment-related reason (i.e. lack of efficacy, toxicity): treatment failure	Difference between each active dose and placebo in proportion of success.	No formal comparison. Missing values at end of treatment (Week 8) will be imputed as failures.