# STATISTICAL ANALYSIS PLAN
# ALN-AGT01-003 (KARDIA-2)

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|---|---|
| **Protocol Title:** | A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication |
| **Short Title:** | Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2) |
| **Study Drug:** | Zilebesiran (ALN-AGT01) |
| **Protocol Date:** | Original protocol, 25 August 2021<br>Amendment 1, 22 March 2022<br>Amendment 2, 22 September 2022<br>Amendment 3, 20 July 2023 |
| **SAP Date:** | Original SAP: 29 March 2022<br>Amendment 1, 06 February 2024<br>Amendment 2, 15 July 2024 |
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| Abbreviation | Definition |
|---|---|
| ABPM | Ambulatory blood pressure monitoring |
| ADA | Anti-drug antibody(ies) |
| AE | Adverse event |
| AGT | Angiotensinogen |
| ALT | Alanine aminotransferase |
| AngI/II | Angiotensin I/II |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| DB | Double-blind |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| eDISH | Evaluation of drug-induced serious hepatotoxicity |
| EOT | End of treatment |
| ET | Early termination |
| ECG | Electrocardiogram |
| FAS | Full analysis set |
| HbA1c | Hemoglobin A1c |
| HBPM | Home blood pressure monitoring |
| HLT | High level term |
| IRT | Interactive Response Technology |
| ISR | Injection site reaction |
| LFT | Liver function test |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model for repeated measurements |
| OLE | Open-label extension |
| PD | Pharmacodynamic(s) |

| Abbreviation | Definition |
|---|---|
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| Q6M | Once every 6 months |
| RAAS | Renin-angiotensin-aldosterone system |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |
| SOC | System Organ Class |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantification |

# 1. INTRODUCTION

This statistical analysis plan (SAP) details comprehensive specifications of the efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data summaries and statistical analyses in support of the clinical study report (CSR) for Study ALN-AGT01-003 (KARDIA-2).

SAP amendment 1 was finalized prior to conducting the analysis of the primary and secondary endpoints measured up to Month 6. Updates to the SAP were made in Amendment 2 to address the handling of data for several patients that were identified, following the primary analysis, to have multiple randomization numbers. Additional details for these patients are included in Section 3. No changes were made to the statistical methodology. Changes to planned analyses specified in this SAP made after database lock will be documented in the CSR.

Table, figure, and listing (TFL) mocked shells and specifications are contained in a separate document.

# 2. STUDY DESIGN

## 2.1. General Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and PD of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. A schematic of the study design is provided in Figure 1.

**Run-in Period**

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1) for at least 4 weeks before Run-in Visit 2 to washout their effects.

**DB Period**

Patients who meet all inclusion/exclusion criteria will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB period as add-on therapy to their protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

Starting at Month 3, additional conventional oral antihypertensives (“escape antihypertensive medications”) may be added to the patient’s protocol-specified background antihypertensive medication per Investigator judgement.

### OLE Period

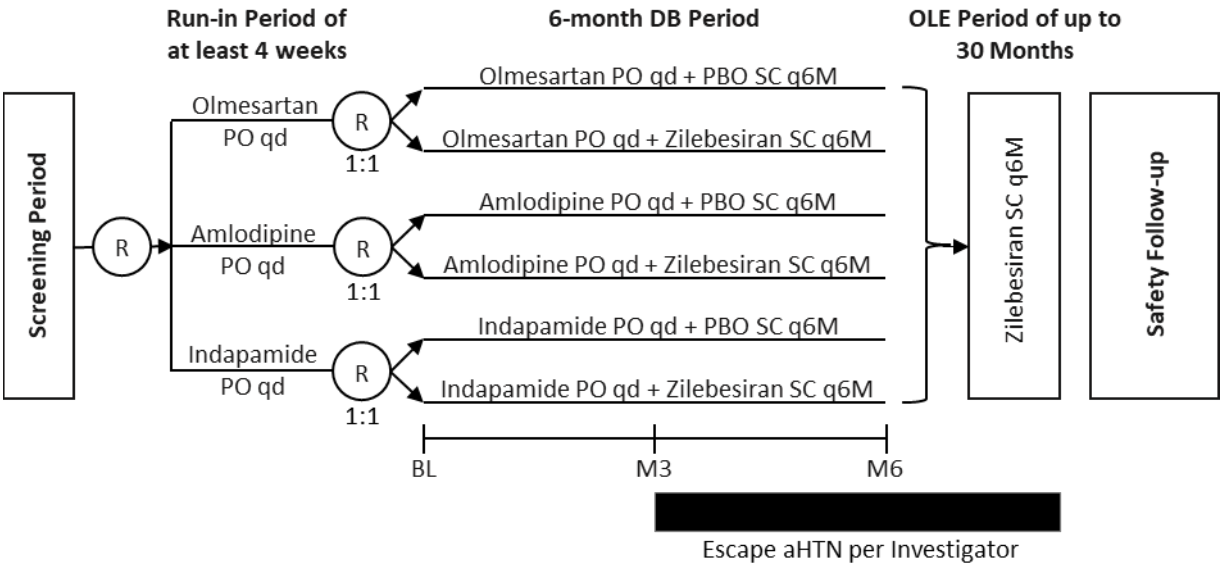
After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may have been eligible to participate in a separate zilebesiran OLE study. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Upon implementation of Protocol Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period. Patients will not receive a dose of study drug at Month 6. Upon completion of predose assessments at the Month 6 visit, patients will enter the Safety Follow-up period. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

### Safety Follow-up Period

Patients will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During the Safety Follow-up period, patients should return to their pre-study medical care (usual care).

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/early termination (ET) assessments should be performed.

**Figure 1 Study Design**




Abbreviations: aHTN=antihypertensive medication; BL=baseline; DB=double-blind; EOT=end of treatment; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); qd=once daily; q6M=once every 6 months; R=randomization; SC=subcutaneous.
Note: Patients may have been eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran once every 6 months in the OLE period for up to 30 additional months during the OLE period until the OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6 month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period. Patients who were previously taking antihypertensives at screening should discontinue these medications at Run-in Visit 1.

## 2.2. Objectives and Endpoints

The following objectives will be evaluated separately for each protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide).

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3 | • Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM |
| Secondary | |
| Through Month 6<br>• To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM<br>• To evaluate the add-on effect of zilebesiran on office blood pressure<br>• To characterize the PD effects of zilebesiran | Key Secondary Endpoints<br>• Change from baseline at Month 3 in office SBP<br>• Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM<br>• Time-adjusted change from baseline through Month 6 in office SBP<br>• Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6<br>Other Secondary Endpoints<br>• Change in 24-hour mean SBP and DBP, assessed by ABPM<br>• Change in office SBP and DBP<br>• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM<br>• Change in serum AGT |
| Exploratory | |
| • To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6) | • Office blood pressure and ABPM control and response rates<br>• Proportion of patients requiring treatment with escape antihypertensive medications<br>• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure<br>• Change in SBP and DBP from baseline assessed by HBPM |
| • To characterize the plasma PK of zilebesiran | • Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran |
| • To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication) | • Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII |

| Objectives | Endpoints |
|---|---|
| • To evaluate the immunogenicity of zilebesiran | • Incidence and titers of ADA |
| • To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements | • Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio |
| • To assess the effect of zilebesiran on metabolic syndrome parameters | • Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile |
| • To characterize the PD effects of zilebesiran (after Month 6) | • Change in serum AGT |
| • To assess the long-term treatment effect of zilebesiran (through Month 36) | • Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM |
| Safety | |
| • To evaluate the safety of zilebesiran in patients with hypertension | • Frequency of AEs |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; HbA1c=hemoglobin A1c; HBPM=home blood pressure monitoring; HOMA= homeostatic model assessment; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

## 2.3. Study Procedure

The Schedule of Assessments is provided in Table 2.

## 2.4. Randomization Methodology

At Run-in Visit 1, patients with screening eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be assigned to receive olmesartan. To avoid over-enrollment, patients with eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be excluded from the study after 100 such patients are randomized to study drug on Day 1.

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 2.6. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

At Day 1, patients will be randomized 1:1 to receive zilebesiran or placebo as an add-on to their protocol-specified background antihypertensive medication using the IRT. Randomization at Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

## 2.5. Blinding

The Sponsor, all site personnel and patients will be blinded to study drug treatment through Month 3 of the 6-month DB period. After the interim analysis at Month 3 is complete, Sponsor staff members who will not have direct roles or responsibilities in interacting with study sites may be unblinded to the analysis results according to the prespecified blinding plan. Site personnel, patients, and Sponsor staff members who have direct roles or responsibilities in interacting with study sites will remain blinded to both Month 3 interim analysis results and treatment assignment until after the analysis of Month 6 data is complete. All Sponsor and site personnel and patients will be blinded to any clinical laboratory result that could potentially unblind them (e.g., AGT levels) until treatment assignment unblinding.

Details about the specifics of the blinding aspects throughout the entire study are available in the Randomization and Blinding Plan.

Any unplanned/emergency unblinding occurring during the DB Period will be documented and reported in the CSR.

Refer to the study Randomization and Blinding Plan for more details.

## 2.6. Determination of Sample Size

Approximately 630 patients will be randomized to receive either zilebesiran or placebo, with sample sizes in each of the patient cohorts with protocol-specified background antihypertensive medication as follows:

- Olmesartan cohort: 300 patients
- Amlodipine cohort: 210 patients
- Indapamide cohort: 120 patients

Assuming a common standard deviation of 16 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM and 15% dropout rate from baseline to Month 3, with 2-sided significance level of 0.05 for each of the comparisons (zilebesiran versus placebo as add-on to olmesartan; zilebesiran versus placebo as add-on to amlodipine; zilebesiran versus placebo as add-on to indapamide), these sample sizes will provide at least 80% power to detect the following difference between zilebesiran versus placebo:

- 5 mmHg as add-on to olmesartan
- 6 mmHg as add-on to amlodipine
- 8 mmHg as add-on to indapamide

The power is assessed by mixed model with repeated measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

# 3. ANALYSIS POPULATIONS

The populations (analysis sets) are defined as follows:

- Modified Randomized Set: All patients who received a randomization number. All by-treatment analyses based on the Modified Randomized Set will be grouped according to the randomized treatment arm.
- Modified Full Analysis Set (mFAS): All randomized patients who received any amount of study drug. All by-treatment analyses based on the mFAS will be grouped according to the randomized treatment arm.
- Modified Safety Analysis Set: All patients who received any amount of study drug. All by-treatment analyses based on the Modified Safety Analysis Set will be grouped according to the treatment actually received.
- Modified PK Analysis Set: All patients who received at least 1 full dose of zilebesiran and have at least 1 non-missing post-dose PK assessment.
- Modified PD Analysis Set: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the Modified PD Analysis Set will be grouped according to the treatment actually received.
- Modified All Zilebesiran Treated Set: All patients who received any amount of zilebesiran, including patients who took zilebesiran during the 6-month DB period, and patients who initially took placebo and then switched to zilebesiran after Month 6 Visit.

For the analyses for 6-month DB period, the primary population used to evaluate efficacy will be the mFAS. Safety will be analyzed using the modified Safety Analysis Set. The modified PK and modified PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The modified All Zilebesiran Treated Set will be used to summarize the efficacy and safety of zilebesiran throughout the 6-month DB period and the OLE period.


## 3.1. Randomization and Treatment Errors

The study has two randomizations. The first randomization is to assign patients to receive one of the three protocol specified background antihypertensive medications. The second randomization is to randomize patients to receive either zilebesiran or placebo on top of each background antihypertensive medication. This section mainly focuses on the second randomization.

For patients who were not treated, not randomized, or received incorrect treatment, the following rules will be used:

- Randomized but not treated: they will be excluded from the modified FAS and modified Safety Analysis Set for efficacy and safety evaluations as actual treatment is missing.
- Treated but not randomized: they will be excluded from the efficacy analyses since randomized treatment is missing but will be reported under the treatment actually received for all safety analyses.
- Randomized but took incorrect treatment: they will be reported under their randomized treatment arm for all efficacy analyses. But for safety analyses, a patient will be reported under the active treatment arm if the patient is randomized to placebo arm and received any dose of zilebesiran by mistake.

# 4. GENERAL STATISTICAL CONSIDERATIONS

## 4.1. General Considerations

In general, data will be summarized for each planned analysis defined in Section 4.7 separately. All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts.

A pooled analysis across all 3 protocol-specified background antihypertensive medication cohorts will also be performed for patient disposition, demographics, baseline characteristics, exposure during the zilebesiran treatment period, by-visit tables during the OLE period and select adverse event analyses.

Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the following descriptive summary statistics: number of patients (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

Study drug is zilebesiran 600 mg or placebo.

The day of the first dose of study drug administered is defined as Day 1. The Study Day of a time point of interest is calculated as follows:

- If on or after Day 1, Study Day = date of interest – date of the first dose of stud y drug + 1
- If prior to Day 1, Study Day = date of interest – date of the first dose of study drug

There is no Day 0. For example, the day before the first study drug dose is defined as Day -1.

For laboratory parameters, assessments collected and recorded as lower than the lower limit of quantification/detection (LLOQ) will be replaced by the LLOQ. Any assessment collected and recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

All descriptive summaries will be presented by treatment arm.

Statistical analyses will be conducted using SAS software Version 9.4 or newer or R version 3.6 or newer.

## 4.2. Blood Pressure Collection and Handling

### 4.2.1. 24-Hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure monitoring (ABPM) is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 4 days.

To summarize the 24-hour ABPM, hourly adjusted mean will be calculated. Hourly adjusted mean will be calculated by two steps:

1. Calculate the hourly mean of BP by each hour of the day (e.g., mean of BP measurements from 16:00 to 16:59). If there is no reading in a specific hour, this hourly mean will be considered as missing.
2. Calculate the 24-hour mean SBP/DBP, daytime and nighttime means of the SBP/DBP based on the hourly means.

### 4.2.2. Office Blood Pressure

The office BP in the sitting position will be used for the analysis. Office BP will be collected with a set of 4 replicates. The average of the last 3 replicates will be calculated and used for analysis. Office BP collected in standing position will be listed only.

### 4.2.3. Home Blood Pressure Monitoring

Home blood pressure will be measured both pre and post randomization. To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization. After Day 1, HBPM will be measured at least once per week. Four sequential blood pressure measurements at 1-minute intervals will be recorded. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements. HBPM will be summarized by weekly average.

Details of the blood pressure collection are in Study Protocol Section 10.

## 4.3. Multiple Comparison/Testing Procedure

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. To control the overall Type I error at $\alpha$=0.05 within each cohort, the primary endpoint and the key secondary endpoints will be tested in hierarchical order.

**Table 1 Multiplicity Procedure**

| Test Step[a] | Endpoint | Success criteria |
|---|---|---|
| 1 | Primary: Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 2 | Key secondary: Change from baseline at Month 3 in office SBP | Nominal p-value < 0.05 |
| 3 | Key secondary: Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 4 | Key secondary: Time-adjusted change from baseline through Month 6 in office SBP | Nominal p-value < 0.05 |
| 5 | key secondary: Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication at Month 6 | Nominal p-value < 0.05 |

[a] If the success criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant

## 4.4. Handling of Missing Data

No imputation will be done for missing values for the primary analysis of the primary endpoint. A sensitivity analysis of the primary endpoint will be performed (details described in Section 5.7.1.3). For all analyses using mixed model repeated measures, no explicit imputation of missing values will be done.

## 4.5. Baseline Definitions

For the analyses of 6-month DB period, for office BP, baseline is the average of the office BP value on Day 1 prior to receiving the first dose of study drug and last non-missing value prior to Day 1 during run-in period. For 24-hour ABPM, baseline is the measurement used for eligibility for randomization to study drug. For HBPM, baseline will be the average of all assessments during the last week prior to receiving the first dose of study drug. For all other endpoints, baseline is the last non-missing value (including unscheduled visit) prior to receiving the first dose of study drug.

For the final analyses, patients initially randomized to placebo and switched to zilebesiran at Month 6 will be summarized in two ways:

- From Day 1. Baseline is the same as the one for the primary analysis.
- From the start of zilebesiran dosing at Month 6. Baseline will be the last assessment prior to Month 6 dosing.

For patients initially randomized to zilebesiran, baseline remains the same as the one for the primary analysis.

## 4.6. Randomization Stratification Factors

Stratification factors are recorded in the IRT database. Key data is integrated into the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database (EDC). In the presence of stratification errors, the stratification used in analysis may not match that in the IRT. A comparison of the number and percentage of patients in each randomization stratification factor in IRT versus the clinical database will be summarized by randomized treatment arm and overall.

## 4.7. Planned Analyses and Data Cutoffs

### 4.7.1. Month 3 Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be performed prior to the primary database lock at the end of the double-blind period. Additional details regarding the interim analysis will be documented in the study Data Management Plan and Month 3 Interim Statistical Analysis Plan for the Month 3 interim analysis.

The analysis will include data on, or prior to, this prespecified cutoff date. For assessments with starting/ending dates (e.g., adverse events [AEs], medications), the starting date will be compared with the pre-specified cutoff date. Data records with starting dates after the specified data cutoff date will be excluded.

### 4.7.2. Month 6 Analysis

The analysis after the end of double-blind period is the Month 6 analysis. The protocol-specified primary, secondary, exploratory and all other pre-specified analysis will be performed after all randomized patients have completed the Month 6 Visit or otherwise withdrawn from the study.

The database will undergo an primary database lock, and the data will be summarized in a CSR.

### 4.7.3. Final Analysis

After all patients reach the end of the study or otherwise withdrawn from the study, the database will undergo a final database lock, and the data will be summarized in a CSR.

A patient is considered to have reached the end of the study if the patient has completed the safety follow-up visits.

# 5. STATISTICAL ANALYSES

## 5.1. Patient Disposition

The number and percentage of patients in the following categories will be summarized by randomized treatment arm and overall based on the modified randomized set:

- Randomized to study drug
- Treated with study drug

- Completed the 6-month double-blind (DB) treatment period
- Withdrawal from study and primary reason for withdrawal from study during 6-month DB period.

