Official Title:	**A Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacodynamics, and Pharmacokinetics of Zilebesiran in Japanese Patients with Mild to Moderate Hypertension**
NCT Number:	**NCT06423352**
Document Date:	**Statistical Analysis Plan, 20 January 2025**

Statistical Analysis Plan

A Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacodynamics, and Pharmacokinetics of Zilebesiran in Japanese Patients with Mild to Moderate Hypertension

Study Drug:	Zilebesiran (ALN-AGT01)
Protocol Date:	Original protocol, 12 Jan 2024 Amendment 1, 18 Oct 2024
Protocol Number:	ALN-AGT01-006
SAP Version:	V1.0
SAP Date:	20 Jan 2025
Sponsor	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
PI	[redacted]
CRO	

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Abbreviations

Abbreviations	Terms
ABPM	Ambulatory blood pressure monitoring
AE	Adverse Event
Ae	Amount excreted
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AOBP	Automated office blood pressure
AST	Aspartate aminotransferase
AUC	Area under the blood concentration time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours post-dose
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated)
AUC_{0-last}	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
$AUC_{\%extrap}$	Percentage of AUC_{0-inf} that is due to extrapolation beyond the last observed non-zero concentration
BLQ	Below Lower limit of quantitation
BMI	Body mass index
C_{max}	Maximum plasma concentration
CL/F	Apparent clearance
CL_R	Renal clearance
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
DB	Double-blind
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of study
fe	Fraction of drug excreted unchanged in urine
FSH	Follicle stimulating hormone
GGT	Gamma glutamyl transferase
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
ISRs	Injection Site Reactions
MRAUC	Metabolite to parent ratio for AUC
MRCMAX	Metabolite to parent ratio for C_{max}
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PT	Preferred Term
QTc	Corrected QT Interval
RAS	Renin-Angiotensin System
RBC	Red blood cells
SAE	Serious Adverse Events
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
SD	Standard Deviation
SEM	Standard Error of the Mean
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event

Tmax	Time to reach maximum plasma concentration
$T_{1/2}$	Apparent terminal elimination half-life
Vz/F	Apparent volume of distribution
λz	Apparent first-order terminal elimination rate constant

1. Introduction

1.1 Statistical Analysis Plan

This document describes the statistical analysis plan for Study ALN-AGT01-006 titled A Phase 1/2, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacodynamics, and Pharmacokinetics of Zilebesiran in Japanese Patients with Mild to Moderate Hypertension. (Protocol number: ALN-AGT01-006).

This document will be finalized as the first version prior to locking of the data or prior to any unblinded analysis. Any modifications or additions hereafter require an amended version with detailed revision history of the changes, reasons, etc.

1.2 Study Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of zilebesiran in Japanese patients with mild to moderate hypertension	• Frequency of AEs. Safety will also be evaluated through vital signs, ECGs, and clinical laboratory assessments.
Secondary	
• To evaluate the PD effect of zilebesiran	• Percent change from baseline in serum AGT at Month 3 and Month 6
• To evaluate the effect of zilebesiran on blood pressure assessed by ABPM	• Change from baseline at Month 3 and Month 6 in 24-hour mean SBP and DBP assessed by ABPM
• To evaluate the effect of zilebesiran on blood pressure assessed by office blood pressure	• Change from baseline at Month 3 and Month 6 in SBP and DBP assessed by office blood pressure
• To characterize the PK of zilebesiran and its metabolite	• Plasma C_{max} and AUC and urine PK of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
Exploratory	
• To assess the effect of zilebesiran on exploratory biomarkers of the RAS pathway	• Change from baseline in plasma renin concentration, plasma renin activity, and aldosterone
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To evaluate the effect of zilebesiran on blood pressure assessed by home blood pressure monitoring through Month 6	• Change from baseline in SBP and DBP assessed by home blood pressure monitoring

Objectives	Endpoints
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To characterize the plasma and urine PK of zilebesiran and its metabolite AS(N-1)3′ zilebesiran	• Plasma and urine parameters of zilebesiran and its metabolite AS(N-1)3′ zilebesiran

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; AUClast=AUC from the time of dosing to the last measurable concentration; Cmax=maximum observed concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; fe=fraction excreted; PD=pharmacodynamics; PK=pharmacokinetics; RAS = renin-angiotensin system; SBP=systolic blood pressure.

2. Definition of Terms

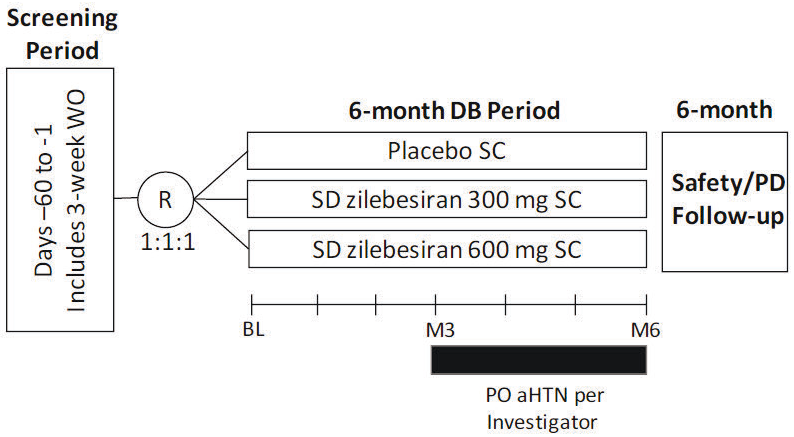
2.1 Synopsis Study Design

This is a single dose, randomized, double-blind, placebo-controlled, parallel-group, Phase 1/2 study to evaluate the safety, tolerability, efficacy, PD, and PK of zilebesiran administered SC in Japanese patients with mild to moderate hypertension.

Before randomization, patients will discontinue prior antihypertensive medication(s) (if taking) for a Washout period of a minimum of 3 weeks. Patients who meet all inclusion criteria and none of the exclusion criteria will be randomized 1:1:1, to receive a single dose of 300 or 600 mg zilebesiran or placebo.

The planned enrollment for this study is 36 patients, each treatment arm will include 12 patients.