The number and percentage of patients that entered into the OLE and/or safety follow up period will be summarized in the following categories:

- Completed 6 Month DB Period
- Entered into OLE period
- Entered into Safety FU period
- Completed the study
- Withdrawal from study and primary reason for withdrawal from study
- Ongoing
- Discontinued from study drug and primary reason for discontinuation from study drug.

In addition to the primary reason for discontinuation of study drug and withdrawal from study, patients will also be categorized if discontinuation/withdrawal was due to COVID-19.

Screen failures and run-in failures will also be summarized.

## 5.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for Modified Full Analysis Set, and also presented in listings.

Age at consent, height, weight, body mass index (BMI), 24-hour ABPM, OBP, and urine albumin-to-creatinine ratio will be summarized using descriptive statistics. Sex, race, ethnicity, country, eGFR, and diabetes mellitus status will be summarized by presenting the frequencies and percentages of patients in each category.

## 5.3. Medical History

Medical history and prior procedures reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0 or newer. Unique patients who report medical history events will be summarized by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). Medical history and prior procedures will also be presented in listings. Analysis will be based on the modified safety analysis set.

## 5.4. Protocol Deviations

Protocol deviations will be classified by medical review prior to each planned analysis database lock, and major protocol deviations will be identified. A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being. (ICH E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry, 2013).

The Sponsor or designee will be responsible for producing the protocol deviation file. This file will include a description of each protocol deviation and classification as major or minor. The protocol deviations will be reviewed and finalized prior to the planned analysis database lock.

All protocol deviations and major protocol deviations will be summarized and listed using modified randomized set.

## 5.5. Study Drug Exposure and Compliance

The following variables will be summarized by descriptive statistics and/or frequency tabulation based on the modified safety analysis set:

- Duration of exposure, defined as: date of last exposure – date of first dose of study drug +1. Date of last exposure is the earliest date of the following:
  - date of last dose of study drug + the length of dosing interval (169 days)
  - date of end of study
  - date of analysis data cutoff
- Number of doses received; as continuous and/or categorical variable
- Number of missed doses; as a categorical variable

For analysis during the Zilebesiran treatment period, zilebesiran exposure will be summarized both within each cohort and across all cohorts in the final analysis based on the modified all zilebesiran treated set.

## 5.6. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version WHO-DD Global B3, March 2023 or newer. Unique patients who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class (or level 2 if not available) and PT. Summaries will be provided for prior and concomitant medications separately. Summaries by ATC and PT will also be provided for both prior and concomitant anti-hypertensive medications.

The proportion of patients with escape antihypertensive medication at each visit, will also be provided by treatment group.

Prior medications are those medications with start date prior to the first dose of study drug.

Concomitant medications are medications, other than the study drug or protocol-specified background antihypertensive medication, administered at or after the first dose of study drug, as well as medications that started prior to the first dose of study drug and are ongoing after the first dose of study drug.

Escape antihypertensive medication is defined as any antihypertensive medication other than background medication (by ATC codes) that were started after the first dose; or background medication with dose increased to be higher than the baseline level.

Protocol-specified background antihypertensive medication, not identified as escape antihypertensive medication, will be excluded from analysis of prior and concomitant medications.

If the medication start date is on or after the date of first dose of study drug, the medication will be summarized as a concomitant medication even if the medication end date is missing.

If the end date of a medication is missing or incomplete, such that it cannot be determined whether it is after the first dose of study drug, it will be counted as a concomitant medication.

For missing or partial dates for medications, the imputation of start and end dates is described in Section 7.4.

Background Medication Compliance

Compliance to background medication (%): (number of tablets returned – number of tablets dispensed) divided by number of expected tablets taken x 100.

Number of expected tablets is the number of days that a patient should be taking background medication during a specific period (Run-in period and 6 month double blind period).

All analysis during the 6-month double-blind treatment period will be based on the modified safety analysis set. All analysis during the zilebesiran treatment will be based on the modified all zilebesiran treated set.

## 5.7. Efficacy Analyses

### 5.7.1. Primary Endpoint

#### 5.7.1.1. Definition of Estimand

The primary objective of the study is to evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3. Primary estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)
- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint: Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
- Population-level summary: Least square mean difference between zilebesiran and placebo in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, on top of each background antihypertensive medication
- Intercurrent events strategy: Hypertensive escape medication taken before Month 3 visit will be considered as an intercurrent event. For patients who require escape antihypertensive medication, given the expected number of such patients at Month 3 is low, hypothetical strategy will be used, i.e., ABPM assessed while patients are on and within 2 weeks after stopping any escape antihypertensive medication will be

excluded for analysis. This will provide the estimated treatment effect of zilebesiran compared with placebo on top of each background antihypertensive medication.

#### 5.7.1.2. Primary Analysis

For each background antihypertensive medication cohort, the hypothesis to be tested for the primary endpoint is:

- $H_0$: $\mu_1 = \mu_0$ (there is no add-on effect of zilebesiran)
- $H_a$: $\mu_1 \neq \mu_0$ (there is add-on effect of zilebesiran)

where $\mu_0$ and $\mu_1$ are the mean change from baseline at Month 3 in 24-hour mean SBP in placebo and zilebesiran arm, respectively.

MMRM model will be used as primary analysis. The model will include treatment, visit, treatment-by-visit, and race (black, all other races) as fixed factors; baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. The LS mean coefficients will be computed using the observed proportion of black patients within each cohort, for all analysis of the primary endpoint as well as all analyses of secondary endpoints using a similar MMRM model.

#### 5.7.1.3. Sensitivity Analyses

For the sensitivity analysis, treatment policy strategy will be used for patients who require escape antihypertensive medication. All collected blood pressure measurements will be analyzed by the same MMRM model as the primary analysis, regardless of the hypertensive escape medication.

Due to the expected long-acting effect of zilebesiran, the commonly used control-based Pattern Mixture Model (PMM) will not be used to assess the missing not at random (MNAR) assumption.

#### 5.7.1.4. Other Analyses

Change from baseline at Month 3 and at Month 6 in SBP assessed by ABPM at each clock hour will be plotted for each treatment group.

### 5.7.2. Secondary Endpoints

#### 5.7.2.1. Key Secondary Endpoints

Secondary objectives of the study are to evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM and office blood pressure through Month 6. The estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)
- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint:
  - Change from baseline at Month 3 in office SBP

  - Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM
  - Time-adjusted change from baseline through Month 6 in office SBP
  - Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication

- Population-level summary:
  - Least square mean difference between zilebesiran and placebo of the change from baseline in SBP on top of each background antihypertensive medication.
  - Odds ratio for BP response rate.
- Intercurrent events strategy:
  - For Month 3 endpoint: Given the expected number of such patients at Month 3 is low, hypothetical strategy will be used.
  - For Month 6 endpoint: Protocol allows escape antihypertensive medication from Month 3 through Month 6. Given the expected proportion of such patients may be large, the treatment policy strategy will be used.

Time-adjusted change is defined as the area under the curve (AUC) of BP change from baseline divided by the duration of the time period. It leads to the weighted average of change from baseline to each scheduled visit. Details of the definition and calculation are in Section 7.4.

Multiplicity adjustment will be applied across primary and the key secondary endpoints. Details of multiplicity control are in Section 4.3.

MMRM model will be used as the primary analysis. The model will include treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, baseline eGFR and corresponding baseline BP as covariates. Least square (LS) mean difference, 95% CI and p-value will be generated.

For the proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6, logistic regression will be used. The model will include treatment as a factor, baseline 24-hour mean SBP and baseline eGFR as covariates.

Sensitivity analysis for secondary endpoints using MMRM will also be evaluated.

  - For Month 3 endpoint: treatment policy strategy will be used for patients who require escape antihypertensive medication. All collected blood pressure measurements will be analyzed.
  - For Month 6 endpoint: hypothetical strategy will be used for patients who require escape antihypertensive medication. Blood pressure measurements while patients are on and within 2 weeks after stopping any escape antihypertensive medication will be excluded for analysis.

#### 5.7.2.2. Other Secondary Endpoints

Other blood pressure related secondary endpoints are:

- Change from baseline at Month 3 in 24-hour mean DBP, assessed by ABPM
- Change from baseline at Month 3 in office DBP
- Time adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP, assessed by ABPM
- Time adjusted change from baseline in office SBP/DBP through Month 3
- Change from baseline at Month 6 in 24-hour mean SBP/DBP, assessed by ABPM
- Change from baseline at Month 6 in office SBP/DBP
- Time adjusted change from baseline through Month 6 in 24-hour mean DBP, assessed by ABPM
- Time adjusted change from baseline through Month 6 in office DBP
- Change from baseline in daytime/nighttime SBP and DBP by ABPM by each visit. Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

In general, the BP related endpoints will be summarized using all collected BP data regardless of the use of escape antihypertensive medication. The same MMRM model will be used with treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, corresponding baseline as a covariate. Least square (LS) mean difference of each zilebesiran dose group compared with placebo dose group, 95% CI and p-value will be generated.

The secondary endpoint of percent change in serum AGT at each visit will be summarized using descriptive statistics. Serum AGT will be analyzed for the 6 month double blinded period, zilebesiran treatment period and the entire study.

### 5.7.3. Exploratory Endpoints

The blood pressure related exploratory endpoints through Month 6 are:

- BP response rate by each visit, defined as
  - Office SBP < 140 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication
  - 24-hour mean DBP assessed by ABPM < 85 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
  - Office DBP < 90 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
- Proportion of patients with escape antihypertensive medication use by each visit
- Change from baseline in pulse pressure by each visit, assessed by ABPM and office BP

- Change from baseline in SBP/DBP by HBPM

To assess the long-term treatment effect of zilebesiran through Month 36, change from baseline in SBP/DBP assessed by ABPM, office BP and HBPM will be summarized.

Body weight, metabolic related exploratory endpoints are:

- Change from baseline in body weight/body mass index (BMI)/waist circumference/waist-to-hip ratio by each visit
- Change from baseline in HbA1c/fasting glucose/insulin/serum lipids by each visit.

Exploratory endpoints will be summarized using descriptive statistics based on all observed data. Missing data will not be imputed.

### 5.7.4. Evaluation of Subgroups

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age (<65; >=65)
- Sex (male; female)
- Race (black; all other races)
- Baseline 24-hour mean SBP assessed by ABPM (<145 mmHg; >=145 mmHg)
- Baseline eGFR (<60; >=60 mL/min/1.73 $m^2$)
- Baseline BMI (<30; >=30 $kg/m^2$)
- Diabetes Mellitus Status (Yes; No)
- For Olmesartan only: Run-in Visit 1 plasma renin concentration (<= Run-in Visit 1 median; > median).

Subgroup analyses will be performed for the primary endpoint and key-secondary endpoints using the MMRM within each subgroup. Model will include treatment, visit, treatment-by-visit interaction, race ([black, all other races], when race is not the subgroup to be analyzed) as fixed factors, baseline eGFR and corresponding baseline BP measurement as covariates. The LS mean coefficient of race will be computed using the observed proportion of black patients within each cohort. Point estimate of treatment effect and 95% confidence interval are to be generated for each subgroup. A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

## 5.8. Pharmacodynamic Analyses

In addition to serum AGT, the PD parameters include plasma renin concentration, aldosterone, AngI and AngII. Summary tables will be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group. In addition to serum AGT percent reduction analyses, the AGT maximum and mean percentage reductions over the 6-month DB period will be summarized using descriptive statistics.

## 5.9. Pharmacokinetic Analyses

Plasma concentrations of zilebesiran and its metabolite will be summarized descriptively. Descriptive statistics for zilebesiran and its metabolite plasma concentrations will include the number of patients, mean, SD, coefficient of variation, geometric mean, geometric mean coefficient of variation, median, minimum, and maximum.

Additional analysis may be done as needed.

## 5.10. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any time during the 6-month DB period, as well as treatment-emergent ADA during the OLE period, will be summarized. All analysis during the 6-month double-blind treatment period will be based on the modified safety analysis set. All analysis during the zilebesiran treatment will be based on the modified all zilebesiran treated set.

Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, as defined below:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

## 5.11. Safety Analyses

### 5.11.1. Adverse Events

Adverse events (AEs) will be classified by the MedDRA coding system (Version 26.0 or newer) and displayed in tables and data listings using SOC and PT.

Treatment-emergent AEs (TEAEs) will be summarized for the 6-month DB period and for the duration of zilebesiran exposure (defined in Section 5.5) separately.

For the 6-month DB period, TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and through Month 6 Visit (prior to Month 6 dosing). For AE occurring in the OLE period, TEAE is defined as any AE occurring or worsening on or after the last dose of study drug up to 6 months after last dose. Treatment related AEs that occur after 6-months are also counted as TEAE.

AEs that occurred or worsened during safety follow-up period will be listed and may be summarized if needed.

Because any worsening AE is reported as a new AE with higher severity, programmatical comparison of severity is not needed for the classification of TEAE. For missing or partial dates for AEs, the imputation of start and end date can be found in Section 7.4. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first dose of study drug.

AEs will be summarized by the numbers and percentages of patients reporting a given AE. An overall table of TEAEs will include:

- any AE,
- any AE related to study drug,
- any serious AE (SAE),
- any SAE related to study drug,
- any severe AE,
- any severe AE related to study drug,
- any AE leading to study drug interruption,
- any study-drug related AE leading to study drug interruption,
- any AE leading to study drug discontinuation,
- any study-drug related AE leading to study drug discontinuation,
- any AE leading to withdrawal from study,
- any study-drug related AE leading to withdrawal from study,
- any AE leading to death.

Tabulations by SOC and PT will be produced for the following:

- AEs,
- Study-drug related AEs,
- AEs by maximum severity,
- Study-drug related AEs by maximum severity,
- Severe AEs,
- SAEs,
- Study-drug related SAEs,
- AEs leading to treatment discontinuation.

Tabulations by PT will be produced for the following:

- AEs,
- Study-drug related AEs,
- SAEs.
- Study-drug related SAEs,

For analysis during the Zilebesiran treatment period, summary of TEAE and tabulations by PT for AEs and SAE, will also include an overall column, pooling all cohorts and treatments in the final analysis.

AEs and AEs related to study-drug will also be summarized by maximum severity.

A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence. An AE with missing severity will be assumed to be severe. An AE with missing study drug relatedness will be assumed to be related.

Listings of all deaths (if any), SAEs, and AEs leading to treatment discontinuation will be provided.

In addition, AE during run-in period will be listed by each background antihypertensive medication cohort.

AEs of Clinical Interest

AEs of special interest or AEs mapping to certain standardized MedDRA queries (SMQs) will be summarized by SOC and PT. Other SMQs or AE groupings may be evaluated.

**Injection Site Reactions [ISRs]**: AEs mapping to the High-Level Term (HLT)= "Injection Site Reactions" using MedDRA dictionary will be included in the summary. Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. In addition, a table of the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose), total number of doses with ISRs and corresponding % of injections with ISR with the most common signs and symptoms reported due to ISRs will be generated.

**Hepatic AEs, including Liver Function Test (LFT) abnormalities**: Analysis of hepatic AEs will include AEs mapping to the Standardized MedDRA Query (SMQ) Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms).

**Acute renal failure** AEs will include AEs mapping to the Standardized MedDRA Query (SMQ) Acute renal failure - comprehensive search (includes all narrow and broad terms). The adjudicated renal events including severity assessments will be summarized or listed.

**Hyperkalemia** AEs will be through Customized MedDRA Query (CMQ) search. PT terms are listed in Section 7.2.

**Hypotension** AEs include AEs mapping to the FDA Medical Queries (FMQ) hypotension search (includes narrow terms), and additional terms potentially related to hypotension. List of additional terms is in Section 7.2.

Frequency (percentages) of these AEs will be summarized by SOC and PT. For analysis during the Zilebesiran treatment period, the summaries for AEs of Clinical Interest will also include an overall column, pooling all cohorts and treatments in the final analysis. Separate listings will be generated of all patients reporting these events.

All AEs will be presented in patient data listings. AEs mapping to the SMQs as described above will also be listed.

Additional summaries of AEs mapping to a COVID-19 custom query are described in Section 5.13.2.

### 5.11.2. Laboratory Data

Clinical laboratory values will be expressed in SI units. Missing laboratory data will not be imputed.

For each continuous clinical laboratory parameter (including hematology, serum chemistry, liver function tests and coagulation studies), descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit. These by-visit tables will use central laboratory data only.

Select clinical laboratory parameters may be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or above. Shift summary from baseline CTCAE grade to maximum (worst) post-baseline grade will be presented for all graded parameters with directionality specified (e.g., hyper or hypo). To determine the worst post-baseline value, all scheduled and unscheduled test results will be used. For hematology and serum chemistry, frequency tables of potentially clinically significant (PCS) abnormalities will be provided.

All laboratory data (both central and local) will be provided in data listings. Out-of-range laboratory results will be presented in a separate listing with proper flags. Local laboratory data, if available, will also be flagged.

Liver Function Tests

A frequency table and a shift table will be produced to summarize the number and percentage of patients in each of the below categories at any post-baseline time point.

- ALT >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALP > 1.5×ULN,
- Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN

In separate evaluation of drug-induced serious hepatotoxicity (eDISH) figures, the peak total bilirubin (as multiple of ULN) at any time post-baseline will be plotted against the peak ALT, AST, ALT or AST level and at any time post-baseline.

A listing for all patients with abnormal liver function tests, defined as an ALT >3×ULN, AST >3×ULN, or total bilirubin >2×ULN at any time point, will also be provided.

Renal function

Estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine (SCr) based on the Modification of Diet in Renal Disease (MDRD) Formula:

- Conventional units – eGFR (mL/min/1.73 $m^2$) = 175 × (SCr[mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ and (× 0.742, if female) and (× 1.212, if African American)
- SI units – eGFR (mL/min/1.73 $m^2$) = 175 × (SCr[µmol/L]/88.4)$^{-1.154}$ × (age)$^{-0.203}$ and (× 0.742, if female) and (× 1.212, if African American)

The eGFR will be categorized into the following categories: ≥90, 60-89, 30-59, 15-29 and <15. A shift table of baseline to worst post-eGFR (i.e. category with the lowest value) will be presented according above categories.