Study Design Schema



Abbreviations: aHTN=antihypertensive medications; BL=baseline; DB=double-blind; M=month; PD=pharmacodynamics; PO=per os (oral); R=randomization; SC=subcutaneous; SD=single dose; WO=washout.
Note: Patients who were previously taking antihypertensives at screening must undergo a washout of these medications for a minimum of 3 weeks during the Screening period.

Below are the treatment groups and their definitions.

Name	Definitions
Placebo	Administered placebo on Day 1 of the 6-month DB Treatment Period.
Zilebesiran 300 mg	Administered 300 mg Zilebesiran SC on Day 1 of the 6-month DB Treatment Period.
Zilebesiran 600 mg	Administered 600 mg Zilebesiran SC on Day 1 of the 6-month DB Treatment Period.

Definition of study periods

Name	Definitions
Screening period	Before the administration of study drug
Double-Blind (DB) Period	From the administration of study drug until the end Month 6 visit (6-month period)
Safety/PD Follow-up	The 6-month period following the Month 6 visit.

2.2 Analysis Population

Analysis Sets	Definitions
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 1 full dose of zilebesiran and have at least 1 evaluable postdose PK assessment.
PD Analysis Set	All patients who received 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.
Full Analysis Set	All randomized participants who received any amount of study drug. All by-treatment analyses based on the Full Analysis Set will be grouped according to the randomized treatment arm.

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. Efficacy will be analyzed using the Full Analysis Set.

2.3 Blinding

Refer to Randomization and Blinding Plan (RBP) for details.

2.4 Analysis time point

The primary analysis will be performed when all patients complete the Month 6 visit or withdraw from the study prior to the Month 6 visit.

The final analysis will be performed when all patients complete the study or withdraw from the study.

A patient is considered to have completed the study if:

- The patient has completed the Month 12 visit (EOS).

- The Investigator, in conjunction with the Sponsor's Medical Monitor, makes a recommendation on a case-by-case basis to discontinue follow-up.

2.5 Safety Assessment

2.5.1 Adverse Events / Treatment-emergent Adverse Events / Serious Adverse Events / Adverse Events of Clinical Interest / Adverse Events Severity / Relationship of the Adverse Event to Study Drug

Item name	**Definitions**
Adverse Event	An AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Treatment-emergent Adverse Event	TEAE is defined as any AE occurring or worsening on or after the first dose of study drug upto 169 days after the study drug administration. Treatment related AEs that occur more than 169 days after the study drug administration (6-month DB period) are also counted as TEAE.
Serious Adverse Events	A Serious Adverse Event is any untoward medical occurrence at any dose: · Results in death. · Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death). · Requires inpatient hospitalization or prolongation of existing hospitalization. · Results in persistent or significant disability or incapacity. · Is a congenital anomaly or birth defect. · Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).
Adverse Events of Clinical Interest	The following are considered to be AEs of clinical interest: · ALT or AST >3×ULN. · Severe or serious ISRs An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR. · Hyperkalemia, defined as any potassium elevation >5.5 mmol/L that has been confirmed by a second measurement (serum or plasma) or that requires clinical intervention. · Hypotension, defined as − clinical signs/symptoms consistent with hypotension, including but not limited to lightheadedness, dizziness, and syncope, coupled with a significantly lower SBP compared to prior visits,

<table>
<tr><th>Item name</th><th>Definitions</th></tr>
<tr><td></td><td>OR − any significantly lower SBP compared to prior visits that requires clinical intervention.
· Clinically significant renal function decline, defined as a decrease in eGFR by ≥30% from baseline and to eGFR <60 mL/min/1.73m2.</td></tr>
<tr><td>Adverse Events Severity</td><td>Adverse events are to be graded according to the categories detailed below:<table><tr><td>Mild:</td><td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td></tr><tr><td>Moderate:</td><td>Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).</td></tr><tr><td>Severe:</td><td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.</td></tr></table></td></tr>
<tr><td>Relationship of the Adverse Event to Study Drug</td><td>Relationship of the Adverse Event to Study Drug should be evaluated by the Investigator by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by the study drug?” A “yes” response indicates that the event is considered as related to the study drug.</td></tr>
</table>

2.5.2 Study Drug Exposure

Duration of exposure to study drug (days) is defined as date of last exposure – date of first dose +1.

Date of last exposure is the earliest date of the following date:

- date of last dose + 169 days (e.g., the length of treatment period or dosing interval)
- date of end of study
- date of analysis data cutoff

2.5.3 Prior and Concomitant Medication, Prior and Concomitant Anti-hypertensive medication

The definition of prior and concomitant medications are below:

- Prior medication: Start date of the drug < 1st day of study drug administration
- Concomitant medication: (Start date of the medication >= 1st day of study drug administration) or (Start date of the drug < 1st day of study drug administration and End date of the medication >= 1st day of study drug administration)

The ATC codes for antihypertension medication are as below:

- C02‑Antihypertensive

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

2.6 Efficacy Assessment

2.6.1 SBP and DBP

Analysis using censoring and analysis using all collected data will be conducted for ABPM and Office Blood Pressure. Analysis using all collected data will be conducted for HBPM

- Censoring data: ABPM/Office Blood Pressure that assessed while patients are on and within 2 weeks after stopping any escape anti-hypertensive medication will be excluded for analysis.
- All collected data: all collected BP data is included in analysis, regardless of the anti-hypertensive escape medication.

2.7 Anti-drug Antibody Analysis (ADA)

Treatment-emergent ADA consists 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

ADA status consists of ADA positive and ADA negative, as defined below:

- ADA positive is defined as patients with confirmed ADA positive results at any visit.
- ADA negative is defined as patients with ADA negative results at all visits, including patients with non-confirmed ADA positive results at screening

ADA post-dose is defined below:

- ADA positive is defined as patients with confirmed ADA positive results at any visit after baseline visit.
- ADA negative is defined as patients with ADA negative results at all visits after baseline visit.

2.8 Analysis Visit

2.8.1 Analysis item except PK data, 24-hour Holter ECG Extraction

Assessment	**Analysis item**	**Analysis visit**
Efficacy	24-hour ABPM (SBP and DBP)	Baseline, Month 3, Month 6
	OBP (SBP and DBP)	Baseline, Day 2, Day 3, Day 8, Day 15, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9 and Month 12
	HBPM (SBP and DBP)	Baseline, Week X (at least once per week after Day 2)
Pharmacodynamic (PD)	Serum AGT	Baseline, Day 8, Day 15, Month 1, Month 2, Month 3, Month 6, Month 9 and Month 12
Biomarker	RAS (Renin concentration, Renin activity assessment and Aldosterone assessment)	Baseline, Month 1, Month 2, Month 3 and Month 6
Safety	Vital sign	Baseline, Day 2, Day 3, Day 8, Day 15, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9 and Month 12
	Weight, Height and BMI	Baseline and Month 6
	Single 12-lead ECG	Baseline and Month 6
	Hematology	Baseline and Month 6
	Serum Chemistry	Baseline, Day 8, Day 15, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9 and Month 12
	Liver Function Tests	Baseline, Day 8, Day 15, Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 9 and Month 12
	Urinalysis	Baseline and Month 6
	Coagulation	Baseline and Month 6
	Glycemic Assessment	Baseline
	Pregnancy Testing/FSH	Baseline
Optional research samples (urine, plasma, serum)	-	Baseline, Month 3 and Month 6
ADA	ADA and titer results	Baseline, Month 1, Month 3, Month 6

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibody; AE=adverse event; AGT=angiotensinogen; DBP=diastolic blood pressure; ECG=electrocardiogram; PD=pharmacodynamics; PK=pharmacokinetics; RAS = renin-angiotensin system; SBP=systolic blood pressure; DNA=deoxyribonucleic acid; FSH=follicle stimulating hormone;

2.8.2 PK 24-hour and Holter ECG Extraction

Analysis item	Analysis visit	Analysis timepoint
Blood PK Sample	Baseline	Predose
	Day 1	30 minutes postdose 1 hour postdose 2 hours postdose 3 hours postdose 4 hours postdose 6 hours postdose 8 hours postdose 12 hours postdose 16 hours postdose
	Day 2	24 hours postdose
	Day 3	48 hours postdose
Pooled urine for PK	Baseline	Predose
	Day 1	>0-6 hours postdose >6-12 hours postdose >12-24 hours postdose
24-hour Holter ECG Extraction	Baseline	Predose
	Day 1	30 minutes postdose 1 hour postdose 2 hours postdose 3 hours postdose 4 hours postdose 6 hours postdose 8 hours postdose 12 hours postdose 16 hours postdose
	Day 2	24 hours postdose

2.8.3 Analysis Visit for Escape Antihypertensive Medication

Escape antihypertensive medication is defined as any antihypertensive medication that was started after the first dose.

The analysis visit for Escape Antihypertensive Medication will be the visits that were censored. The Office BP records that were censored will be used to identify the visits for Escape Antihypertensive Medication.

3. Case and Data Handling

3.1 Handling of missing or partial dates

3.1.1 Handling of missing and partial dates for adverse events

a) Tables

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.

b) Listings:

Imputed dates will not be presented in the listings.

3.1.2 Handling of missing and partial dates for concomitant medication

a) Tables

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.

b) Listings:

Imputed dates will not be presented in the listings.

3.1.3 Handling of missing and partial dates except concomitant medication and adverse events

Imputation for missing dates is not considered.

3.2 Handling of PK data and Urine PK data

3.2.1 Handling of BLQ values

3.2.1.1 For Non Compartmental Analysis (NCA)

BLQ value is imputed to 0 before Tmax and left as missing after Tmax.

3.2.1.2 For figures and summary tables of concentration

BLQ is imputed to 0

For semi-logarithmic Scale figures, BLQ value is imputed to 0.01, instead of zero.

3.2.1.3 For listings of concentration

BLQ values are reported as the raw data.

3.2.2 Handling of PK parameter

The PK parameters $t_{½}$, $AUC_{0\text{-}inf}$, CL/F, and Vz /F will be presented for only subjects in whom λz can be estimated. $AUC_{0\text{-}inf}$ will be reported for only subjects in whom $AUC_{\%extrap}$ <=25%.

3.3 Handling of Safety Data

3.3.1 Handling of Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities and summarized by System Organ Class (SOC) and PT by dose level and overall. AEs, SAEs, study-drug related AEs, AEs leading to withdrawal from study, and AEs leading to death will be summarized by SOC and PT for each treatment arm and overall. Additionally Hepatic AEs, including AEs of LFT abnormalities, Hyperkalemia, Hypotension, Potential Hypotension and Acute renal failure will be summarized by SOC and PT for each treatment arm and overall. AEs, SAEs, and study-drug related AEs will be summarized by PT for each treatment arm and overall. By-patient listings will also be provided.

1) For summary tables

Treatment-emergent Adverse Event from throughout the double-blind treatment period will be included.

- First study drug administration date Onset date of Adverse Events <= first study drug administration + 169 days.
- Treatment related AEs that occur after 169 days of first study drug administration are also counted as TEAE.

AEs with Missing or partial dates will be handled per section 3.1.1.

An AE with missing severity will be assumed to be severe.

An AE with missing study drug relatedness will be assumed to be related.

2) For listings

All Adverse Events from screening period through safety-follow up period will be included.

Missing study drug relatedness and missing severity will be presented as collected in the EDC.

3.3.1.1 Number of Patients with Events

If more than one Adverse Event occurred in a same patient (Relationship of the Adverse Event to Study drug if counting the Relationship of the Adverse Event to Study drug, Serious Adverse

Events if counting the Serious Adverse Event, Adverse Event of Clinical Interest if counting Adverse Event of Clinical Interest, Adverse Event Severity if counting Adverse Event Severity), the number of patients with event occurrence will be counted as one (summary processing performed).

A patient with more than one occurrence of the same AE in a particular SOC/PT will be counted only once for the SOC/PT using the severest event (summary processing performed).

3.3.1.2 Number of Events

If more than one Adverse Event occurred in a same patient (Relationship of the Adverse Event to Study drug if counting the Relationship of the Adverse Event to Study drug, Serious Adverse Event if counting the Serious Adverse Event, Adverse Event of Clinical Interest if counting Adverse Event of Clinical Interest, Adverse Event Severity if counting Adverse Event Severity), each event will be counted respectively (no summary processing performed).