Serum Potassium

Potassium lab values will be categorized into the following categories: <=4.5, >4.5 to <=5.0, >5.0 to <=5.5, >5.5 to <=6.0 & >6.0 (mmol/L). A shift table of baseline to worst post-baseline potassium (i.e. category with the highest value) will be presented. Patients with at least one post baseline potassium value >5.5 and >6.0 (mmol/L) will also be summarized.

### 5.11.3. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm and overall interpretation.

Post-baseline overall interpretation (normal vs. abnormal) will be summarized in frequency table by treatment and visit.

All ECG data for each patient will be provided in a data listing.

### 5.11.4. Vital Signs

For vital signs except blood pressure, descriptive statistics for actual values and change from baseline by visit will be provided for each variable. Vital sign measurements will be presented by treatment and patient ID in a data listing, with abnormal vital signs flagged.

### 5.11.5. Evaluation of Subgroups

AE summary tables will be separately generated for each of the subgroups as defined for the primary efficacy endpoint (except for baseline BP, see Section 5.7.4).

## 5.12. Interim Analysis

An analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted prior to the primary database lock by a small group of designated people who will not have direct roles or responsibilities in interacting with study sites. No formal interim analysis is planned before the analysis at Month 3 (see Section 4.7.1).

## 5.13. COVID-19

Additional data are collected to characterize the impact of the COVID-19 pandemic on general study conduct and disposition, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidance (including FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

### 5.13.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 5.1.

Impact on study participation due to COVID-19 will be presented in data listings.

### 5.13.2. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will be presented. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

AEs mapping to the COVID-19 custom query will also be presented in a data listing.

# 6. CHANGES FROM PLANNED ANALYSES

Original SAP

| Section of the SAP | Summary of change from protocol | Rationale |
|---|---|---|
| | — | — |

Amendment 1

| Section of the SAP | Summary of change from original SAP | Rationale |
|---|---|---|
| Section 1 | SAP finalization has been changed to prior to treatment unblinding for Month 6 analysis from Month 3 analysis | Additional SAP was created for Month 3 Interim analysis. |
| Section 2.1 | Updated OLE Period definition, Safety Follow-up Period definition and study design figure | Updates from protocol amendment. |
| Section 2.2 | Updated Exploratory objective “To assess the long-term treatment effect of zilebesiran” (Changed from Month 18 to Month 36) | Updates from protocol amendment. |
| Section 2.5,<br>Section 4.7.1,<br>Section 5.12 | Updated text around the month 3 analysis | Additional SAP was created for Month 3 Interim analysis. |
| Section 3 | PPD CCI [redacted] | CCI [redacted] PPD<br>PPD . |

| Section of the SAP | Summary of change from original SAP | Rationale |
|---|---|---|
| Section 5.1 | Split Patient Disposition into two sections<br>• Six-month double-blind period<br>• OLE/Safety Follow up period | Protocol removed the OLE period and OLE study. New summarizes required for study complexity. |
| Section 5.2 | Included urine albumin-to-creatinine ratio and diabetes mellitus status | Requested by study team. |
| Section 5.5 | Compliance is calculated as a percentage of the number of tablets taken over expected number of tablets. | Requested by study team. |
| Section 5.6 | Added analysis for prior and concomitant anti-hypertensive medications and definitions of escape medications | Requested by study team. |
| Section 5.6 | Clarified that background medication should not be included in Prior and Concomitant Medications analysis | Requested by study team. |
| Section 5.7.1.2,<br>Section 5.7.4 | Added texted about model correction for observed proportion of black patients | Model was updated to use observed proportion of black patients within the study. |
| Section 5.7.2.1 | Added baseline eGFR as a covariate to logistic regression | Covariate added to match MMRM analysis covariates. |
| Section 5.7.2.1 | Added sensitivity to key secondary endpoints | Requested by study team. |
| Section 5.7.4 | Added additional subgroups of baseline BMI and Run-in 1 Plasma renin Concentration | Requested by study team. |
| Section 5.11.1 | Added text for TEAE during OLE period | Requested by study team. |
| Section 5.11.1 | Added additional AECI of Acute renal failure, Hyperkalemia, and Hypotension | Requested by study team. |
| Section 5.11.2 | Added section for Renal Function and Serum Potassium | Requested by study team. |
| Section 5.13.1 | Updated to only include listing for COVID-19 impact | Limited data is collected on COVID-19 impact. |

Amendment 2

| Section of the SAP | Summary of change from original SAP | Rationale |
|---|---|---|
| Section 3 | Added text for modified study populations | To remove from the analysis populations 4 unique patients who enrolled in the study multiple times (3 patients) or who enrolled in the study while enrolled in another clinical study (1 patient) |
| Section 4.1 | Added text for pooled analysis across cohorts for specific analyses for the Zilebesiran treatment period, for the final analysis | To provide additional analyses to support assessment of safety |
| Section 5.1 | Added a category of "Completed 6 Month DB Period" to the disposition summary for the patients who entered into the OLE/Safety Follow-Up period | To ensure all necessary categories are analyzed for the disposition summary of the OLE/Safety Follow-Up period. |
| Section 5.5 | Added text for pooling exposure across all background cohorts for the Zilebesiran treatment period, for the final analysis | To provide additional analyses to support assessment of safety |
| Section 5.11.1 | Added severe AE and severe related AE to the summary of AE section | To provide additional analyses to support assessment of safety |
| Section 5.11.1 | Added Study-drug related SAE to the Tabulations by SOC and PT | Clarification to list minor changes to analyses |
| Section 5.11.1 | Added Study-drug related SAE to the Tabulations by PT | Clarification to list minor changes to analyses |
| Section 5.11.1 | Added text that select AE outputs during the Zilebesiran treatment period will have an overall column across all cohorts, for the final analysis<br>(AE by PT, SAE by PT and all AECI SOC by PT tables) | To provide additional analyses to support assessment of safety |

# 7. APPENDICES

## 7.1. List of Escape Antihypertensive Medication ATC Code

The ATC codes for escape medications are:

- C02 - Antihypertensives
- C03 - Diuretics
- C07 - Beta blocking agents
- C08 - Calcium channel blockers
- C09 - Agents acting on the renin-angiotensin system

## 7.2. Preferred Terms for Hyperkalemia and Potentially Related to Hypotension

Hyperkalemia:

| |
|---|
| Hyperkalemia |
| Blood potassium increased |
| Blood potassium abnormal |

Potential Hypotension:

| |
|---|
| Blood pressure fluctuation |
| Labile blood pressure |
| Orthostatic intolerance |
| Circulatory collapse |
| Distributive shock |
| Dizziness |
| Dizziness exertional |
| Dizziness postural |
| Hypoperfusion |
| Peripheral circulatory failure |
| Presyncope |
| Procedural shock |
| Shock |
| Shock symptom |
| Syncope |
| Cardiovascular insufficiency |
| Hypotensive crisis |
| Hypotensive transfusion reaction |
| Orthostatic hypotension |
| Vasolplegia syndrome |
| Blood pressure abnormal |
| Blood pressure ambulatory abnormal |
| Blood pressure ambulatory decreased |
| Blood pressure diastolic abnormal |
| Blood pressure immeasurable |
| Blood pressure orthostatic abnormal |
| Blood pressure orthostatic decreased |
| Blood pressure systolic decreased |
| Blood pressure systolic inspiratory decreased |
| Mean arterial pressure decreased |
| Loss of consciousness |

## 7.3. Protocol Schedule of Assessments

Schedule of assessments are listed in Table 2.

## Table 2 Schedule of Assessments

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | | | | Safety Follow-up |
| **Study Visit (Month)** | Screening Period | Run-In Visit 1 | Run-In Visit 2 | | W2 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M18 | M24 | M30 | M36/EOT/ET | Q6M post last dose of study drug |
| **Study Day (±Visit Window)** | D-75 to -1 | | | D1 | D15±2 | D29±2 | D57±7 | D85±7 | D113±7 | D141±7 | D169±7 | D197±7 | D225±7 | D253±7 | D337±7 | D505±14 | D673±14 | D841±14 | D1009±14 | ±14 |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Assign patient identification no. | X | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | | | | | | |
| Serum pregnancy test/FSH screening | X | | | | | | | | | | | | | | | | | | | |
| Creatinine clearance | X | | | | | | | | | | | | | | | | | | | |
| Full physical exam | X | | | X | | | | | | | X | | | | | | | | X | |
| Height and BMI | | | | X | | | | X | | | X | | | X | X | X | X | X | X | |
| Body weight | X | | X | X | | | | X | | | X | | | X | X | X | X | X | X | |
| Single 12-Lead ECG | X | | | X | | | | | | | X | | | | X | X | X | X | X | |
| Serum chemistry[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Run-in Period[a]** | | **Double-blind Period[a]** | | | | | | | | **OLE Period (Optional)[a]** | | | | | | | | **Safety Follow-up** |
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18** | **M24** | **M30** | **M36/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | **D-75 to -1** | | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **D673±14** | **D841±14** | **D1009±14** | **±14** |
| Hematology, urinalysis, coagulation[c] | X | | X | X | | | | X | | | X | | | X | X | X | X | X | X | X |
| LFTs[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| Spot urine for albumin and creatinine[c] | X | | X | X | | | | X | | | X | | | | X | X | X | X | X | |
| Fasting plasma glucose, insulin, lipid panel, and HbA1c[c] | X | | X | X | | | | X | | | X | | | | X | | | | X | |
| Vital signs and office blood pressure[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 24-hour ABPM[e] | | | X | | | | X | X | | | X | | | X | X | | | | X[h] | |
| HBPM[f] | | | X | At least once per week | | | | | | | | | | | | | | | | |
| Discontinue prior oral antihypertensive medications (if taking) | | X | | | | | | | | | | | | | | | | | | |
| Urine pregnancy test[b] | | X | | X | | | | | | | X | | | | X | X | X | X | X | |
| RAAS biomarkers: renin concentration, aldosterone, AngI/II | | X | | X | | | | X | | | | | | | | | | | | |
| Optional exploratory biomarkers (urine, plasma, serum) | | X | | X | | X | | X | | | X | | | X | X | | | | X | |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Run-in Period[a]** | | **Double-blind Period[a]** | | | | | | | | **OLE Period (Optional)[a]** | | | | | | | | **Safety Follow-up** |
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18** | **M24** | **M30** | **M36/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | | **D-75 to -1** | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **D673±14** | **D841±14** | **D1009±14** | **±14** |
| Randomization to protocol-specified background antihypertensive medication | | X | | | | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication administration | | Daily | | | | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication pill count | | | X | X | | X | X | X | X | X | X | | | | | | | | | |
| Plasma for PK | | | | X | | | | | | | X | | | | | | | | | |
| Immunogenicity (ADA) | | | | X | | | | X | | | X | | | X | X | X | X | X | X | X |
| Serum AGT | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist circumference and waist-to-hip ratio | | | | X | | | | | | | X | | | | X | X | X | X | X | |
| Exploratory DNA sample (optional) | | | | X | | | | | | | | | | | | | | | | |
| Neurologic evaluation[g] and symptom-directed physical exam | | | | | | | | | | | | | | | X | X | X | X | | X |
| Randomization to zilebesiran or placebo | | | | X | | | | | | | | | | | | | | | | |
| Study drug administration (zilebesiran or placebo) | | | | X | | | | | | | X | | | | X | X | X | X | | |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | | | | Safety Follow-up |
| **Study Visit (Month)** | Screening Period | Run-In Visit 1 | Run-In Visit 2 | | W2 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M18 | M24 | M30 | M36/EOT/ET | Q6M post last dose of study drug |
| **Study Day (±Visit Window)** | D-75 to -1 | | | D1 | D15±2 | D29±2 | D57±7 | D85±7 | D113±7 | D141±7 | D169±7 | D197±7 | D225±7 | D253±7 | D337±7 | D505±14 | D673±14 | D841±14 | D1009±14 | ±14 |
| AEs | Continuous | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | | | | | | | | |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; No.=number; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin, aldosterone, and Ang I/II) should be performed before physical examinations and 12-lead ECGs.
- Run-in Visit 2 should occur at least 4 weeks after Run-in Visit 1.
- Patients may have been eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran beginning at the Month 6 visit and continue for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

- Patients will be asked to perform Safety Follow-up visits once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

[b] When applicable, pregnancy test results must be known prior to dosing with study drug at dosing visits.

[c] Laboratory assessments at Day 1 do not need to be repeated, per Investigator discretion, if they were collected within 7 days before Day 1 at Run-in Visit 2.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications or study drug (as applicable).

[e] ABPM recordings associated with study drug dosing visits should be obtained within 7 days before the visit and results reviewed before dosing.

[f] HBPM should be measured at least 3 times during the week prior to the second randomization to establish baseline. After Day 1, HBPM should be measured at least once per week in the morning upon waking and may be increased at the Investigator's discretion if more frequent measurement is warranted. HBPM is not required on days when ABPM is being assessed. In the Safety Follow-up period, the frequency of HBPM assessments can be reduced after the first Safety Follow-up visit per Investigator judgement.

[g] Neurological evaluation will also be performed as part of the full physical examination.

[h] ABPM should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12 and has not had an ABPM within the last 3 months. ABPM should not be performed at Month 36.

## 7.4. Time-Adjusted Change from Baseline

Time-adjusted change from baseline is the area under the curve (AUC) divided by time interval. It leads to a weighted average of all scheduled change from baseline during that time interval.

E.g., ABPM is assessed at Month 2, 3 and 6. Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM is:

1. AUC is calculated as: $\left[\frac{1}{2}(y_2 + y_3) * 1 + \frac{1}{2}(y_3 + y_6) * 3\right]$
2. Time interval is 4 months, from Month 2 to Month 6. AUC divided by time interval is

$$AUC/4 = 0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$$

Where $y_2$, $y_3$ and $y_6$ are the 24-hour mean ABPM at Month 2, 3, and 6.

Table 3 listed all time-adjusted endpoints and the weights of the assessments.

**Table 3 Time-Adjusted Endpoints**

| Time-adjusted Endpoint | Weighted average |
|---|---|
| Time-adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP assessed by ABPM | $0.5 * y_2 + 0.5 * y_3$ |
| Time-adjusted change from baseline through Month 3 in office SBP/DBP | $0.25 * y_1 + 05 * y_2 + 0.25 * y_3$ |
| Time-adjusted change from baseline through Month 6 in 24-hour mean SBP/DBP assessed by ABPM | $0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$ |
| Time-adjusted change from baseline through Month 6 in office SBP/DBP | $0.1 * y_1 + 0.2 * y_2 + 0.2 * y_3 + 0.2 * y_4 + 0.2 * y_5 + 0.1 * y_6$ |

## 7.5. Missing or Partial Dates

### 7.5.1. Prior and Concomitant Medications

For medications with partial start or end dates: the first day/month will be imputed for start date, and the last day/month will be imputed for end date. For medications with a completely missing start date, the medications will be considered as started one day prior to the first dose of study drug. If an imputed start date is after the collected end date, the end date will be used as the imputed start date. For medications with a completely missing end date or an imputed end date that is after the earliest date of: end of study date, data cutoff date or date of death, the latter (i.e., the earliest date of: end of study date, data cutoff date or date of death) will be used as the imputed end date.

### 7.5.2. Adverse Events

For records with fully or partially missing AE onset date, conventions for the imputation is as below:

- AE onset dates with missing day and non-missing month will be imputed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.
- AE onset dates with missing month will be imputed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.
- If year of the AE start date is missing, the onset date will be imputed as the first day of dosing, except if it can be unequivocally determined (from the partial or complete stop date) that the event occurred prior to the first dose of study drug, in which case the AE onset date will not be imputed.
- If an imputed onset date is after the collected AE end date, the end date will be used as the imputed onset date.

### 7.5.3. Others

For other incomplete dates, unless otherwise specified, the following conventions will be used for the calculation of duration (e.g., time in years since diagnosis):

- Missing day: the first day of the month will be used.
- Missing month: the January 1 of the non-missing year will be used.
- Missing year: no duration will be calculated.

# STATISTICAL ANALYSIS PLAN
# ALN-AGT01-003 (KARDIA-2)

| | |
|---|---|
| **Protocol Title:** | A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication |
| **Short Title:** | Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2) |
| **Study Drug:** | Zilebesiran (ALN-AGT01) |
| **Protocol Date:** | Original protocol, 25 August 2021<br>Amendment 1, 22 March 2022<br>Amendment 2, 22 September 2022<br>Amendment 3, 20 July 2023 |
| **SAP Date:** | Original SAP: 29 March 2022<br>Amendment 1, 06 February 2024 |
| **Sponsor:** | Alnylam Pharmaceuticals, Inc.<br>300 Third Street<br>Cambridge, MA 02142 USA<br>Telephone: +1-617-551-8200 |

# APPROVAL SIGNATURE PAGE

**This document has been authored, approved, and signed electronically on the final page by the following:**

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ABPM | Ambulatory blood pressure monitoring |
| ADA | Anti-drug antibody(ies) |
| AE | Adverse event |
| AGT | Angiotensinogen |
| ALT | Alanine aminotransferase |
| AngI/II | Angiotensin I/II |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| DB | Double-blind |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| eDISH | Evaluation of drug-induced serious hepatotoxicity |
| EOT | End of treatment |
| ET | Early termination |
| ECG | Electrocardiogram |
| FAS | Full analysis set |
| HbA1c | Hemoglobin A1c |
| HBPM | Home blood pressure monitoring |
| HLT | High level term |
| IRT | Interactive Response Technology |
| ISR | Injection site reaction |
| LFT | Liver function test |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model for repeated measurements |
| OLE | Open-label extension |
| PD | Pharmacodynamic(s) |

| Abbreviation | Definition |
|---|---|
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| Q6M | Once every 6 months |
| RAAS | Renin-angiotensin-aldosterone system |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |
| SOC | System Organ Class |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantification |

# 1. INTRODUCTION

This statistical analysis plan (SAP) details comprehensive specifications of the efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data summaries and statistical analyses in support of the clinical study report (CSR) for Study ALN-AGT01-003 (KARDIA-2). This SAP version is finalized prior to conducting the analysis of the primary and secondary endpoints measured up to Month 6. Changes to planned analyses specified in this SAP made after database lock will be documented in the CSR.