3.3.2 Handling of Prior and Concomitant Medication, Prior and Concomitant Anti-hypertensive Medication

In the tabulation of prior/concomitant medications (System organ class, High level term, Preferred Term), if the same patient uses multiple medications corresponding to the same System organ class, High level term, Preferred Term code when counting the Preferred Term, High level term when counting High level term, System organ class when counting System organ class, the data will be tabulated as one drug.

3.3.3 Handling of all evaluation safety items except for Adverse Events, Prior and Concomitant Medication, Prior and Concomitant Anti-hypertensive medication

- Missing data will not be imputed.
- If outliers are excluded from the analysis, they will be specified, and the reasons for exclusion should be stated.
- For the listing and figure by patient, not only scheduled visit data but also unscheduled visit data will be used. For figures by patient based on Labs, only central labs will be presented.
- For the table and figure of summary statistics, only scheduled visit data will be used. For tables and figures of summary statistics based on Labs, only central labs will be presented.

3.4 Handling of missing data

Imputation for missing data is not considered.

3.5 Handling of time course data

3.5.1 Calculation of Number of Days

Number of Days is calculated by the following formula:

- If after first study drug administration date, Number of Days (n) = date of interest –first study drug administration date + 1
- If prior to first study drug administration date, Number of Days (n) = date of interest – first study drug administration date

Number of Days are negative when the day of interest is prior to first study drug administration date, positive when day of interest is after first study drug administration date. Number of Days never takes 0.

3.5.2 Time Windows

For tables and figures, the visit will be defined as the following:

- For actual visits on EDC except unscheduled visit, end of treatment visit, early termination visit and end of study visit, the visit will be used as it is for analysis.
- For actual visits on EDC of unscheduled visits, the data from this visit will be used to calculate baseline, worst post baseline, and maximum post baseline only. Post baseline unscheduled visits will not be considered for by-visit analysis.
- For actual visits on EDC of end of treatment visit, early termination visit and end of study visit, the analysis visit will be as the following table. The day of administration of the investigational drug is defined as "Day 1"

Analysis visit	**Reference date**	**Time window**
Day 8	Day 8	Day 5 ~ Day 11
Day 15	Day 15	Day 12 ~ Day 18
Month 1	Day 29	Day 24 ~ Day 34
Month 2	Day 57	Day 52 ~ Day 62
Month 3	Day 85	Day 78 ~ Day 92
Month 4	Day 113	Day 106 ~ Day 120
Month 5	Day 141	Day 134 ~ Day 148
Month 6	Day 169	Day 162 ~ Day 176
Month 9	Day 253	Day 239 ~ Day 267
Month 12	Day 337	Day 323 ~ Day 351

For all listings, the visit will be displayed as the visit on EDC.

4. Statistical Analysis

4.1 Details of the Analysis Method

4.1.1 Summary Statistics

Continuous data except plasma PK parameters and pooled urine PK parameters will be summarized using descriptive statistics including number of patients, mean, standard deviation, SEM, median, minimum, and maximum.

Plasma PK concentration, urine PK concentration, Plasma PK parameters and pooled urine of PK parameters will be summarized using descriptive statistics including number of patients, number of BLQ and percentage (%), mean, standard deviation, SEM, CV(%), median, minimum, maximum, geometric mean, and geometric mean CV (%).

Categorical variables will be summarized using frequencies and percentages.

Results will be presented as the estimated value for each treatment group, Placebo, zilebesiran 300 mg, zilebesiran 600 mg, Total zilebesiran and Overall Total.

4.1.2 Baseline

For office BP, baseline is the mean seated office BP on Day 1 prior to receiving the first dose of study drug.

For 24-hour ABPM, baseline is the last measurement prior to receiving the first dose of study drug.

For HBPM, baseline is the average of all assessments during 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.

4.1.3 Percentage of patients

The percentage is calculated by the following formula (unless otherwise indicated):

$$\text{Percentage}(\%)=\frac{\text{Applicable patients}}{\text{Patients per group in the analysis population}}\times 100$$

Unless otherwise noted, the denominator will be based on the analysis population.

4.1.4 Change from baseline and Percent change from baseline

The change from baseline and the percent change from baseline will be calculated using the following formula.

Change from baseline = Postdose value - Baseline value

$$\text{Percent of change}(\%)=\frac{\text{Postdose value-Baseline value}}{\text{Baseline value}}\times 100$$

4.1.5 CV(%)

$$\text{CV}(\%)=\frac{\text{SD}}{\text{Mean}}\times 100$$

Geometric CV(%)=[sqrt(exp(s^2) -1)×100] s^2:Variance on the natural logarithm scale

4.2 Display Digit of the Calculated Value

4.2.1 Display digits of summary statistics, etc.

Mean, SD, SEM, Median

Round to 1 more decimal place than the display digit.

Min, Max

Round to the same number of decimal places as the display digit.

4.2.2 Representation orders of magnitude of proportions (%), CV(%), and geometric CV(%)

Round to the first decimal place.

5. Patient Disposition

5.1 Summary of Screening Failure

Target population	:	All Screened Patients
Group	:	Overall Total
Content of analysis	:	Calculate the number of patients and the percentages by groups for the following items: Screening Pass Screen failure Reason for Screen failure ・ Inclusion/Exclusion Criteria ・ Serious Adverse Event ・ Death, specify ・ Lost to follow-up ・ Physician Decision ・ Study Terminated by Sponsor ・ Withdrawal by Patient ・ Other, specify
Definitions	:	All Screened Patients are all cases in which informed consent was obtained. The denominator of proportions is the target population by groups.

5.2 Patient Disposition for 6-Month DB Period and Safety/PD Follow-up Period

Target population	:	Randomized Patients

Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	Dosed Completed 6-Month DB period Withdrawal from study during 6-Month DB period Completed Study Withdrawal from study During the Safety/PD Follow-up Period Primary reason for withdrawal from study during 6-Month DB period • Adverse Event • Death • Lost to Follow-Up • Physician Decision • Pregnancy • Protocol Deviation • Study Terminated by Sponsor Primary reason for withdrawal from study during Safety/PD Follow-up period • Adverse Event • Death • Lost to Follow-Up • Physician Decision • Pregnancy • Protocol Deviation • Study Terminated by Sponsor
Definition	:	The denominator of proportions is the target population by groups.