Table, figure, and listing (TFL) mocked shells and specifications are contained in a separate document.

# 2. STUDY DESIGN

## 2.1. General Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and PD of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. A schematic of the study design is provided in Figure 1.

**Run-in Period**

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1) for at least 4 weeks before Run-in Visit 2 to washout their effects.

**DB Period**

Patients who meet all inclusion/exclusion criteria will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB period as add-on therapy to their protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

Starting at Month 3, additional conventional oral antihypertensives (“escape antihypertensive medications”) may be added to the patient’s protocol-specified background antihypertensive medication per Investigator judgement.

**OLE Period**

After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may have been eligible to participate in a separate zilebesiran OLE study. If an individual patient reached Month 6 prior to availability of the separate OLE study,

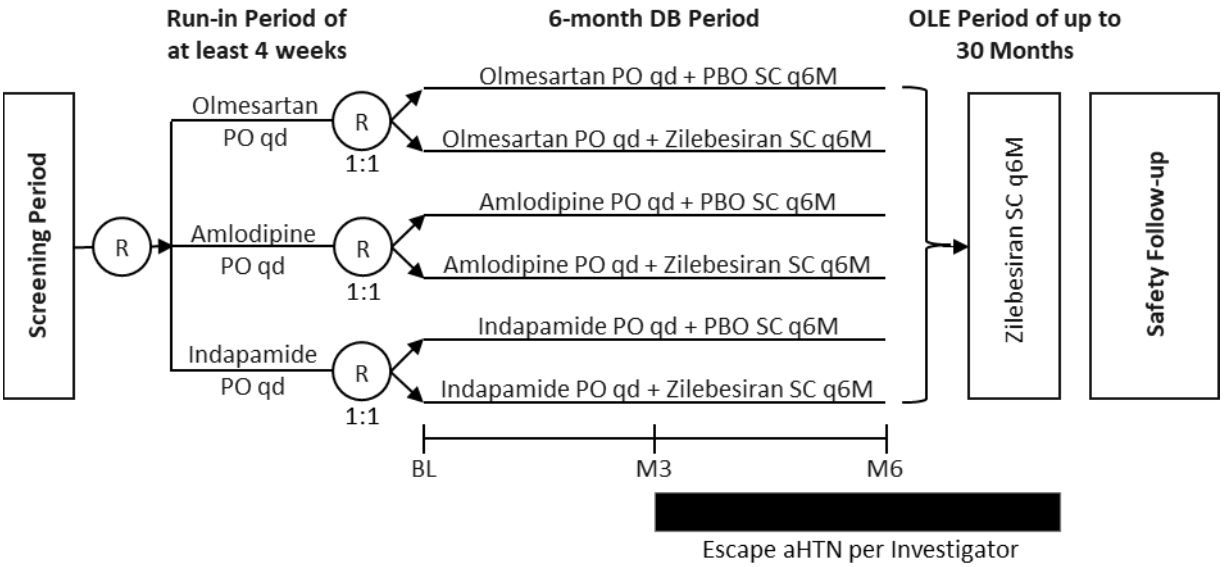
they may have received open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Upon implementation of Protocol Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period. Patients will not receive a dose of study drug at Month 6. Upon completion of predose assessments at the Month 6 visit, patients will enter the Safety Follow-up period. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

**Safety Follow-up Period**

Patients will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During the Safety Follow-up period, patients should return to their pre-study medical care (usual care).

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/early termination (ET) assessments should be performed.

**Figure 1 Study Design**




Abbreviations: aHTN=antihypertensive medication; BL=baseline; DB=double-blind; EOT=end of treatment; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); qd=once daily; q6M=once every 6 months; R=randomization; SC=subcutaneous.
Note: Patients may have been eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran once every 6 months in the OLE period for up to 30 additional months during the OLE period until the OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6 month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period. Patients who were previously taking antihypertensives at screening should discontinue these medications at Run-in Visit 1.

## 2.2. Objectives and Endpoints

The following objectives will be evaluated separately for each protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide).

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3 | • Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM |
| Secondary | |
| Through Month 6<br>• To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM<br>• To evaluate the add-on effect of zilebesiran on office blood pressure<br>• To characterize the PD effects of zilebesiran | Key Secondary Endpoints<br>• Change from baseline at Month 3 in office SBP<br>• Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM<br>• Time-adjusted change from baseline through Month 6 in office SBP<br>• Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6<br>Other Secondary Endpoints<br>• Change in 24-hour mean SBP and DBP, assessed by ABPM<br>• Change in office SBP and DBP<br>• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM<br>• Change in serum AGT |
| Exploratory | |
| • To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6) | • Office blood pressure and ABPM control and response rates<br>• Proportion of patients requiring treatment with escape antihypertensive medications<br>• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure<br>• Change in SBP and DBP from baseline assessed by HBPM |
| • To characterize the plasma PK of zilebesiran | • Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran |
| • To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication) | • Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII |

| Objectives | Endpoints |
|---|---|
| • To evaluate the immunogenicity of zilebesiran | • Incidence and titers of ADA |
| • To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements | • Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio |
| • To assess the effect of zilebesiran on metabolic syndrome parameters | • Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile |
| • To characterize the PD effects of zilebesiran (after Month 6) | • Change in serum AGT |
| • To assess the long-term treatment effect of zilebesiran (through Month 36) | • Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM |
| Safety | |
| • To evaluate the safety of zilebesiran in patients with hypertension | • Frequency of AEs |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; HbA1c=hemoglobin A1c; HBPM=home blood pressure monitoring; HOMA= homeostatic model assessment; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

## 2.3. Study Procedure

The Schedule of Assessments is provided in Table 2.

## 2.4. Randomization Methodology

At Run-in Visit 1, patients with screening eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be assigned to receive olmesartan. To avoid over-enrollment, patients with eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be excluded from the study after 100 such patients are randomized to study drug on Day 1.

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 2.6. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

At Day 1, patients will be randomized 1:1 to receive zilebesiran or placebo as an add-on to their protocol-specified background antihypertensive medication using the IRT. Randomization at Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

## 2.5. Blinding

The Sponsor, all site personnel and patients will be blinded to study drug treatment through Month 3 of the 6-month DB period. After the interim analysis at Month 3 is complete, Sponsor staff members who will not have direct roles or responsibilities in interacting with study sites may be unblinded to the analysis results according to the prespecified blinding plan. Site personnel, patients, and Sponsor staff members who have direct roles or responsibilities in interacting with study sites will remain blinded to both Month 3 interim analysis results and treatment assignment until after the analysis of Month 6 data is complete. All Sponsor and site personnel and patients will be blinded to any clinical laboratory result that could potentially unblind them (e.g., AGT levels) until treatment assignment unblinding.

Details about the specifics of the blinding aspects throughout the entire study are available in the Randomization and Blinding Plan.

Any unplanned/emergency unblinding occurring during the DB Period will be documented and reported in the CSR.

Refer to the study Randomization and Blinding Plan for more details.

## 2.6. Determination of Sample Size

Approximately 630 patients will be randomized to receive either zilebesiran or placebo, with sample sizes in each of the patient cohorts with protocol-specified background antihypertensive medication as follows:

- Olmesartan cohort: 300 patients
- Amlodipine cohort: 210 patients
- Indapamide cohort: 120 patients

Assuming a common standard deviation of 16 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM and 15% dropout rate from baseline to Month 3, with 2-sided significance level of 0.05 for each of the comparisons (zilebesiran versus placebo as add-on to olmesartan; zilebesiran versus placebo as add-on to amlodipine; zilebesiran versus placebo as add-on to indapamide), these sample sizes will provide at least 80% power to detect the following difference between zilebesiran versus placebo:

- 5 mmHg as add-on to olmesartan
- 6 mmHg as add-on to amlodipine
- 8 mmHg as add-on to indapamide

The power is assessed by mixed model with repeated measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

# 3. ANALYSIS POPULATIONS

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug. All by-treatment analyses based on the Safety Analysis Set will be grouped according to the treatment actually received.
- PK Analysis Set: All patients who received at least 1 full dose of zilebesiran and have at least 1 non-missing post-dose PK assessment.
- PD Analysis Set: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- All Zilebesiran Treated Set: All patients who received any amount of zilebesiran, including patients who took zilebesiran during the 6-month DB period, and patients who initially took placebo and then switched to zilebesiran after Month 6 Visit.

For the analyses for 6-month DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All Zilebesiran Treated Set will be used to summarize the efficacy and safety of zilebesiran throughout the 6-month DB period and the OLE period.

PPD CCI
CCI PPD . CCI

## 3.1. Randomization and Treatment Errors

The study has two randomizations. The first randomization is to assign patients to receive one of the three protocol specified background antihypertensive medications. The second randomization is to randomize patients to receive either zilebesiran or placebo on top of each background antihypertensive medication. This section mainly focuses on the second randomization.

For patients who were not treated, not randomized, or received incorrect treatment, the following rules will be used:

- Randomized but not treated: they will be excluded from the FAS and Safety Analysis Set for efficacy and safety evaluations as actual treatment is missing.
- Treated but not randomized: they will be excluded from the efficacy analyses since randomized treatment is missing but will be reported under the treatment actually received for all safety analyses.
- Randomized but took incorrect treatment: they will be reported under their randomized treatment arm for all efficacy analyses. But for safety analyses, a patient

will be reported under the active treatment arm if the patient is randomized to placebo arm and received a dose of zilebesiran by mistake.

# 4. GENERAL STATISTICAL CONSIDERATIONS

## 4.1. General Considerations

In general, data will be summarized for each planned analysis defined in Section 4.7 separately. All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts.

Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the following descriptive summary statistics: number of patients (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

Study drug is zilebesiran 600mg or placebo.

The day of the first dose of study drug administered is defined as Day 1. The Study Day of a time point of interest is calculated as follows:

- If on or after Day 1, Study Day = date of interest – date of the first dose of study drug + 1
- If prior to Day 1, Study Day = date of interest – date of the first dose of study drug

There is no Day 0. For example, the day before the first study drug dose is defined as Day -1.

For laboratory parameters, assessments collected and recorded as lower than the lower limit of quantification/detection (LLOQ) will be replaced by the LLOQ. Any assessment collected and recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

All descriptive summaries will be presented by treatment arm.

Statistical analyses will be conducted using SAS software Version 9.4 or newer or R version 3.6 or newer.

## 4.2. Blood Pressure Collection and Handling

### 4.2.1. 24-Hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure monitoring (ABPM) is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 4 days.

To summarize the 24-hour ABPM, hourly adjusted mean will be calculated. Hourly adjusted mean will be calculated by two steps:

1. Calculate the hourly mean of BP by each hour of the day (e.g., mean of BP measurements from 16:00 to 16:59). If there is no reading in a specific hour, this hourly mean will be considered as missing.
2. Calculate the 24-hour mean SBP/DBP, daytime and nighttime means of the SBP/DBP based on the hourly means.

### 4.2.2. Office Blood Pressure

The office BP in the sitting position will be used for the analysis. Office BP will be collected with a set of 4 replicates. The average of the last 3 replicates will be calculated and used for analysis. Office BP collected in standing position will be listed only.

### 4.2.3. Home Blood Pressure Monitoring

Home blood pressure will be measured both pre and post randomization. To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization. After Day 1, HBPM will be measured at least once per week. Four sequential blood pressure measurements at 1-minute intervals will be recorded. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements. HBPM will be summarized by weekly average.

Details of the blood pressure collection are in Study Protocol Section 10.

## 4.3. Multiple Comparison/Testing Procedure

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. To control the overall Type I error at $\alpha$=0.05 within each cohort, the primary endpoint and the key secondary endpoints will be tested in hierarchical order.

**Table 1 Multiplicity Procedure**

| Test Step[a] | Endpoint | Success criteria |
|---|---|---|
| 1 | Primary: Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 2 | Key secondary: Change from baseline at Month 3 in office SBP | Nominal p-value < 0.05 |
| 3 | Key secondary: Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 4 | Key secondary: Time-adjusted change from baseline through Month 6 in office SBP | Nominal p-value < 0.05 |
| 5 | key secondary: Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication at Month 6 | Nominal p-value < 0.05 |

[a] If the success criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant

## 4.4. Handling of Missing Data

No imputation will be done for missing values for the primary analysis of the primary endpoint. A sensitivity analysis of the primary endpoint will be performed (details described in Section 5.7.1.3). For all analyses using mixed model repeated measures, no explicit imputation of missing values will be done.

## 4.5. Baseline Definitions

For the analyses of 6-month DB period, for office BP, baseline is the average of the office BP value on Day 1 prior to receiving the first dose of study drug and last non-missing value prior to Day 1 during run-in period. For 24-hour ABPM, baseline is the measurement used for eligibility for randomization to study drug. For HBPM, baseline will be the average of all assessments during the last week prior to receiving the first dose of study drug. For all other endpoints, baseline is the last non-missing value (including unscheduled visit) prior to receiving the first dose of study drug.

For the final analyses, patients initially randomized to placebo and switched to zilebesiran at Month 6 will be summarized in two ways:

- From Day 1. Baseline is the same as the one for the primary analysis.
- From the start of zilebesiran dosing at Month 6. Baseline will be the last assessment prior to Month 6 dosing.

For patients initially randomized to zilebesiran, baseline remains the same as the one for the primary analysis.

## 4.6. Randomization Stratification Factors

Stratification factors are recorded in the IRT database. Key data is integrated into the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database (EDC). In the presence of stratification errors, the stratification used in analysis may not match that in the IRT. A comparison of the number and percentage of patients in each randomization stratification factor in IRT versus the clinical database will be summarized by randomized treatment arm and overall.

## 4.7. Planned Analyses and Data Cutoffs

### 4.7.1. Month 3 Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be performed prior to the primary database lock at the end of the double-blind period. Additional details regarding the interim analysis will be documented in the study Data Management Plan and Month 3 Interim Statistical Analysis Plan for the Month 3 interim analysis.

The analysis will include data on, or prior to, this prespecified cutoff date. For assessments with starting/ending dates (e.g., adverse events [AEs], medications), the starting date will be compared with the pre-specified cutoff date. Data records with starting dates after the specified data cutoff date will be excluded.

### 4.7.2. Month 6 Analysis

The analysis after the end of double-blind period is the Month 6 analysis. The protocol-specified primary, secondary, exploratory and all other pre-specified analysis will be performed after all randomized patients have completed the Month 6 Visit or otherwise withdrawn from the study.

The database will undergo an primary database lock, and the data will be summarized in a CSR.

### 4.7.3. Final Analysis

After all patients reach the end of the study or otherwise withdrawn from the study, the database will undergo a final database lock, and the data will be summarized in a CSR.

A patient is considered to have reached the end of the study if the patient has completed the safety follow-up visits.

# 5. STATISTICAL ANALYSES

## 5.1. Patient Disposition

The number and percentage of patients in the following categories will be summarized by randomized treatment arm and overall:

- Randomized to study drug
- Treated with study drug
- Completed the 6-month double-blind (DB) treatment period
- Withdrawal from study and primary reason for withdrawal from study during 6-month DB period.

The number and percentage of patients that entered into the OLE and/or safety follow up period will be summarized in the following categories:

- Entered into OLE period
- Entered into Safety FU period
- Completed the study
- Withdrawal from study and primary reason for withdrawal from study
- Ongoing
- Discontinued from study drug and primary reason for discontinuation from study drug.

In addition to the primary reason for discontinuation of study drug and withdrawal from study, patients will also be categorized if discontinuation/withdrawal was due to COVID-19.

Screen failures and run-in failures will also be summarized.

## 5.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for Full Analysis Set, and also presented in listings.

Age at consent, height, weight, body mass index (BMI), 24-hour ABPM, OBP, and urine albumin-to-creatinine ratio will be summarized using descriptive statistics. Sex, race, ethnicity, country, eGFR, and diabetes mellitus status will be summarized by presenting the frequencies and percentages of patients in each category.

## 5.3. Medical History

Medical history and prior procedures reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0 or newer. Unique patients who report medical history events will be summarized by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). Medical history and prior procedures will also be presented in listings.

## 5.4. Protocol Deviations

Protocol deviations will be classified by medical review prior to each planned analysis database lock, and major protocol deviations will be identified. A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being. (ICH E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry, 2013).

The Sponsor or designee will be responsible for producing the protocol deviation file. This file will include a description of each protocol deviation and classification as major or minor. The protocol deviations will be reviewed and finalized prior to the planned analysis database lock.

All protocol deviations and major protocol deviations will be summarized and listed.

## 5.5. Study Drug Exposure and Compliance

The following variables will be summarized by descriptive statistics and/or frequency tabulation:

- Duration of exposure, defined as: date of last exposure – date of first dose of study drug +1. Date of last exposure is the earliest date of the following:
  - date of last dose of study drug + the length of dosing interval (169 days)
  - date of end of study
  - date of analysis data cutoff
- Number of doses received; as continuous and/or categorical variable
- Number of missed doses; as a categorical variable

## 5.6. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version WHO-DD Global B3, March 2023 or newer. Unique patients who reported medications

will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class (or level 2 if not available) and PT. Summaries will be provided for prior and concomitant medications separately. Summaries by ATC and PT will also be provided for both prior and concomitant anti-hypertensive medications.

The proportion of patients with escape antihypertensive medication at each visit, will also be provided by treatment group.

Prior medications are those medications with start date prior to the first dose of study drug.

Concomitant medications are medications, other than the study drug or protocol-specified background antihypertensive medication, administered at or after the first dose of study drug, as well as medications that started prior to the first dose of study drug and are ongoing after the first dose of study drug.