5.3 Summary of Data Sets Analyzed

Target population	:	Randomized Patients
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	Calculate the number of patients and the percentages by groups for the following items: • Safety Analysis Set • Pharmacokinetic Analysis Set • Pharmacodynamic Analysis Set • Full Analysis Set
Definitions	:	The denominator of proportions is the target population by groups.

5.4 Summary of Protocol Deviations

Target population	:	Randomized Patients
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	Calculate the number of patients and the percentages by groups for the following items: • Patients with at least one protocol deviation • Patients with at least one major protocol deviation • Reason for protocol deviation
Definitions	:	All Screened Patients are all cases in which informed consent was obtained.

		The denominator of proportions is the target population by groups. Multiple answers are counted in each reason. Before randomization: Deviation date <= randomized date. 6-Month DB period: 6-Month DB period start date <= Deviation date <= 6-Month DB period end date. Safety/PD Follow-up period: Safety/PD Follow-up period start date <= Deviation date <= Safety/PD Follow-up period end date.

6. Demographic and other baseline characteristics

6.1 Demographic and Other Baseline Characteristics

Target population	:	Safety Analysis Set
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・Summaries of demographic and other baseline characteristics will be presented for all patients in the target population. ・For categorical data and ordinal data, calculate the number of patients and percentages by groups. For continuous data, calculate the summary statistics by groups.
Definitions	:	・The denominator of proportions is the target population by groups.

[Background items]

Data	Items [Units]	Classification	Remarks
Continuous	Age at Informed Consent [years]	-	
	Height [cm]	-	
	Weight (Baseline) [kg]	-	
	BMI [kg/m^2]	-	
	eGFR [mL/min/1.73m^2]	-	
Categorical	Age category [years]	<65, >=65	
	Sex	Male, Female	
	Race	Asian	
	BMI Category [kg/m^2]	<25, >=25 to <30, >=30	
	eGFR category [mL/min/1.73m^2]	>=90, >=60 to <90	
	Baseline ABPM category [mmHg] Systolic blood pressure	<145, >=145	

6.2 Baseline Blood Pressure

Target population	:	Full Analysis Set
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Analysis Items	:	24-hour ABPM (mmHg) (Systolic blood pressure, Diastolic blood pressure), Daytime ABPM (mmHg) (Systolic blood pressure, Diastolic blood pressure), Nighttime ABPM (mmHg) (Systolic blood pressure, Diastolic blood pressure), OBP (mmHg) (Systolic blood pressure, Diastolic blood pressure), HBPM (mmHg) (Systolic blood pressure, Diastolic blood pressure)
Content of analysis	:	・Calculate the summary statistics of baseline Systolic blood pressure and Diastolic blood pressure by 24-hour ABPM, Daytime ABPM, Nighttime

		ABPM, OBP and HBPM by groups.
Definitions	:	・Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

6.3 Summary of Medical/Surgical History

Target population	:	Safety Analysis Set
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Analysis Items	:	Medical/Surgical History
Content of analysis	:	・The number and percentages of patients with at least one medical/surgical history will be summarized by groups. ・The number and percentage of patients who has medical/surgical history will be summarized by groups, System organ class, High level term and Preferred Term.
Definitions	:	・The denominator is the target population by groups ・In the tabulation of medical/surgical history, if the same patient had multiple medical/surgical history corresponding to the same same System organ class, High level term, Preferred Term code when counting the Preferred Term, same System organ class, High level term when counting High level term, same System organ class when counting System organ class, the data will be tabulated as one medical/surgical history

6.4 Study Drug Administration

Target population	:	Safety Analysis Set
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Analysis Items	:	Study Drug Administration (Yes/No), Full dose successful Administration (Yes/No), Total duration of study exposure (days), and Dose Administered (continuous data)
Content of analysis	:	・For Study Drug Administration and Full dose successful Administration, the number of patients and percentage will be calculated by groups. ・Calculate the summary statistics of Total duration of study exposure (day) and Dose Administrated by groups.
Definitions	:	・The denominator of proportions is the target population by groups.

7. Efficacy Evaluation

7.1 SBP and DBP

7.1.1 Summary of All Collected ABPM/OBP

Target population	:	Full Analysis Set
Analysis	:	SBP, DBP by ABPM and office blood pressure

Items		
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline for each parameter by groups and analysis time points.

7.1.2 Summary of ABPM/OBP Censored by Concomitant Anti-Hypertensive Medication

Target population	:	Full Analysis Set
Analysis Items	:	SBP, DBP by ABPM and office blood pressure
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline for each parameter by groups and analysis time points.

7.1.3 Summary of All Collected ABPM by Day/Night Time Measurements

Target population	:	Full Analysis Set
Analysis Items	:	SBP, DBP by ABPM
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline for each parameter by groups and analysis time points day/night time.
Definition	:	・Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

7.1.4 Summary of ABPM ratio of Nighttime to Daytime Systolic Blood Pressure

Target population	:	Full Analysis Set
Analysis Items	:	SBP by ABPM
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the number of patients and the percentages by groups and categories of SBP. ・Category is as follows: < 0.9, 0.9 to < 1.0, >= 1.0, Missing

Definitions	:	・The denominator of proportions is the target population by groups. ・Daytime is defined as 6 am to 9:59 pm and nighttime is defined as 10 pm to 5:59 am.

7.1.5 Treatment Responder in ABPM/OBP by Treatment and Visit

Target population	:	Full Analysis Set
Analysis Items	:	Reduction from baseline of >= 5 mmHg and >=10 mmHg in SBP by ABPM/OBP
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Count the number of patients for each analysis items by groups.
Definition	:	・The denominator of proportions is the target population by groups.

7.1.6 Summary of SBP and DBP assessed by HBPM

Target population	:	Full Analysis Set
Analysis Items	:	SBP, DBP by HBPM
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline for each parameter by groups and analysis time points.