Escape antihypertensive medication is defined as any antihypertensive medication other than background medication (by ATC codes) that were started after the first dose; or background medication with dose increased to be higher than the baseline level.

Protocol-specified background antihypertensive medication, not identified as escape antihypertensive medication, will be excluded from analysis of prior and concomitant medications.

If the medication start date is on or after the date of first dose of study drug, the medication will be summarized as a concomitant medication even if the medication end date is missing.

If the end date of a medication is missing or incomplete, such that it cannot be determined whether it is after the first dose of study drug, it will be counted as a concomitant medication.

For missing or partial dates for medications, the imputation of start and end dates is described in Section 7.4.

Background Medication Compliance

Compliance to background medication (%): (number of tablets returned – number of tablets dispensed) divided by number of expected tablets taken x 100.

Number of expected tablets is the number of days that a patient should be taking background medication during a specific period (Run-in period and 6 month double blind period).

## 5.7. Efficacy Analyses

### 5.7.1. Primary Endpoint

#### 5.7.1.1. Definition of Estimand

The primary objective of the study is to evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3. Primary estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)

- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint: Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
- Population-level summary: Least square mean difference between zilebesiran and placebo in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, on top of each background antihypertensive medication
- Intercurrent events strategy: Hypertensive escape medication taken before Month 3 visit will be considered as an intercurrent event. For patients who require escape antihypertensive medication, given the expected number of such patients at Month 3 is low, hypothetical strategy will be used, i.e., ABPM assessed while patients are on and within 2 weeks after stopping any escape antihypertensive medication will be excluded for analysis. This will provide the estimated treatment effect of zilebesiran compared with placebo on top of each background antihypertensive medication.

#### 5.7.1.2. Primary Analysis

For each background antihypertensive medication cohort, the hypothesis to be tested for the primary endpoint is:

- $H_0$: $\mu_1 = \mu_0$ (there is no add-on effect of zilebesiran)
- $H_a$: $\mu_1 \neq \mu_0$ (there is add-on effect of zilebesiran)

where $\mu_0$ and $\mu_1$ are the mean change from baseline at Month 3 in 24-hour mean SBP in placebo and zilebesiran arm, respectively.

MMRM model will be used as primary analysis. The model will include treatment, visit, treatment-by-visit, and race (black, all other races) as fixed factors; baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. The LS mean coefficients will be computed using the observed proportion of black patients within each cohort, for all analysis of the primary endpoint as well as all analyses of secondary endpoints using a similar MMRM model.

#### 5.7.1.3. Sensitivity Analyses

For the sensitivity analysis, treatment policy strategy will be used for patients who require escape antihypertensive medication. All collected blood pressure measurements will be analyzed by the same MMRM model as the primary analysis, regardless of the hypertensive escape medication.

Due to the expected long-acting effect of zilebesiran, the commonly used control-based Pattern Mixture Model (PMM) will not be used to assess the missing not at random (MNAR) assumption.

#### 5.7.1.4. Other Analyses

Change from baseline at Month 3 and at Month 6 in SBP assessed by ABPM at each clock hour will be plotted for each treatment group.

### 5.7.2. Secondary Endpoints

#### 5.7.2.1. Key Secondary Endpoints

Secondary objectives of the study are to evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM and office blood pressure through Month 6. The estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)
- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint:
  - Change from baseline at Month 3 in office SBP
  - Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM
  - Time-adjusted change from baseline through Month 6 in office SBP
  - Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication
- Population-level summary:
  - Least square mean difference between zilebesiran and placebo of the change from baseline in SBP on top of each background antihypertensive medication.
  - Odds ratio for BP response rate.
- Intercurrent events strategy:
  - For Month 3 endpoint: Given the expected number of such patients at Month 3 is low, hypothetical strategy will be used.
  - For Month 6 endpoint: Protocol allows escape antihypertensive medication from Month 3 through Month 6. Given the expected proportion of such patients may be large, the treatment policy strategy will be used.

Time-adjusted change is defined as the area under the curve (AUC) of BP change from baseline divided by the duration of the time period. It leads to the weighted average of change from baseline to each scheduled visit. Details of the definition and calculation are in Section 7.4.

Multiplicity adjustment will be applied across primary and the key secondary endpoints. Details of multiplicity control are in Section 4.3.

MMRM model will be used as the primary analysis. The model will include treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, baseline eGFR and corresponding baseline BP as covariates. Least square (LS) mean difference, 95% CI and p-value will be generated.

For the proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6, logistic regression will be used. The model will include treatment as a factor, baseline 24-hour mean SBP and baseline eGFR as covariates.

Sensitivity analysis for secondary endpoints using MMRM will also be evaluated.

- For Month 3 endpoint: treatment policy strategy will be used for patients who require escape antihypertensive medication. All collected blood pressure measurements will be analyzed.
- For Month 6 endpoint: hypothetical strategy will be used for patients who require escape antihypertensive medication. Blood pressure measurements while patients are on and within 2 weeks after stopping any escape antihypertensive medication will be excluded for analysis.

#### 5.7.2.2. Other Secondary Endpoints

Other blood pressure related secondary endpoints are:

- Change from baseline at Month 3 in 24-hour mean DBP, assessed by ABPM
- Change from baseline at Month 3 in office DBP
- Time adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP, assessed by ABPM
- Time adjusted change from baseline in office SBP/DBP through Month 3
- Change from baseline at Month 6 in 24-hour mean SBP/DBP, assessed by ABPM
- Change from baseline at Month 6 in office SBP/DBP
- Time adjusted change from baseline through Month 6 in 24-hour mean DBP, assessed by ABPM
- Time adjusted change from baseline through Month 6 in office DBP
- Change from baseline in daytime/nighttime SBP and DBP by ABPM by each visit. Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

In general, the BP related endpoints will be summarized using all collected BP data regardless of the use of escape antihypertensive medication. The same MMRM model will be used with treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, corresponding baseline as a covariate. Least square (LS) mean difference of each zilebesiran dose group compared with placebo dose group, 95% CI and p-value will be generated.

The secondary endpoint of percent change in serum AGT at each visit will be summarized using descriptive statistics.

### 5.7.3. Exploratory Endpoints

The blood pressure related exploratory endpoints through Month 6 are:

- BP response rate by each visit, defined as

  - Office SBP < 140 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication
  - 24-hour mean DBP assessed by ABPM < 85 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
  - Office DBP < 90 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
- Proportion of patients with escape antihypertensive medication use by each visit
- Change from baseline in pulse pressure by each visit, assessed by ABPM and office BP
- Change from baseline in SBP/DBP by HBPM

To assess the long-term treatment effect of zilebesiran through Month 36, change from baseline in SBP/DBP assessed by ABPM, office BP and HBPM will be summarized.

Body weight, metabolic related exploratory endpoints are:

- Change from baseline in body weight/body mass index (BMI)/waist circumference/waist-to-hip ratio by each visit
- Change from baseline in HbA1c/fasting glucose/insulin/serum lipids by each visit.

Exploratory endpoints will be summarized using descriptive statistics based on all observed data. Missing data will not be imputed.

### 5.7.4. Evaluation of Subgroups

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age (<65; >=65)
- Sex (male; female)
- Race (black; all other races)
- Baseline 24-hour mean SBP assessed by ABPM (<145 mmHg; >=145 mmHg)
- Baseline eGFR (<60; >=60 mL/min/1.73 $m^2$)
- Baseline BMI (<30; >=30 $kg/m^2$)
- Diabetes Mellitus Status (Yes; No)
- For Olmesartan only: Run-in Visit 1 plasma renin concentration (<= Run-in Visit 1 median; > median).

Subgroup analyses will be performed for the primary endpoint and key-secondary endpoints using the MMRM within each subgroup. Model will include treatment, visit, treatment-by-visit interaction, race ([black, all other races], when race is not the subgroup to be analyzed) as fixed factors, baseline eGFR and corresponding baseline BP measurement as covariates. The LS mean coefficient of race will be computed using the observed proportion of black patients within each cohort. Point estimate of treatment effect and 95% confidence interval are to be generated for

each subgroup. A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

## 5.8. Pharmacodynamic Analyses

In addition to serum AGT, the PD parameters include plasma renin concentration, aldosterone, AngI and AngII. Summary tables may be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group. In addition to serum AGT percent reduction analyses, the AGT maximum and mean percentage reductions over the 6-month DB period will be summarized using descriptive statistics.

## 5.9. Pharmacokinetic Analyses

Plasma concentrations of zilebesiran and its metabolite will be summarized descriptively. Descriptive statistics for zilebesiran and its metabolite plasma concentrations will include the number of patients, mean, SD, coefficient of variation, geometric mean, geometric mean coefficient of variation, median, minimum, and maximum.

Additional analysis may be done as needed.

## 5.10. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any time during the 6-month DB period, as well as treatment-emergent ADA during the OLE period, will be summarized. Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, as defined below:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

## 5.11. Safety Analyses

### 5.11.1. Adverse Events

Adverse events (AEs) will be classified by the MedDRA coding system (Version 26.0 or newer) and displayed in tables and data listings using SOC and PT.

Treatment-emergent AEs (TEAEs) will be summarized for the 6-month DB period and for the duration of zilebesiran exposure (defined in Section 5.5) separately.

For the 6-month DB period, TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and through Month 6 Visit (prior to Month 6 dosing). For AE occurring in the OLE period, TEAE is defined as any AE occurring or worsening on or after the last dose of study drug up to 6 months after last dose. Treatment related AEs that occur after 6-months are also counted as TEAE.

AEs that occurred or worsened during safety follow-up period will be listed and may be summarized if needed.

Because any worsening AE is reported as a new AE with higher severity, programmatical comparison of severity is not needed for the classification of TEAE. For missing or partial dates for AEs, the imputation of start and end date can be found in Section 7.4. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first dose of study drug.

AEs will be summarized by the numbers and percentages of patients reporting a given AE. An overall table of TEAEs will include:

- any AE,
- any AE related to study drug,
- any serious AE (SAE),
- any SAE related to study drug,
- any AE leading to study drug interruption,
- any study-drug related AE leading to study drug interruption,
- any AE leading to study drug discontinuation,
- any study-drug related AE leading to study drug discontinuation,
- any AE leading to withdrawal from study,
- any study-drug related AE leading to withdrawal from study,
- any AE leading to death.

Tabulations by SOC and PT will be produced for the following:

- AEs,
- Study-drug related AEs,
- AEs by maximum severity,
- Study-drug related AEs by maximum severity,
- Severe AEs,
- SAEs,
- AEs leading to treatment discontinuation.

Tabulations by PT will be produced for the following:

- AEs,
- Study-drug related AEs,
- SAEs.

AEs and AEs related to study-drug will also be summarized by maximum severity.

A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Patients who report multiple occurrences of the same AE (preferred term) will be classified

according to the most severe occurrence. An AE with missing severity will be assumed to be severe. An AE with missing study drug relatedness will be assumed to be related.

Listings of all deaths (if any), SAEs, and AEs leading to treatment discontinuation will be provided.

In addition, AE during run-in period will be listed by each background antihypertensive medication cohort.

AEs of Clinical Interest

AEs of special interest or AEs mapping to certain standardized MedDRA queries (SMQs) will be summarized by SOC and PT. Other SMQs or AE groupings may be evaluated.

**Injection Site Reactions [ISRs]**: AEs mapping to the High-Level Term (HLT)= "Injection Site Reactions" using MedDRA dictionary will be included in the summary. Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. In addition, a table of the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose), total number of doses with ISRs and corresponding % of injections with ISR with the most common signs and symptoms reported due to ISRs will be generated.

**Hepatic AEs, including Liver Function Test (LFT) abnormalities**: Analysis of hepatic AEs will include AEs mapping to the Standardized MedDRA Query (SMQ) Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms).

**Acute renal failure** AEs will include AEs mapping to the Standardized MedDRA Query (SMQ) Acute renal failure - comprehensive search (includes all narrow and broad terms). The adjudicated renal events including severity assessments will be summarized or listed.

**Hyperkalemia** AEs will be through Customized MedDRA Query (CMQ) search. PT terms are listed in Section 7.2.

**Hypotension** AEs include AEs mapping to the FDA Medical Queries (FMQ) hypotension search (includes narrow terms), and additional terms potentially related to hypotension. List of additional terms is in Section 7.2.

Frequency (percentages) of these AEs will be summarized by SOC and PT. Separate listings will be generated of all patients reporting these events.

All AEs will be presented in patient data listings. AEs mapping to the SMQs as described above will also be listed.

Additional summaries of AEs mapping to a COVID-19 custom query are described in Section 5.13.2.

### 5.11.2. Laboratory Data

Clinical laboratory values will be expressed in SI units. Missing laboratory data will not be imputed.

For each continuous clinical laboratory parameter (including hematology, serum chemistry, liver function tests and coagulation studies), descriptive statistics will be presented for the actual

values, change from baseline, and percent change from baseline by visit. These by-visit tables will use central laboratory data only.

Select clinical laboratory parameters may be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or above. Shift summary from baseline CTCAE grade to maximum (worst) post-baseline grade will be presented for all graded parameters with directionality specified (e.g., hyper or hypo). To determine the worst post-baseline value, all scheduled and unscheduled test results will be used. For hematology and serum chemistry, frequency tables of potentially clinically significant (PCS) abnormalities will be provided.

All laboratory data (both central and local) will be provided in data listings. Out-of-range laboratory results will be presented in a separate listing with proper flags. Local laboratory data, if available, will also be flagged.

Liver Function Tests

A frequency table and a shift table will be produced to summarize the number and percentage of patients in each of the below categories at any post-baseline time point.

- ALT >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALP > 1.5×ULN,
- Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN

In separate evaluation of drug-induced serious hepatotoxicity (eDISH) figures, the peak total bilirubin (as multiple of ULN) at any time post-baseline will be plotted against the peak ALT, AST, ALT or AST level and at any time post-baseline.

A listing for all patients with abnormal liver function tests, defined as an ALT >3×ULN, AST >3×ULN, or total bilirubin >2×ULN at any time point, will also be provided.

Renal function

Estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine (SCr) based on the Modification of Diet in Renal Disease (MDRD) Formula:

- Conventional units – eGFR (mL/min/1.73 $m^2$) = 175 × (SCr[mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ and (× 0.742, if female) and (× 1.212, if African American)
- SI units – eGFR (mL/min/1.73 $m^2$) = 175 × (SCr[µmol/L]/88.4)$^{-1.154}$ × (age)$^{-0.203}$ and (× 0.742, if female) and (× 1.212, if African American)

The eGFR will be categorized into the following categories: ≥90, 60-89, 30-59, 15-29 and <15. A shift table of baseline to worst post-eGFR (i.e. category with the lowest value) will be presented according above categories.

Serum Potassium

Potassium lab values will be categorized into the following categories: <=4.5, >4.5 to <=5.0, >5.0 to <=5.5, >5.5 to <=6.0 & >6.0 (mmol/L). A shift table of baseline to worst post-baseline potassium (i.e. category with the highest value) will be presented. Patients with at least one post baseline potassium value >5.5 and >6.0 (mmol/L) will also be summarized.

### 5.11.3. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm and overall interpretation.

Post-baseline overall interpretation (normal vs. abnormal) will be summarized in frequency table by treatment and visit.

All ECG data for each patient will be provided in a data listing.

### 5.11.4. Vital Signs

For vital signs except blood pressure, descriptive statistics for actual values and change from baseline by visit will be provided for each variable. Vital sign measurements will be presented by treatment and patient ID in a data listing, with abnormal vital signs flagged.

### 5.11.5. Evaluation of Subgroups

AE summary tables will be separately generated for each of the subgroups as defined for the primary efficacy endpoint (except for baseline BP, see Section 5.7.4).

## 5.12. Interim Analysis

An analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted prior to the primary database lock by a small group of designated people who will not have direct roles or responsibilities in interacting with study sites. No formal interim analysis is planned before the analysis at Month 3 (see Section 4.7.1).

## 5.13. COVID-19

Additional data are collected to characterize the impact of the COVID-19 pandemic on general study conduct and disposition, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidance (including FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

### 5.13.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 5.1.

Impact on study participation due to COVID-19 will be presented in data listings.

### 5.13.2. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will be presented. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

AEs mapping to the COVID-19 custom query will also be presented in a data listing.

# 6. CHANGES FROM PLANNED ANALYSES

Original SAP

| Section of the SAP | Summary of change from protocol | Rationale |
|---|---|---|
| | — | — |

Amendment 1

| Section of the SAP | Summary of change from original SAP | Rationale |
|---|---|---|
| Section 1 | SAP finalization has been changed to prior to treatment unblinding for Month 6 analysis from Month 3 analysis | Additional SAP was created for Month 3 Interim analysis. |
| Section 2.1 | Updated OLE Period definition, Safety Follow-up Period definition and study design figure | Updates from protocol amendment. |
| Section 2.2 | Updated Exploratory objective "To assess the long-term treatment effect of zilebesiran" (Changed from Month 18 to Month 36) | Updates from protocol amendment. |
| Section 2.5,<br>Section 4.7.1,<br>Section 5.12 | Updated text around the month 3 analysis | Additional SAP was created for Month 3 Interim analysis. |
| Section 3 | PPD CCI [redacted] | CCI [redacted] PPD<br>PPD . |
| Section 5.1 | Split Patient Disposition into two sections<br>• Six-month double-blind period<br>• OLE/Safety Follow up period | Protocol removed the OLE period and OLE study. New summarizes required for study complexity. |

| Section of the SAP | Summary of change from original SAP | Rationale |
|---|---|---|
| Section 5.2 | Included urine albumin-to-creatinine ratio and diabetes mellitus status | Requested by study team. |
| Section 5.5 | Compliance is calculated as a percentage of the number of tablets taken over expected number of tablets. | Requested by study team. |
| Section 5.6 | Added analysis for prior and concomitant anti-hypertensive medications and definitions of escape medications | Requested by study team. |
| Section 5.6 | Clarified that background medication should not be included in Prior and Concomitant Medications analysis | Requested by study team. |
| Section 5.7.1.2, Section 5.7.4 | Added texted about model correction for observed proportion of black patients | Model was updated to use observed proportion of black patients within the study. |
| Section 5.7.2.1 | Added baseline eGFR as a covariate to logistic regression | Covariate added to match MMRM analysis covariates. |
| Section 5.7.2.1 | Added sensitivity to key secondary endpoints | Requested by study team. |
| Section 5.7.4 | Added additional subgroups of baseline BMI and Run-in 1 Plasma renin Concentration | Requested by study team. |
| Section 5.11.1 | Added text for TEAE during OLE period | Requested by study team. |
| Section 5.11.1 | Added additional AECI of Acute renal failure, Hyperkalemia, and Hypotension | Requested by study team. |
| Section 5.11.2 | Added section for Renal Function and Serum Potassium | Requested by study team. |
| Section 5.13.1 | Updated to only include listing for COVID-19 impact | Limited data is collected on COVID-19 impact. |

# 7. APPENDICES

## 7.1. List of Escape Antihypertensive Medication ATC Code

The ATC codes for escape medications are:

- C02 - Antihypertensives
- C03 - Diuretics
- C07 - Beta blocking agents
- C08 - Calcium channel blockers
- C09 - Agents acting on the renin-angiotensin system

## 7.2. Preferred Terms for Hyperkalemia and Potentially Related to Hypotension

Hyperkalemia:

| |
|---|
| Hyperkalemia |
| Blood potassium increased |
| Blood potassium abnormal |

Potential Hypotension:

| |
|---|
| Blood pressure fluctuation |
| Labile blood pressure |
| Orthostatic intolerance |
| Circulatory collapse |
| Distributive shock |
| Dizziness |
| Dizziness exertional |
| Dizziness postural |
| Hypoperfusion |
| Peripheral circulatory failure |
| Presyncope |
| Procedural shock |
| Shock |
| Shock symptom |
| Syncope |
| Cardiovascular insufficiency |
| Hypotensive crisis |
| Hypotensive transfusion reaction |
| Orthostatic hypotension |
| Vasolplegia syndrome |
| Blood pressure abnormal |
| Blood pressure ambulatory abnormal |
| Blood pressure ambulatory decreased |
| Blood pressure diastolic abnormal |
| Blood pressure immeasurable |
| Blood pressure orthostatic abnormal |
| Blood pressure orthostatic decreased |
| Blood pressure systolic decreased |
| Blood pressure systolic inspiratory decreased |
| Mean arterial pressure decreased |
| Loss of consciousness |

## 7.3. Protocol Schedule of Assessments

Schedule of assessments are listed in Table 2.

## Table 2 Schedule of Assessments

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Run-in Period[a]** | | **Double-blind Period[a]** | | | | | | | | **OLE Period (Optional)[a]** | | | | | | | | **Safety Follow-up** |
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18** | **M24** | **M30** | **M36/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | **D-75 to -1** | | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **D673±14** | **D841±14** | **D1009±14** | **±14** |
| Informed consent | X | | | | | | | | | | | | | | | | | | | |
| Assign patient identification no. | X | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | | | | | | |
| Serum pregnancy test/FSH screening | X | | | | | | | | | | | | | | | | | | | |
| Creatinine clearance | X | | | | | | | | | | | | | | | | | | | |
| Full physical exam | X | | | X | | | | | | | X | | | | | | | | X | |
| Height and BMI | | | | X | | | | X | | | X | | | X | X | X | X | X | X | |
| Body weight | X | | X | X | | | | X | | | X | | | X | X | X | X | X | X | |
| Single 12-Lead ECG | X | | | X | | | | | | | X | | | | X | X | X | X | X | |
| Serum chemistry[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | | | | Safety Follow-up |
| **Study Visit (Month)** | Screening Period | Run-In Visit 1 | Run-In Visit 2 | D1 | W2 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M18 | M24 | M30 | M36/EOT/ET | Q6M post last dose of study drug |
| **Study Day (±Visit Window)** | D-75 to -1 | | | D1 | D15±2 | D29±2 | D57±7 | D85±7 | D113±7 | D141±7 | D169±7 | D197±7 | D225±7 | D253±7 | D337±7 | D505±14 | D673±14 | D841±14 | D1009±14 | ±14 |
| Hematology, urinalysis, coagulation[c] | X | | X | X | | | | X | | | X | | | X | X | X | X | X | X | X |
| LFTs[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| Spot urine for albumin and creatinine[c] | X | | X | X | | | | X | | | X | | | | X | X | X | X | X | |
| Fasting plasma glucose, insulin, lipid panel, and HbA1c[c] | X | | X | X | | | | X | | | X | | | | X | | | | X | |
| Vital signs and office blood pressure[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 24-hour ABPM[e] | | | X | | | | X | X | | | X | | | X | X | | | | X[h] | |
| HBPM[f] | | | X | At least once per week | | | | | | | | | | | | | | | | |
| Discontinue prior oral antihypertensive medications (if taking) | | X | | | | | | | | | | | | | | | | | | |
| Urine pregnancy test[b] | | X | | X | | | | | | | X | | | | X | X | X | X | X | |
| RAAS biomarkers: renin concentration, aldosterone, AngI/II | | X | | X | | | | X | | | | | | | | | | | | |
| Optional exploratory biomarkers (urine, plasma, serum) | | X | | X | | X | | X | | | X | | | X | X | | | | X | |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | | | | Safety Follow-up |
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | **D1** | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18** | **M24** | **M30** | **M36/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | | **D-75 to -1** | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **D673±14** | **D841±14** | **D1009±14** | **±14** |
| Randomization to protocol-specified background antihypertensive medication | | X | | | | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication administration | | Daily | | | | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication pill count | | | X | X | | X | X | X | X | X | X | | | | | | | | | |
| Plasma for PK | | | | X | | | | | | | X | | | | | | | | | |
| Immunogenicity (ADA) | | | | X | | | | X | | | X | | | X | X | X | X | X | X | X |
| Serum AGT | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist circumference and waist-to-hip ratio | | | | X | | | | | | | X | | | | X | X | X | X | X | |
| Exploratory DNA sample (optional) | | | | X | | | | | | | | | | | | | | | | |
| Neurologic evaluation[g] and symptom-directed physical exam | | | | | | | | | | | | | | | X | X | X | X | | X |
| Randomization to zilebesiran or placebo | | | | X | | | | | | | | | | | | | | | | |
| Study drug administration (zilebesiran or placebo) | | | | X | | | | | | | X | | | | X | X | X | X | | |

| | *Shading indicates visits that must be performed at the site* | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | | | | Safety Follow-up |
| **Study Visit (Month)** | Screening Period | Run-In Visit 1 | Run-In Visit 2 | D1 | W2 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M18 | M24 | M30 | M36/EOT/ET | Q6M post last dose of study drug |
| **Study Day (±Visit Window)** | D-75 to -1 | | | D1 | D15±2 | D29±2 | D57±7 | D85±7 | D113±7 | D141±7 | D169±7 | D197±7 | D225±7 | D253±7 | D337±7 | D505±14 | D673±14 | D841±14 | D1009±14 | ±14 |
| AEs | Continuous | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | | | | | | | | |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; No.=number; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin, aldosterone, and Ang I/II) should be performed before physical examinations and 12-lead ECGs.
- Run-in Visit 2 should occur at least 4 weeks after Run-in Visit 1.
- Patients may have been eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran beginning at the Month 6 visit and continue for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

- Patients will be asked to perform Safety Follow-up visits once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

[b] When applicable, pregnancy test results must be known prior to dosing with study drug at dosing visits.

[c] Laboratory assessments at Day 1 do not need to be repeated, per Investigator discretion, if they were collected within 7 days before Day 1 at Run-in Visit 2.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications or study drug (as applicable).

[e] ABPM recordings associated with study drug dosing visits should be obtained within 7 days before the visit and results reviewed before dosing.

[f] HBPM should be measured at least 3 times during the week prior to the second randomization to establish baseline. After Day 1, HBPM should be measured at least once per week in the morning upon waking and may be increased at the Investigator's discretion if more frequent measurement is warranted. HBPM is not required on days when ABPM is being assessed. In the Safety Follow-up period, the frequency of HBPM assessments can be reduced after the first Safety Follow-up visit per Investigator judgement.

[g] Neurological evaluation will also be performed as part of the full physical examination.

[h] ABPM should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12 and has not had an ABPM within the last 3 months. ABPM should not be performed at Month 36.

## 7.4. Time-Adjusted Change from Baseline

Time-adjusted change from baseline is the area under the curve (AUC) divided by time interval. It leads to a weighted average of all scheduled change from baseline during that time interval.

E.g., ABPM is assessed at Month 2, 3 and 6. Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM is:

1. AUC is calculated as: $\left[\frac{1}{2}(y_2 + y_3) * 1 + \frac{1}{2}(y_3 + y_6) * 3\right]$
2. Time interval is 4 months, from Month 2 to Month 6. AUC divided by time interval is

$$AUC/4 = 0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$$

Where $y_2$, $y_3$ and $y_6$ are the 24-hour mean ABPM at Month 2, 3, and 6.

Table 3 listed all time-adjusted endpoints and the weights of the assessments.

**Table 3 Time-Adjusted Endpoints**

| Time-adjusted Endpoint | Weighted average |
|---|---|
| Time-adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP assessed by ABPM | $0.5 * y_2 + 0.5 * y_3$ |
| Time-adjusted change from baseline through Month 3 in office SBP/DBP | $0.25 * y_1 + 05 * y_2 + 0.25 * y_3$ |
| Time-adjusted change from baseline through Month 6 in 24-hour mean SBP/DBP assessed by ABPM | $0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$ |
| Time-adjusted change from baseline through Month 6 in office SBP/DBP | $0.1 * y_1 + 0.2 * y_2 + 0.2 * y_3 + 0.2 * y_4 + 0.2 * y_5 + 0.1 * y_6$ |

## 7.5. Missing or Partial Dates

### 7.5.1. Prior and Concomitant Medications

For medications with partial start or end dates: the first day/month will be imputed for start date, and the last day/month will be imputed for end date. For medications with a completely missing start date, the medications will be considered as started one day prior to the first dose of study drug. If an imputed start date is after the collected end date, the end date will be used as the imputed start date. For medications with a completely missing end date or an imputed end date that is after the earliest date of: end of study date, data cutoff date or date of death, the latter (i.e., the earliest date of: end of study date, data cutoff date or date of death) will be used as the imputed end date.

### 7.5.2. Adverse Events

For records with fully or partially missing AE onset date, conventions for the imputation is as below:

- AE onset dates with missing day and non-missing month will be imputed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.
- AE onset dates with missing month will be imputed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.
- If year of the AE start date is missing, the onset date will be imputed as the first day of dosing, except if it can be unequivocally determined (from the partial or complete stop date) that the event occurred prior to the first dose of study drug, in which case the AE onset date will not be imputed.
- If an imputed onset date is after the collected AE end date, the end date will be used as the imputed onset date.

### 7.5.3. Others

For other incomplete dates, unless otherwise specified, the following conventions will be used for the calculation of duration (e.g., time in years since diagnosis):

- Missing day: the first day of the month will be used.
- Missing month: the January 1 of the non-missing year will be used.
- Missing year: no duration will be calculated.

# STATISTICAL ANALYSIS PLAN
# ALN-AGT01-003 (KARDIA-2)

| | |
|---|---|
| **Protocol Title:** | A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication |
| **Short Title:** | Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2) |
| **Study Drug:** | Zilebesiran (ALN-AGT01) |
| **Protocol Date:** | Original protocol, 25 August 2021<br>Amendment 1, 22 March 2022 |
| **SAP Date:** | Original SAP: 29 March 2022 |
| **Sponsor:** | Alnylam Pharmaceuticals, Inc.<br>300 Third Street<br>Cambridge, MA 02142 USA<br>Telephone: +1-617-551-8200 |

# APPROVAL SIGNATURE PAGE

**This document has been authored, approved, and signed electronically on the final page by the following:**

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Alnylam Pharmaceuticals, Inc.

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ABPM | Ambulatory blood pressure monitoring |
| ADA | Anti-drug antibody(ies) |
| AE | Adverse event |
| AGT | Angiotensinogen |
| ALT | Alanine aminotransferase |
| AngI/II | Angiotensin I/II |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| DB | Double-blind |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| eDISH | Evaluation of drug-induced serious hepatotoxicity |
| EOT | End of treatment |
| ET | Early termination |
| ECG | Electrocardiogram |
| FAS | Full analysis set |
| HbA1c | Hemoglobin A1c |
| HBPM | Home blood pressure monitoring |
| HLT | High level term |
| IRT | Interactive Response Technology |
| ISR | Injection site reaction |
| LFT | Liver function test |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model for repeated measurements |
| OLE | Open-label extension |

| Abbreviation | Definition |
|---|---|
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| Q6M | Once every 6 months |
| RAAS | Renin-angiotensin-aldosterone system |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |
| SOC | System Organ Class |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantification |

# 1. INTRODUCTION

This statistical analysis plan (SAP) details comprehensive specifications of the efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data summaries and statistical analyses in support of the clinical study report (CSR) for Study ALN-AGT01-003 (KARDIA-2). This SAP is finalized prior to treatment unblinding for conducting the analysis of the primary and secondary endpoints measured at Month 3, which will occur after all patients complete the Month 3 visit or withdraw from the study prior to the Month 3 visit. Changes to planned analyses specified in this SAP made after database lock will be documented in the CSR.

Table, figure, and listing (TFL) mocked shells and specifications are contained in a separate document.

# 2. STUDY DESIGN

## 2.1. General Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and PD of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. A schematic of the study design is provided in Figure 1.

**Run-in Period**

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1) for at least 4 weeks before Run-in Visit 2 to washout their effects.

**DB Period**

Patients who meet all inclusion/exclusion criteria will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB period as add-on therapy to their protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the patient's protocol-specified background antihypertensive medication per Investigator judgement.

### OLE Period

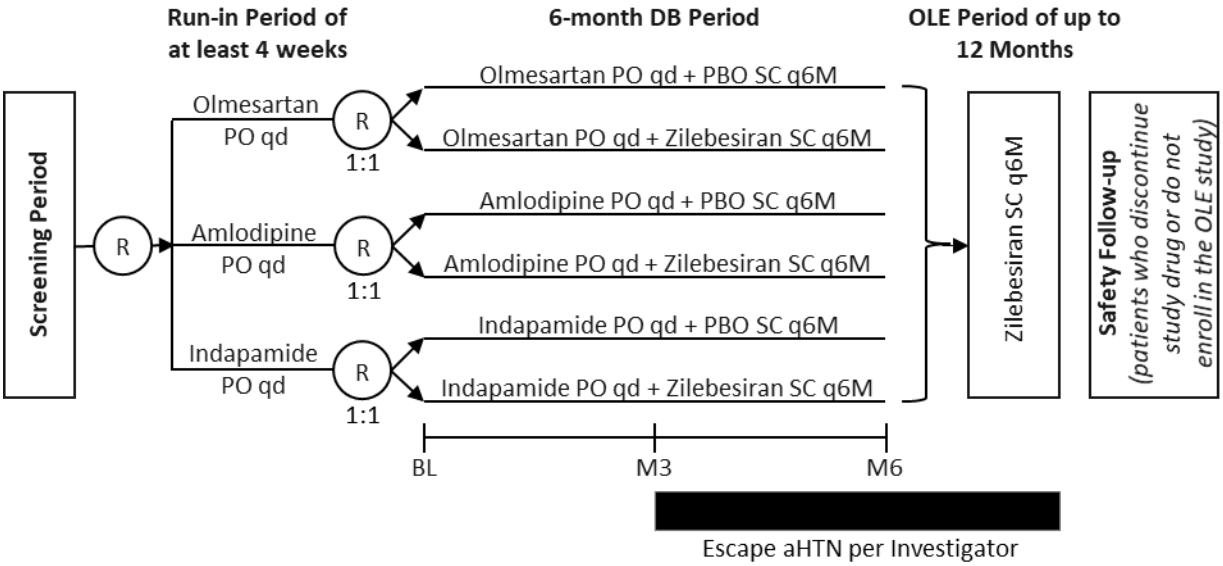
After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 12 additional months until the separate OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into that OLE study at Month 6, 12, or 18 (first visit after the separate OLE study is open).

### Safety Follow-up Period

Patients who discontinue study drug or do not enroll in the separate zilebesiran OLE study will be asked to complete Safety Follow-up visits once every 6 months after their last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months, whichever comes earlier.

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

**Figure 1 Study Design**




Abbreviations: aHTN=antihypertensive medication; BL=baseline; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); qd=once daily; q6M=once every 6 months; R=randomization; SC=subcutaneous.
Note: Patients may be eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran once every 6 months in the OLE period for up to 12 additional months until the OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into the separate OLE study at Month 6, 12, or 18 (first visit after the separate OLE study is open). Patients who were previously taking antihypertensives at screening should undergo a washout of these medications for at least 4 weeks during the Run-in period.

## 2.2. Objectives and Endpoints

The following objectives will be evaluated separately for each protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide).

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3 | • Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM |
| Secondary | |
| Through Month 6<br>• To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM<br>• To evaluate the add-on effect of zilebesiran on office blood pressure<br>• To characterize the PD effects of zilebesiran | Key Secondary Endpoints<br>• Change from baseline at Month 3 in office SBP<br>• Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM<br>• Time-adjusted change from baseline through Month 6 in office SBP<br>• Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6<br>Other Secondary Endpoints<br>• Change in 24-hour mean SBP and DBP, assessed by ABPM<br>• Change in office SBP and DBP<br>• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM<br>• Change in serum AGT |
| Exploratory | |
| • To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6) | • Office blood pressure and ABPM control and response rates<br>• Proportion of patients requiring treatment with escape antihypertensive medications<br>• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure<br>• Change in SBP and DBP from baseline assessed by HBPM |
| • To characterize the plasma PK of zilebesiran | • Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran |

| Objectives | Endpoints |
|---|---|
| • To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication) | • Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII |
| • To evaluate the immunogenicity of zilebesiran | • Incidence and titers of ADA |
| • To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements | • Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio |
| • To assess the effect of zilebesiran on metabolic syndrome parameters | • Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile |
| • To characterize the PD effects of zilebesiran (after Month 6) | • Change in serum AGT |
| • To assess the long-term treatment effect of zilebesiran (through Month 18) | • Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM |
| Safety | |
| • To evaluate the safety of zilebesiran in patients with hypertension | • Frequency of AEs |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; Ang=angiotensin; BMI=body mass index; DBP=diastolic blood pressure; HbA1c=hemoglobin A1c; HBPM=home blood pressure monitoring; HOMA= homeostatic model assessment; PD=pharmacodynamic; PK=pharmacokinetic; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

## 2.3. Study Procedure

The Schedule of Assessments is provided in Table 2.