7.1.7 Spaghetti Plot of All Collected Systolic Blood Pressure/Diastolic Blood Pressure Assessed by 24-Hour ABPM/OBP during 6-Month DB period

Target population	:	Full Analysis Set
Analysis Items	:	SBP and DBP by ABPM/OBP
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and change from baseline of each analysis item by group, analysis visit in 6-Month DB period

7.1.8 Mean (+/- SEM) Change from Baseline in All Collected Systolic Blood Pressure/Diastolic Blood Pressure Assessed by 24-Hour ABPM/OBP during 6-Month DB period

Target population	:	Full Analysis Set
Analysis	:	SBP and DBP by ABPM/OBP

Items		
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Trend diagram of Mean ± SEM will be presented graphically by groups, analysis visit in 6-Month DB period

7.1.9 Mean (+/- SEM) Change from Baseline in Censored Systolic Blood Pressure/Diastolic Blood Pressure Assessed by 24-Hour ABPM/OBP during 6-Month DB period

Target population	:	Full Analysis Set
Analysis Items	:	SBP and DBP by ABPM/OBP
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Trend diagram of Mean ± SEM will be presented graphically by groups, analysis visit in 6-Month DB period

7.1.10 Proportion of Patients with Escape Antihypertensive Medication by Visit

Target population	:	Full Analysis Set
Analysis Items	:	Patients with Escape Antihypertensive Medication
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.3
Content of analysis	:	・The number of patients with Escape Antihypertensive Medication and the percentage will be calculated for each group.
Definition	:	・The denominator of proportions is the target population by groups.

8. Pharmacodynamic Evaluation

8.1 Summary of serum AGT

Target population	:	PD Analysis Set
Analysis Items	:	Serum AGT
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline, percent change from baseline for each parameter by groups and analysis time points. ・Calculate the summary statistics of maximum post-baseline percent change, time to Maximum post-baseline percent change (day) by groups.

8.2 Mean (+/- SEM) Serum AGT

Target population	:	PD Analysis Set
Analysis Items	:	Serum AGT
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Trend diagram of Mean ± SEM of measurement value and percent change from baseline will be presented graphically by groups, analysis visit in 6-Month DB period ・Trend diagram of Mean ± SEM of measurement value and percent change from baseline will be presented graphically by groups, analysis visit in 6-Month DB period and Safety/PD Follow-up period

8.3 Spaghetti Plot of Serum AGT

Target population	:	PD Analysis Set
Analysis Items	:	Serum AGT
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and percent change from baseline of AGT by group, analysis visit in 6-Month DB period ・Spaghetti Plot for measurement value and percent change from baseline of AGT by group, analysis visit in 6-Month DB period and Safety/PD Follow-up period

8.4 Spaghetti Plot of Serum AGT by ADA Status during 6-Month DB Period

Target population	:	PD Analysis Set
Analysis Items	:	Serum AGT
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and percent change from baseline of AGT by group, patient and analysis visit in 6-Month DB period, ADA Status

9. Biomarker Evaluation

9.1 Summary of change from baseline in plasma renin concentration, plasma renin activity, and aldosterone

Target population	:	PD Analysis Set

Analysis Items	:	Plasma renin concentration, plasma renin activity, and aldosterone (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of change from baseline for plasma renin concentration, plasma renin activity, and aldosterone by groups and analysis time points.

9.2 Mean (+/- SEM) Exploratory Biomarkers by Visit

Target population	:	PD Analysis Set
Analysis Items	:	Plasma renin concentration, plasma renin activity, and aldosterone (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Trend diagram of Mean ± SEM of measurement value and percent change from baseline will be presented graphically by groups, analysis visit in 6-Month DB period

9.3 Spaghetti Plot of Exploratory Biomarkers

Target population	:	PD Analysis Set
Analysis Items	:	Plasma renin concentration, plasma renin activity, and aldosterone (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and percent change from baseline of each analysis item by group, analysis visit in 6-Month DB period

10. Anti-drug antibodies ADA

10.1 Summary of ADA Results

Target population	:	Safety Analysis Set
Analysis Items	:	Anti-drug antibodies (ADA)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Baseline, post-dose, treatment-emergent ADA
Content of analysis	:	・Calculate the number of patients with the measurement value, ADA-positive at baseline by groups. and timepoint (baseline, post-dose and treatment-emergent ADA) ・Calculate the titer (min, max) by groups. and timepoint (baseline, post-dose and treatment-emergent ADA)

Definitions	:	・The denominator of proportions is the target population by groups.

11. Pharmacokinetics Evaluation

11.1 Summary of Plasma Zilebesiran Concentrations/ Urine Zilebesiran Concentrations/ Metabolite Plasma AS(N-1)3′ Zilebesiran Concentrations/ Metabolite Urine AS(N-1)3′ Zilebesiran Concentrations

Target population	:	PK Analysis Set
Analysis Items	:	Plasma zilebesiran concentrations, Urine zilebesiran concentrations, Metabolite plasma AS(N-1)3′ zilebesiran concentrations, Metabolite urine AS(N-1)3′ zilebesiran concentrations
Group	:	Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.2
Content of analysis	:	・Calculate the summary statistics of analysis items by groups and analysis time points.

11.2 Mean (+/- SEM) Plasma Zilebesiran Concentrations/ Urine Zilebesiran Concentrations/ Metabolite Plasma AS(N-1)3′ Zilebesiran Concentrations/Metabolite Urine AS(N-1)3′ Zilebesiran Concentrations - Linear Scale/Semi-logarithmic Scale

Target population	:	PK Analysis Set
Analysis Items	:	Plasma zilebesiran concentrations, Urine zilebesiran concentrations, Metabolite plasma AS(N-1)3′ zilebesiran concentrations, Metabolite urine AS(N-1)3′ zilebesiran concentrations
Group	:	Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.2
Content of analysis	:	・Trend diagram of Mean ± SEM of measurement value will be presented graphically on both Linear Scale and Semi-logarithmic Scale by groups, analysis visit in 6-Month DB period

11.3 Spaghetti Plot of Plasma Zilebesiran Concentrations/Metabolite Plasma AS(N-1)3′ Zilebesiran Concentrations by ADA Status - Linear Scale and Semi-logarithmic Scale

Target population	:	PK Analysis Set
Analysis Items	:	Plasma Zilebesiran concentrations, Metabolite plasma AS(N-1)3′ zilebesiran concentrations
Group	:	Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.2
Content of analysis	:	・Spaghetti Plot for measurement value of each analysis items on both Linear Scale and Semi-logarithmic Scale by group, analysis visit in 6-Month DB period

11.4 Summary of Plasma Zilebesiran Pharmacokinetic Parameters/Metabolite Plasma AS(N-1)3′ Zilebesiran Parameters

Target population	:	PK Analysis Set
Analysis Items	:	$AUC_{0\text{-}24}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, C_{max}, T_{max}, $T_{1/2}$, CL/F, Vz/F, λz for Zilebesiran. $AUC_{0\text{-}24}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, C_{max}, T_{max}, $T_{1/2}$, CL/F, Vz/F, λz, MRCMAX, MRAUC for AS(N-1)3′ Zilebesiran.
Group	:	Zilebesiran 300 mg, Zilebesiran 600 mg
Content of analysis	:	・Calculate the summary statistics of analysis items by groups. ・PK parameters: $T_{1/2}$, AUC0-inf, CL/F, and Vz/F will be presented for only those patients in whom λz can be estimated.