## 2.4. Randomization Methodology

At Run-in Visit 1, patients with screening eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be assigned to receive olmesartan. To avoid over-enrollment, patients with eGFR <45 mL/min/1.73m$^2$ or urine albumin:creatinine ≥300mg/g will be excluded from the study after 100 such patients are randomized to study drug on Day 1.

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 2.6. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

At Day 1, patients will be randomized 1:1 to receive zilebesiran or placebo as an add-on to their protocol-specified background antihypertensive medication using the IRT. Randomization at Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening eGFR (<60 or ≥60 mL/min/1.73m$^2$).

## 2.5. Blinding

The Sponsor, all site personnel and patients will be blinded to study drug treatment through Month 3 of the 6-month DB period. After the database lock to support the analysis of the primary endpoint and secondary endpoints measured at Month 3 is complete, Sponsor staff members who will not have direct roles or responsibilities in interacting with study sites will be unblinded to the analysis results according to the prespecified blinding plan. Site personnel, patients, and Sponsor staff members who have direct roles or responsibilities in interacting with study sites will remain blinded to treatment assignment until after the analysis of Month 6 data is complete. All Sponsor and site personnel and patients will be blinded to any clinical laboratory result that could potentially unblind them (e.g., AGT levels) until unblinding

Details about the specifics of the blinding aspects throughout the entire study are available in the Randomization and Blinding Plan.

Any unplanned/emergency unblinding occurring during the DB Period will be documented and reported in the CSR.

Refer to the study Randomization and Blinding Plan for more details.

## 2.6. Determination of Sample Size

Approximately 630 patients will be randomized to receive either zilebesiran or placebo, with sample sizes in each of the patient cohorts with protocol-specified background antihypertensive medication as follows:

- Olmesartan cohort: 300 patients
- Amlodipine cohort: 210 patients
- Indapamide cohort: 120 patients

Assuming a common standard deviation of 16 mmHg in change from baseline in 24-hour mean SBP assessed by ABPM and 15% dropout rate from baseline to Month 3, with 2-sided significance level of 0.05 for each of the comparisons (zilebesiran versus placebo as add-on to olmesartan; zilebesiran versus placebo as add-on to amlodipine; zilebesiran versus placebo as add-on to indapamide), these sample sizes will provide at least 80% power to detect the following difference between zilebesiran versus placebo:

- 5 mmHg as add-on to olmesartan
- 6 mmHg as add-on to amlodipine
- 8 mmHg as add-on to indapamide

The power is assessed by mixed model with repeated measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and

treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

# 3. ANALYSIS POPULATIONS

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug. All by-treatment analyses based on the Safety Analysis Set will be grouped according to the treatment actually received.
- PK Analysis Set: All patients who received at least 1 full dose of zilebesiran and have at least 1 non-missing post-dose PK assessment.
- PD Analysis Set: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- All Zilebesiran Treated Set: All patients who received any amount of zilebesiran, including patients who took zilebesiran during the 6-month DB period, and patients who initially took placebo and then switched to zilebesiran after Month 6 Visit.

For the analyses for 6-month DB period, the primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

The All Zilebesiran Treated Set will be used to summarize the efficacy and safety of zilebesiran throughout the 6-month DB period and the OLE period.

## 3.1. Randomization and Treatment Errors

The study has two randomizations. The first randomization is to assign patients to receive one of the three protocol specified background antihypertensive medication. The second randomization is to randomize patients to receive either zilebesiran or placebo on top of each backgrouup antihypertensive medication. This section mainly focuses on the second randomization.

For patients who were not treated, not randomized, or received incorrect treatment, the following rules will be used:

- Randomized but not treated: they will be excluded from the FAS and Safety Analysis Set for efficacy and safety evaluations as actual treatment is missing.
- Treated but not randomized: they will be excluded from the efficacy analyses since randomized treatment is missing but will be reported under the treatment actually received for all safety analyses.
- Randomized but took incorrect treatment: they will be reported under their randomized treatment arm for all efficacy analyses. But for safety analyses, a patient

will be reported under the active treatment arm if the patient is randomized to placebo arm and received an active dose by mistake.

# 4. GENERAL STATISTICAL CONSIDERATIONS

## 4.1. General Considerations

In general, data will be summarized for each planned analysis defined in Section 4.7 separately. All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts.

Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the following descriptive summary statistics: number of patients (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

Study drug is zilebesiran 600mg Q6M or placebo.

The day of the first dose of study drug administered is defined as Day 1. The Study Day of a time point of interest is calculated as follows:

- If on or after Day 1, Study Day = date of interest – date of the first dose of study drug + 1
- If prior to Day 1, Study Day = date of interest – date of the first dose of study drug

There is no Day 0. For example, the day before the first study drug dose is defined as Day -1.

For laboratory parameters, assessments collected and recorded as lower than the lower limit of quantification/detection (LLOQ) will be replaced by the LLOQ. Any assessment collected and recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

All descriptive summaries will be presented by treatment arm.

Statistical analyses will be conducted using SAS software Version 9.4 or newer or R version 3.6 or newer.

## 4.2. Blood Pressure Collection and Handling

### 4.2.1. 24-Hour Ambulatory Blood Pressure Monitoring

24-hour ambulatory blood pressure monitoring (ABPM) is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study within 4 days.

To summarize the 24-hour ABPM, hourly adjusted mean will be calculated. Hourly adjusted mean will be calculated by two steps:

1. Calculate the hourly mean of BP by each hour of the day (e.g., mean of BP measurements from 16:00 to 16:59). If there is no reading in a specific hour, this hourly mean will be considered as missing.
2. Calculate the 24-hour mean SBP/DBP, daytime and nighttime means of the SBP/DBP based on the hourly means.

### 4.2.2. Office Blood Pressure

The office BP in the sitting position will be used for the analysis. Office BP will be collected with a set of 4 replicates. The average of the last 3 replicates will be calculated and used for analysis. Office BP collected in standing position will be listed only.

### 4.2.3. Home Blood Pressure Monitoring

Home blood pressure will be measured both pre and post randomization. To establish baseline, each patient should measure HBPM during the week (with at least 3 successful readings) immediately prior to randomization. After Day 1, HBPM will be measured at least once per week. 4 sequential blood pressure measurements at 1-minute intervals will be recorded. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements. HBPM will be summarized by weekly average.

Details of the blood pressure collection are in Study Protocol Section 10.

## 4.3. Multiple Comparison/Testing Procedure

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. To control the overall Type I error at $\alpha$=0.05 within each cohort, the primary endpoint and the key secondary endpoints will be tested in hierarchical order.

**Table 1 Multiplicity Procedure**

| Test Step [a] | Endpoint | Success criteria |
|---|---|---|
| 1 | Primary: Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 2 | Key secondary: Change from baseline at Month 3 in office SBP | Nominal p-value < 0.05 |
| 3 | Key secondary: Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM | Nominal p-value < 0.05 |
| 4 | Key secondary: Time-adjusted change from baseline through Month 6 in office SBP | Nominal p-value < 0.05 |
| 5 | key secondary: 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication at Month 6 | Nominal p-value < 0.05 |

[a] If the success criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant

## 4.4. Handling of Missing Data

No imputation will be done for missing values for the primary analysis of the primary endpoint. A sensitivity analysis of the primary endpoint will be performed (details described in Section 5.7.1.3). For all analyses using mixed model repeated measures, no explicit imputation of missing values will be done.

## 4.5. Baseline Definitions

For the analyses of 6-month DB period, for office BP, baseline is the average of the office BP value on Day 1 prior to receiving the first dose of study drug and last non-missing value prior to Day 1 during run-in period. For 24-hour ABPM, baseline is the measurement used for eligibility for randomization to study drug. For HBPM, baseline will be the average of all assessments during the last week prior to receiving the first dose of study drug. For all other endpoints, baseline is the last non-missing value (including unscheduled visit) prior to receiving the first dose of study drug.

For the final analyses, patients initially randomized to placebo and switched to zilebesiran at Month 6 will be summarized in two ways:

- From Day 1. Baseline is the same as the one for the primary analysis
- From the start of zilebesiran dosing at Month 6. Baseline will be the last assessment prior to Month 6 dosing.

For patients initially randomized to zilebesiran, baseline remains the same as the one for the primary analysis.

## 4.6. Randomization Stratification Factors

Stratification factors are recorded in the IRT database. Key data is integrated into the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database (EDC). In the presence of stratification errors, the stratification used in analysis may not match that in the IRT. A comparison of the number and percentage of patients in each randomization stratification factor in IRT versus the clinical database will be summarized by randomized treatment arm and overall.

## 4.7. Planned Analyses and Data Cutoffs

### 4.7.1. Month 3 Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be performed after the last randomized patient has completed Month 3 Visit or otherwise discontinued the study. For the Month 3 analysis, as this study will be ongoing with some patients in the 6-month DB period, OLE period or safety follow-up period, the study database will undergo an interim database lock at the Month 3 cutoff dates (i.e., data in EDC will be cleaned, frozen and electronically signed by investigators; external laboratory data will be cleaned and will undergo quality assurance). Additional details regarding the interim database locks will be documented in the study Data Management Plan.

The analysis will include data on, or prior to, this prespecified cutoff date. For assessments with starting/ending dates (e.g., adverse events [AEs], medications), the starting date will be compared with the pre-specified cutoff date. Data records with starting dates after the specified data cutoff date will be excluded.

### 4.7.2. Month 6 Analysis

The analysis after the end of double-blind period is the Month 6 analysis. The analysis will be performed after all randomized patients have completed the Month 6 Visit or otherwise withdrawn from the study.

The database will undergo an interim database lock, and the data will be summarized in a CSR.

### 4.7.3. Final Analysis

After all patients reach the end of the study, the database will undergo a final database lock, and the data will be summarized in a CSR.

A patient is considered to have reached the end of the study if the patient:

- has completed at least the Month 6 visit and enrolled in the OLE study, or
- has completed the Safety Follow-up visits for patients who discontinue study drug, withdraw from the study, or do not enroll in the OLE study.

# 5. STATISTICAL ANALYSES

## 5.1. Patient Disposition

The number and percentage of patients in the following categories will be summarized by randomized treatment arm and overall:

- Randomized to study drug
- Treated with study drug
- Completed the 6-month double-blind (DB) treatment period
- Discontinuation and primary reason during 6-month DB period
- Withdrawal from study and primary reason for withdrawal from study
- Completed the OLE period
- Completed the study
- Rollover to the separate OLE study

In addition to the primary reason for discontinuation of treatment and withdrawal from study, patients will also be categorized if discontinuation/withdrawal was due to COVID-19.

## 5.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for Full Analysis Set, and also presented in listings.

Age at consent, height, weight, body mass index (BMI), 24-hour ABPM and OBP, eGFR will be summarized using descriptive statistics. Sex, race, ethnicity, and country will be summarized by presenting the frequencies and percentages of patients in each category.

## 5.3. Medical History

Medical history and prior procedures reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1 or newer. Unique patients who report medical history events will be summarized by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT).

## 5.4. Protocol Deviations

Protocol deviations will be classified by medical review prior to each planned analysis database lock, and major protocol deviations will be identified. A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being. (ICH E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry, 2013).

The Sponsor or designee will be responsible for producing the protocol deviation file. This file will include a description of each protocol deviation and classification as major or minor. The protocol deviations will be reviewed and finalized prior to the planned analysis database lock.

All protocol deviations and major protocol deviations will be summarized and listed.

## 5.5. Study Drug Exposure and Compliance

The following variables will be summarized by descriptive statistics and/or frequency tabulation:

- Duration of exposure, defined as: date of last exposure – date of first dose of study drug +1. Date of last exposure is the earliest date of the following:
  - date of last dose of study drug + the length of dosing interval (169 days)
  - date of end of study
  - date of analysis data cutoff
- Number of doses received; as continuous and/or categorical variable
- Number of missed doses; as a categorical variable
- Compliance to background medication: number of pills taken/number of pills dispensed
- Total exposure (patient years)

## 5.6. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version WHO-DD Global B3, March 2021 or newer. Unique patients who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class (or level 2 if not available) and PT. Summaries will be provided for prior and concomitant medications separately.

Prior medications are those medications with start date prior to the first dose of study drug.

Concomitant medications are medications, other than the study drug or protocol-specified background antihypertensive medication, administered at or after the first dose of study drug, as well as medications that started prior to the first dose of study drug and are ongoing after the first dose of study drug.

If the medication start date is on or after the date of first dose of study drug, the medication will be summarized as a concomitant medication even if the medication end date is missing.

If the end date of a medication is missing or incomplete, such that it cannot be determined whether it is after the first dose of study drug, it will be counted as a concomitant medication.

For missing or partial dates for medications, the imputation of start and end dates is described in Section 7.2

## 5.7. Efficacy Analyses

### 5.7.1. Primary Endpoint

#### 5.7.1.1. Definition of Estimand

The primary objective of the study is to evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3. Primary estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)
- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint: Change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM
- Population-level summary: Least square mean difference between zilebesiran and placebo in change from baseline at Month 3 in 24-hour mean SBP assessed by ABPM, on top of each background antihypertensive medication
- Intercurrent events strategy: Hypertensive escape medication taken before Month 3 visit will be considered as an intercurrent event. For patients who require escape antihypertensive medication, given the expected number of such patients at Month 3 is low, hypothetical strategy will be used, i.e., ABPM assessed while patients are on and within 2 weeks after stopping any escape antihypertensive medication will be excluded for analysis. This will provide the estimated treatment effect of zilebesiran compared with placebo on top of each background antihypertensive medication.

#### 5.7.1.2. Primary Analysis

For each background antihypertensive medication cohort, the hypothesis to be tested for the primary endpoint is:

- $H_0$: $\mu_1 = \mu_0$ (there is no add-on effect of zilebesiran)
- $H_a$: $\mu_1 \neq \mu_0$ (there is add-on effect of zilebesiran)

where $\mu_0$ and $\mu_1$ are the mean change from baseline at Month 3 in 24-hour mean SBP in placebo and zilebesiran arm, respectively.

MMRM model will be used as primary analysis. The model will include treatment, time, treatment-by-time, and race (black, all other races) as fixed factors; baseline 24-hour mean SBP assessed by ABPM and screening eGFR as covariates.

#### 5.7.1.3. Sensitivity Analyses

For the sensitivity analysis, treatment policy strategy will be used for patients who require escape antihypertensive medication. All collected blood pressure measurements will be analyzed by the same MMRM model as the primary analysis, regardless of the hypertensive escape medication.

Due to the expected long-acting effect of zilebesiran, the commonly used control-based Pattern Mixture Model (PMM) will not be used to assess the missing not at random (MNAR) assumption.

#### 5.7.1.4. Other Analyses

To demonstrate zilebesiran consistently controls blood pressure over the 24-hour period, change from baseline at Month 3 in SBP assessed by ABPM at each clock hour will be plotted for each treatment group.

### 5.7.2. Secondary Endpoints

#### 5.7.2.1. Key Secondary Endpoints

Secondary objectives of the study are to evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM and office blood pressure through Month 6. The estimand is defined as:

- Treatment condition: add-on therapy: placebo or zilebesiran 600 mg Q6M in addition to one of the protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide)
- Target population: patients with hypertension not adequately controlled by a standard of care antihypertensive medication
- Endpoint:
  - Change from baseline at Month 3 in office SBP
  - Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM
  - Time-adjusted change from baseline through Month 6 in office SBP

  - 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication

- Population-level summary: Least square mean difference between zilebesiran and placebo of the change from baseline in SBP on top of each background antihypertensive medication. Odds ratio for BP response rate.
- Intercurrent events strategy:
  - For Month 3 endpoint: Given the expected number of such patients at Month 3 is low, hypothetical strategy will be used.
  - For Month 6 endpoint: Protocol allows escape antihypertensive medication from Month 3 through Month 6. Given the expected proportion of such patients may be large, the treatment policy strategy will be used.

Time-adjusted change is defined as the area under the curve (AUC) of BP change from baseline divided by the duration of the time period. It leads to the weighted average of change from baseline to each scheduled visit. Details of the definition and calculation are in Section 7.2.

Multiplicity adjustment will be applied across primary and the key secondary endpoints. Details of multiplicity control are in Section 4.3 .

MMRM model will be used as the primary analysis. The model will include treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, baseline eGFR and corresponding baseline BP as covariates. Least square (LS) mean difference, 95% CI and p-value will be generated.

For the proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6, logistic regression will be used. The model will include treatment as a factor and baseline 24-hour mean SBP as a covariate.

#### 5.7.2.2. Other Secondary Endpoints

Other blood pressure related secondary endpoints are:

- Change from baseline at Month 3in 24-hour mean DBP, assessed by ABPM
- Change from baseline at Month 3 in office DBP.
- Time adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP, assessed by ABPM
- Time adjusted change from baseline in office SBP/DBP through Month 3
- Change from baseline at Month 6 in 24-hour mean SBP/DBP, assessed by ABPM
- Change from baseline at Month 6 in office SBP/DBP
- Time adjusted change from baseline through Month 6 in 24-hour mean DBP, assessed by ABPM
- Time adjusted change from baseline through Month 6 in office DBP

- Change from baseline in daytime/nighttime SBP and DBP by ABPM by each visit. Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

In general, the BP related endpoints will be summarized using all collected BP data regardless of the use of escape antihypertensive medication. The same MMRM model will be used with treatment, visit, treatment-by-visit interaction, race (black, all other races) as fixed factors, corresponding baseline as a covariate. Least square (LS) mean difference of each zilebesiran dose group compared with placebo dose group, 95% CI and p-value will be generated.

The secondary endpoint of percent change in serum AGT at each visit will be summarized using descriptive statistics.

### 5.7.3. Exploratory Endpoints

The blood pressure related exploratory endpoints through Month 6 are:

- BP response rate by each visit, defined as
  - Office SBP < 140 mmHg and/or reduction from baseline ≥ 20 mmHg without escape antihypertensive medication
  - 24-hour mean DBP assessed by ABPM < 85 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
  - Office DBP < 90 mmHg and/or reduction from baseline ≥ 10 mmHg without escape antihypertensive medication
- Proportion of patients with escape antihypertensive medication use by each visit
- Change from baseline in pulse pressure by each visit, assessed by ABPM and office BP
- Change from baseline in SBP/DBP by HBPM

To assess the long-term treatment effect of zilebesiran through Month 18, change from baseline in SBP/DBP assessed by ABPM, office BP and HBPM will be summarized.

Body weight, metabolic related exploratory endpoints are:

- Change from baseline in body weight/body mass index (BMI)/waist circumference/waist-to-hip ratio by each visit
- Change from baseline in HbA1c/fasting glucose/insulin/serum lipids by each visit

Exploratory endpoints will be summarized using descriptive statistics based on all observed data. Missing data will not be imputed.

### 5.7.4. Evaluation of Subgroups

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age (<65; >=65)
- Sex

- Race (black; all other races)
- Baseline 24-hour mean SBP assessed by ABPM (<145 mmHg, >=145 mmHg)
- Baseline eGFR (<60; >=60 mL/min)

Subgroup analyses will be performed for the primary endpoint and key-secondary endpoints using the MMRM within each subgroup. Model will include treatment, visit, treatment-by-visit interaction, race ([black, all other races], when race is not the subgroup to be analyzed) as fixed factors, baseline eGFR and corresponding baseline BP measurement as covariates. Point estimate of treatment effect and 95% confidence interval are to be generated for each subgroup. A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

## 5.8. Pharmacodynamic Analyses

In addition to serum AGT, the PD parameters include plasma renin concentration, aldosterone, AngI and AngII. Summary tables may be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group. In addition to serum AGT percent reduction analyses, the AGT maximum and mean percentage reductions over the 6-month DB period will be summarized using descriptive statistics.

## 5.9. Pharmacokinetic Analyses

Plasma concentrations of zilebesiran and its metabolite will be summarized descriptively. Descriptive statistics for zilebesiran and its metabolite plasma concentrations will include the number of patients, mean, SD, coefficient of variation, geometric mean, geometric mean coefficient of variation, median, minimum, and maximum.

Additional analysis may be done as needed.

## 5.10. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any time during the 6-month DB period, as well as treatment-emergent ADA during the OLE period, will be summarized. Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, as defined below:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

## 5.11. Safety Analyses

### 5.11.1. Adverse Events

Adverse events (AEs) will be classified by the MedDRA coding system (Version 23.1 or newer) and displayed in tables and data listings using SOC and PT.

Treatment-emergent AEs (TEAEs) will be summarized for the 6-month DB period and for the duration of zilebesiran exposure (defined in Section 5.5) separately.

For the 6-month DB period, TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and through Month 6 Visit (prior to Month 6 dosing).

For the summary of duration of zilebesiran exposure, TEAE is defined as any AE occurring or worsening on or after the first dose of zilebesiran and through the last date of zilebesiran exposure.

AEs that occurred or worsened during safety follow-up period will be listed and may be summarized if needed.

Because any worsening AE is reported as a new AE with higher severity, programmatical comparison of severity is not needed for the classification of TEAE. For missing or partial dates for AEs, the imputation of start and end date can be found in Section 7.2. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first dose of study drug.

AEs will be summarized by the numbers and percentages of patients reporting a given AE. An overall table of TEAEs will include:

- any AE,
- any AE related to study drug,
- any serious AE (SAE),
- any SAE related to study drug,
- any AE leading to study drug discontinuation,
- any drug-related AE leading to study drug discontinuation,
- any AE leading to death.

Tabulations by SOC and PT will be produced for the following:

- AEs,
- Treatment-related AEs,
- AEs by maximum severity,
- Treatment-related AEs by maximum severity,
- Severe AEs,
- SAEs,
- AEs leading to treatment discontinuation.

Tabulations by PT will be produced for the following:

- AEs,
- Treatment-related AEs,

- SAEs.

A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence. An AE with missing severity will be assumed to be severe. An AE with missing study drug relatedness will be assumed to be related.

Listings of all deaths (if any), SAEs, and AEs leading to treatment discontinuation will be provided.

In addition, AE during run-in period will be summarized and listed by each background antihypertensive medication cohort.

AEs of Clinical Interest

AEs of special interest or AEs mapping to certain standardized MedDRA queries (SMQs) will be summarized by SOC and PT. Other SMQs or AE groupings may be evaluated.

**Injection Site Reactions [ISRs]**: AEs mapping to the High-Level Term (HLT)= "Injection Site Reactions" using MedDRA dictionary will be included in the summary. Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. In addition, a table of the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose), total number of doses with ISRs and corresponding % of injections with ISR with the most common signs and symptoms reported due to ISRs will be generated.

**Hepatic AEs, including Liver Function Test (LFT) abnormalities**: Analysis of hepatic AEs will include AEs mapping to the Standardized MedDRA Query (SMQ) Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms). Frequency (percentages) of hepatic AEs will be summarized by SOC and PT. A separate listing will be generated of all patients reporting these events.

All AEs will be presented in patient data listings. AEs mapping to the SMQs as described above will also be listed.

Additional summaries of AEs mapping to a COVID-19 custom query are described in Section 5.13.2.

### 5.11.2. Laboratory Data

Clinical laboratory values will be expressed in SI units. Missing laboratory data will not be imputed.

For each continuous clinical laboratory parameter (including hematology, serum chemistry, liver function tests and coagulation studies), descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit. These by-visit tables will use central laboratory data only.

Select clinical laboratory parameters may be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or above. Shift summary from baseline CTCAE grade to maximum (worst) post-baseline grade will be presented for all graded parameters with directionality specified (e.g., hyper or hypo). To determine the worst post-baseline value, all scheduled and unscheduled test results will be used. For

hematology and serum chemistry, frequency tables of potentially clinically significant (PCS) abnormalities will be provided.

All laboratory data (both central and local) will be provided in data listings. Out-of-range laboratory results will be presented in a separate listing with proper flags. Local laboratory data, if available, will also be flagged.

Liver Function Tests

A frequency table and a shift table will be produced to summarize the number and percentage of patients in each of the below categories at any post-baseline time point.

- ALT >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALP > 1.5×ULN,
- Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN

In separate evaluation of drug-induced serious hepatotoxicity (eDISH) figures, the peak total bilirubin (as multiple of ULN) at any time post-baseline will be plotted against the peak ALT, AST, ALT or AST level and at any time post-baseline.

A listing for all patients with abnormal liver function tests, defined as an ALT >3×ULN, AST >3×ULN, or total bilirubin >2×ULN at any time point, will also be provided.

### 5.11.3. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm and overall interpretation.

Post-baseline overall interpretation (normal vs. abnormal) will be summarized in frequency table by treatment and visit.

All ECG data for each patient will be provided in a data listing.

### 5.11.4. Vital Signs

For vital signs except blood pressure, descriptive statistics for actual values and change from baseline by visit will be provided for each variable. Vital sign measurements will be presented by treatment and patient ID in a data listing, with abnormal vital signs flagged.

### 5.11.5. Evaluation of Subgroups

AE summary tables will be separately generated for each of the subgroups as defined for the primary efficacy endpoint (except for baseline BP, see Section 5.7.4).

## 5.12. Interim Analysis

No interim analysis is planned for this study.

## 5.13. COVID-19

Additional data are collected to characterize the impact of the COVID-19 pandemic on general study conduct and disposition, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidance (including FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

### 5.13.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 5.1.

Impact on study participation due to COVID-19, including missing visits, visit location changes, study drug dosing changes and missing doses, will be summarized descriptively overall and by visit on the patient level, and overall on the event level. Patient- and event-level summaries of the impact on study participation due to COVID-19 may also be generated by site and/or region.

Impact on study participation due to COVID-19 will be presented in data listings at patient and visit level.

### 5.13.2. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will be presented. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

AEs mapping to the COVID-19 custom query will also be presented in a data listing.

# 6. CHANGES FROM PLANNED ANALYSES

Original SAP

| Section of the SAP | Summary of change from protocol | Rationale |
|---|---|---|
| — | — | — |

# 7. APPENDICES

## 7.1. Protocol Schedule of Assessments

Schedule of assessments are listed in Table 2.

## Table 2 Schedule of Assessments

| *Shading indicates visits that must be performed at the site* | | Run-in Period[a] | | Double-blind Period[a] | | | | | | | | OLE Period (Optional)[a] | | | | | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Visit (Month)** | Screening Period | Run-In Visit 1 | Run-In Visit 2 | | W2 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M18/EOT/ET | Q6M post last dose of study drug |
| **Study Day (±Visit Window)** | D-60 to -1 | | | D1 | D15±2 | D29±2 | D57±7 | D85±7 | D113±7 | D141±7 | D169±7 | D197±7 | D225±7 | D253±7 | D337±7 | D505±14 | ±14 |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Assign patient identification no. | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | | | |
| Serum pregnancy test/FSH screening | X | | | | | | | | | | | | | | | | |
| Full physical exam | X | | | X | | | | | | | X | | | | | X | |
| Height, body weight, and BMI | | | | X | | | | X | | | X | | | X | X | X | |
| Single 12-Lead ECG | X | | | X | | | | | | | X | | | | X | X | |
| Serum chemistry[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| Hematology, urinalysis, coagulation[c] | X | | X | X | | | | X | | | X | | | X | X | X | X |
| LFTs[c] | X | | X | X | X | X | X | X | X | | X | X | X | X | X | X | X |
| Spot urine for albumin and creatinine[c] | X | | X | X | | | | X | | | X | | | | X | X | |

| *Shading indicates visits that must be performed at the site* | | **Run-in Period[a]** | | **Double-blind Period[a]** | | | | | | | | **OLE Period (Optional)[a]** | | | | | **Safety Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | **D-60 to -1** | | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **±14** |
| Fasting plasma glucose, insulin, lipid panel, and HbA1c[c] | X | | X | X | | | | X | | | X | | | | X | X | |
| Vital signs and office blood pressure[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 24-hour ABPM[e] | | | X | | | | X | X | | | X | | | X | X | X[h] | |
| HBPM[f] | | | X | At least 3x/week | | | | | | | | | | | | | |
| Discontinue prior oral antihypertensive medications (if taking) | | X | | | | | | | | | | | | | | | |
| Urine pregnancy test[b] | | X | | X | | | | | | | X | | | | X | X | |
| RAAS biomarkers: renin concentration, aldosterone, Ang I/II | | X | | X | | | | X | | | | | | | | | |
| Optional exploratory biomarkers (urine, plasma, serum) | | X | | X | | X | | X | | | X | | | X | X | X | |
| Randomization to protocol-specified background antihypertensive medication | | X | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication administration | | Daily | | | | | | | | | | | | | | | |
| Protocol-specified background antihypertensive medication pill count | | | X | X | | X | X | X | X | X | X | | | | | | |

| *Shading indicates visits that must be performed at the site* | | **Run-in Period[a]** | | **Double-blind Period[a]** | | | | | | | | **OLE Period (Optional)[a]** | | | | | **Safety Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Visit (Month)** | **Screening Period** | **Run-In Visit 1** | **Run-In Visit 2** | | **W2** | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** | **M12** | **M18/EOT/ET** | **Q6M post last dose of study drug** |
| **Study Day (±Visit Window)** | | **D-60 to -1** | | **D1** | **D15±2** | **D29±2** | **D57±7** | **D85±7** | **D113±7** | **D141±7** | **D169±7** | **D197±7** | **D225±7** | **D253±7** | **D337±7** | **D505±14** | **±14** |
| 24-hour urine for sodium and creatinine | | | X | | | | | X | | | | | | | | | |
| Plasma for PK | | | | X | | | | | | | X | | | | | | |
| Immunogenicity (ADA) | | | | X | | | | X | | | X | | | X | X | X | X |
| Serum AGT | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist circumference and waist-to-hip ratio | | | | X | | | | | | | X | | | | X | X | |
| Exploratory DNA sample (optional) | | | | X | | | | | | | | | | | | | |
| Neurologic evaluation[g] and symptom-directed physical exam | | | | | | | | | | | | | | | X | | X |
| Randomization to zilebesiran or placebo | | | | X | | | | | | | | | | | | | |
| Study drug administration (zilebesiran or placebo) | | | | X | | | | | | | X | | | | X | | |
| AEs | | Continuous | | | | | | | | | | | | | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | | | | | |

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; No.=number; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections should be performed before physical examinations and 12-lead ECGs.
- Run-in Visit 2 should occur at least 4 weeks after Run-in Visit 1.
- Patients may be eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran beginning at the Month 6 visit and continue for up to 12 additional months until the separate OLE study is open and then transition at Month 12 or 18 (first visit after the separate OLE study is open). Patients who rollover at Month 6 should complete all assessments scheduled for the Month 6 visit except for study drug administration. Patients who rollover at Month 12 should complete the EOT visit instead of the assessments scheduled at Month 12.
- Patients who discontinue study drug at any time during the study or do not enroll in the separate OLE study will be asked to perform Safety Follow-up visits once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed.

Footnotes:

[a] **All assessments, except for postdose PK sample collection, are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

[b] When applicable, pregnancy test results must be known prior to dosing with study drug at dosing visits.

[c] Laboratory assessments at Day 1 do not need to be repeated, per Investigator discretion, if they were collected within 7 days before Day 1 at Run-in Visit 2.

[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications or study drug (as applicable).

[e] ABPM recordings associated with study drug dosing visits should be obtained within 7 days before the visit and results reviewed before dosing. In the Safety Follow-up period, ABPM assessments may be reduced and are optional per Investigator judgement.

[f] HBPM should be measured in the morning upon waking. HBPM must be collected daily for at least 1 week during the Run-in period starting at 3 weeks of run-in (1 week prior to Run-in Visit 2). HBPM is not required at times when ABPM is being assessed. In the Safety Follow-up period, the frequency of HBPM assessments can be reduced after the first Safety Follow-up visit per Investigator judgement.

[g] Neurological evaluation will also be performed as part of the full physical examination.

[h] ABPM should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12 and has not had an ABPM within the last 3 months. ABPM should not be performed at Month 18.

## 7.2. Time-Adjusted Change from Baseline

Time-adjusted change from baseline is the area under the curve (AUC) divided by time interval. It leads to a weighted average of all scheduled change from baseline during that time interval.

E.g., ABPM is assessed at Month 2, 3 and 6. Time-adjusted change from baseline through Month 6 in 24-hour mean SBP assessed by ABPM is:

1. AUC is calculated as: $\left[\frac{1}{2}(y_2 + y_3) * 1 + \frac{1}{2}(y_3 + y_6) * 3\right]$
2. Time interval is 4 months, from Month 2 to Month 6. AUC divided by time interval is

$$AUC/4 = 0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$$

Where $y_2$, $y_3$ and $y_6$ are the 24-hour mean ABPM at Month 2, 3, and 6.

Table 3 listed all time-adjusted endpoints and the weights of the assessments.

**Table 3 Time-Adjusted Endpoints**

| Time-adjusted Endpoint | Weighted average |
|---|---|
| Time-adjusted change from baseline through Month 3 in 24-hour mean SBP/DBP assessed by ABPM | $0.5 * y_2 + 0.5 * y_3$ |
| Time-adjusted change from baseline through Month 3 in office SBP/DBP | $0.25 * y_1 + 05 * y_2 + 0.25 * y_3$ |
| Time-adjusted change from baseline through Month 6 in 24-hour mean SBP/DBP assessed by ABPM | $0.125 * y_2 + 0.5 * y_3 + 0.375 * y_6$ |
| Time-adjusted change from baseline through Month 6 in office SBP/DBP | $0.1 * y_1 + 0.2 * y_2 + 0.2 * y_3 + 0.2 * y_4 + 0.2 * y_5 + 0.1 * y_6$ |

## 7.3. Missing or Partial Dates

### 7.3.1. Prior and Concomitant Medications

For medications with partial start or end dates: the first day/month will be imputed for start date, and the last day/month will be imputed for end date. For medications with a completely missing start date, the medications will be considered as started one day prior to the first dose of study drug. If an imputed start date is after the collected end date, the end date will be used as the imputed start date. For medications with a completely missing end date or an imputed end date that is after the earliest date of: end of study date, data cutoff date or date of death, the latter (i.e., the earliest date of: end of study date, data cutoff date or date of death) will be used as the imputed end date.

### 7.3.2. Adverse Events

For records with fully or partially missing AE onset date, conventions for the imputation is as below:

- AE onset dates with missing day and non-missing month will be imputed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.
- AE onset dates with missing month will be imputed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.
- If year of the AE start date is missing, the onset date will be imputed as the first day of dosing, except if it can be unequivocally determined (from the partial or complete stop date) that the event occurred prior to the first dose of study drug, in which case the AE onset date will not be imputed.
- If an imputed onset date is after the collected AE end date, the end date will be used as the imputed onset date.

### 7.3.3. Others

For other incomplete dates, unless otherwise specified, the following conventions will be used for the calculation of duration (e.g., time in years since diagnosis):

- Missing day: the first day of the month will be used.
- Missing month: the January 1 of the non-missing year will be used.
- Missing year: no duration will be calculated.