11.5 Summary of Pooled urine Zilebesiran Pharmacokinetic Parameters/Metabolite Urine AS(N-1)3′ Zilebesiran Parameters

Target population	:	PK Analysis Set
Analysis Items	:	Ae, fe, and CL_R
Group	:	Zilebesiran 300 mg, Zilebesiran 600 mg
Content of analysis	:	・Calculate the summary statistics of analysis items by groups.

12. Safety Evaluation

12.1 Adverse Events

12.1.1 Overall summary of Treatment-emergent Adverse Events

Target population	:	Safety Analysis Set
Analysis Items	:	・Treatment-emergent Adverse Events Study Drug Related Treatment-emergent Adverse Event ・Treatment-emergent Serious Adverse Events Study Drug Related Treatment-emergent Serious Adverse Events ・Severe Treatment-emergent Adverse Events Study Drug Related Severe Treatment-emergent Adverse Events ・Treatment-emergent Adverse Events leading to withdrawal from study Study Drug Related Treatment-emergent Adverse Events leading to withdrawal from study ・Death
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・Calculate the number of patients with the event and the percentages, the number of events by groups.
Definitions	:	・The denominator of proportions is the target population by groups.

		・For Death, all fatal serious AEs are summarized, regardless of treatment-emergent classification.

12.1.2 Summary of Treatment-emergent Adverse Events by SOC and PT

Target population	:	Safety Analysis Set
Analysis Items	:	・Treatment-emergent Adverse Events ・Study Drug Related Treatment-emergent Adverse Events ・Treatment-emergent Serious Adverse Events ・Study Drug Related Treatment-emergent Serious Adverse Events ・Treatment-emergent Adverse Events leading to withdrawal from study ・Treatment-emergent Adverse Events leading to death ・Hepatic Treatment-emergent Adverse Events including AEs of LFT abnormalities ・Treatment-emergent Adverse Events of Hyperkalemia ・Treatment-emergent Adverse Events of Hypotension and Potential Hypotension ・Treatment-emergent Adverse Events of Acute Renal Failure
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number of patients with the event and the percentage, the number of events will be calculated for each group.
Definitions	:	・The denominator of proportions is the target population by groups. ・Hepatic AEs, including AEs of Liver Function Test (LFT) abnormalities (SMQ all narrow and broad terms) ・Hyperkalemia (CMQ) (Refer to Appendix 3) ・Hypotension (FMQ narrow terms) ・Potential Hypotension (Refer to Appendix 3) ・Acute renal failure (SMQ all narrow and broad terms)

12.1.3 Summary of Treatment-emergent Adverse Events by Maximum Severity by SOC and PT

Target population	:	Safety Analysis Set
Analysis Items	:	Treatment-emergent Adverse Events, Study Drug Related Treatment-emergent Adverse Events
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number of patients with the event, and the percentage will be calculated by groups and severity. ・For symptoms (SOC, PT), the number of patients with symptoms and the percentage will be calculated by groups and severity.
Definitions	:	・Severity: Mild, Moderate, Severe ・If multiple AEs with the same SOC (PT for the PT tabulation) occurs to the same patient, then count that patient into the worst severity. ・The denominator of proportions is the target population by groups.

12.1.4 Summary of Treatment-emergent Adverse Events by PT

Target population	:	Safety Analysis Set
Analysis Items	:	Treatment-emergent Adverse Events, Study Drug Related Treatment-emergent Adverse Events, Treatment-emergent Serious Adverse Events
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number of patients with the event and the percentage, the number of events will be calculated for each group.
Definition	:	・The denominator of proportions is the target population by groups.

12.1.5 Summary of Injection Site Reactions (ISRs)

Target population	:	Safety Analysis Set
Analysis Items	:	Injection Site Reactions
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number of patients and the percentage, the number of signs and symptoms will be calculated for each group.
Definition	:	・The denominator of proportions is the target population by groups.

12.1.6 Summary of Most Common (>=5%) Treatment-emergent Adverse Events by SOC and PT

Target population	:	Safety Analysis Set
Analysis Items	:	Most common (>=5%) Treatment-emergent Adverse Events
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number of patients with the event, and the percentage will be calculated by groups ・For symptoms (SOC, PT), the number of patients with symptoms and the percentage will be calculated by groups.
Definitions	:	・The denominator of proportions is the target population by groups. ・Most common (>=5%) Treatment-emergent Adverse Events are the events (PTs) with higher than or equal to 5% patients in any treatment group (Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg).

12.2 Vital Signs, Weight, Height and BMI

12.2.1 Summary of Vital Sign Tests, Weight, Height and BMI by Visit

Target population	:	Safety Analysis Set
Analysis	:	Height, Weight, BMI, Body temperature, Heart Rate, Respiratory Rate

Items		
Group	:	Placebo, Zilebesiran 300 mg, zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline and percent change from baseline for each quantitative item of the vital sign tests, Height, Weight, and BMI by groups and analysis time points.

12.2.2 Summary of Orthostatic Hypotension during 6-Month DB Period

Target population	:	Safety Analysis Set
Analysis Items	:	SBP, DBP
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・The number of patients with orthostatic hypotension, the number of patients with assessment and the percentage of patients with orthostatic hypotension will be calculated for each group
Definition	:	・Orthostatic hypotension is defined as SBP drop ≥20 mmHg or DBP ≥10 mmHg from sitting to standing.

12.2.3 Summary of Abnormalities in Vital Sign Tests

Target population	:	Safety Analysis Set
Analysis Items	:	Weight, Body temperature, Heart Rate, Respiratory Rate
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・The number and percentages of patients by groups, analysis items and category. ・Category is as follow: Weight: Increment >=7%, Decrement >=7% Heart Rate: >100 bpm, Increment >15 bpm, Increment >30 bpm, <60 bpm, Decrement >15 bpm, Decrement >30 bpm Respiratory Rate: >20 breaths/min, <12 breaths/min Body temperature: >38 ºC, <36 ºC Office SBP (mmHg): > 160 mmHg, Increment > 40 mmHg, < 90 mmHg, Decrement > 40 mmHg Office DBP (mmHg): > 100 mmHg, Increment > 20 mmHg, < 50 mmHg, Decrement > 20 mmHg
Definition	:	・If multiple observation occurs to the same patient, then count that patient as one patient.

12.3 ECG

12.3.1 Summary of Electrocardiogram Results by Visit

Target population	:	Safety Analysis Set
Analysis Items	:	ECG Ventricular rate, RR Interval, PR Interval, QRS Duration, QT Interval, QTcF Interval
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Single 12-lead ECG: Refer to section 2.8.1 24-hour Holter ECG: Refer to section 2.8.2
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline and percent change from baseline for each quantitative item of the ECG test by groups and analysis time points. ・The baseline will be determined according to the Analysis Group ・The summary will be done for both Single 12-lead ECG and 24-hour Holter ECG.

12.3.2 Summary of Rhythm, Overall Interpretation of Electrocardiogram, Change from Baseline Electrocardiogram by Visit

Target population	:	Safety Analysis Set
Analysis Items	:	Rhythm, Overall Interpretation of ECG, Change from Baseline ECG
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Single 12-lead ECG: Refer to section 2.8.1 24-hour Holter ECG: Refer to section 2.8.2
Content of analysis	:	・Calculate the number of patients and the percentages by groups, analysis time points, ECG test and categories ・Category is as follows: Rhythm: Normal; Abnormal, not clinically significant; Abnormal, clinically significant; Not Evaluable; Missing Overall Interpretation of ECG: Normal; Abnormal, not clinically Significant; Abnormal, clinically significant; Missing Change from Baseline ECG: No significant worsening from baseline; Clinically significant worsening from baseline; Missing ・The summary will be done for both Single 12-lead ECG and 24-hour Holter ECG.
Definitions	:	・The denominator of proportions is the target population by groups.

12.3.3 Shifts from Baseline to Worst Post-Baseline in QTcF Intervals on 24-hour Holter Electrocardiogram

Target population	:	Safety Analysis Set
Analysis Items	:	Worst Post-Baseline Value in QTcF Intervals, Maximum Change from Baseline in QTcF Intervals

Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Content of analysis	:	・Create shift table for baseline data and post-dose visit data by analysis items and categories ・Category is as follows: Worst Post-Baseline Value (msec): <=450, >450 to 480, >480 to 500, >500, Missing, Total Maximum Change from Baseline (msec): <=30, >30 to 60, >60, Missing, Total
Definitions	:	・If the patient performs the test but there is not assessment result data will be analyzed as “Missing” ・The denominator of proportions is the target population by groups.

12.4 Laboratory Parameters

12.4.1 Summary of Laboratory Parameters by Visit

Target population	:	Safety Analysis Set
Analysis Items	:	Hematology, Serum Chemistry, Liver Function Tests, Urinalysis, Coagulation (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the summary statistics of measurement value, change from baseline and percent change from baseline for each quantitative item of the laboratory test by groups and analysis time points.

Items of Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR[a]	Chloride
Triglycerides	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Glycemic Assessment	
HbA1c	
Immunogenicity	
Anti-drug antibodies	
Pregnancy Testing/FSH Screening	
β-human chorionic gonadotropin (females of childbearing potential only)	FSH (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin A1c; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; RBCs=red blood cells.
[a] Refer to the Laboratory Manual for further instructions on calculating eGFR.

12.4.2 Shifts from Baseline to Worst Post-Baseline for Laboratory Parameters during 6-month DB Period

Target population	:	Safety Analysis Set
Analysis	:	Hematology, Serum Chemistry, Liver Function Tests, Urinalysis,

Items		Coagulation (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Create shift table for baseline to worst post-baseline data by groups, laboratory test and grade. ・Grade is as follows: Low, Normal, High, Total
Definitions	:	・The denominator of proportions is the target population by groups.

12.4.3 Summary of Post-Baseline Potentially Clinically Significant Abnormalities for Clinical Laboratory Data during 6-Month DB Period

Target population	:	Safety Analysis Set
Analysis Items	:	Hematology, Serum Chemistry
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Calculate the number of patients and the percentages by groups, analysis items and categories ・Category for Hematology is as follows Hemoglobin (g/L): <100 Lymphocytes ($x10^9$/L): <0.8, <0.5, >12 Neutrophils ($x10^9$/L): <1.5, <1.0, ≥12 Platelet Count ($x10^9$/L): <75, <50, ≥600 WBC Count ($x10^9$/L): <3.0, ≥16 ・Category for Serum Chemistry is as follows: Albumin (g/L): <30 Calcium (mmol/L): <2.0, >2.9 Creatinine (umol/L): >2xBaseline, >3xBaseline or >4 mg/dL eGFR(mL/min/1.73m^2): ≥30% Decrease from Baseline Plasma Glucose (mmol/L): <3.0, ≥13.9 Serum Glucose (mmol/L): <3.0, ≥13.9 Phosphate (mmol/L): <0.6 Potassium (mmol/L): <3.0, >5.5, >6.0 Sodium (mmol/L): <130, >155 ・Calculate for Serum Chemistry with Confirmed by repeat measure is as follows: Creatinine (umol/L): >2xBaseline, Confirmed by repeat measure eGFR(mL/min/1.73m^2): ≥30% Decrease from Baseline, Confirmed by repeat measure Potassium (mmol/L): >5.5, Confirmed by repeat measure
Definitions	:	・The denominator of proportions is the target population by groups. ・Repeat measure: the abnormal criteria was present for consecutive (non-missing) collections.

12.4.4 Shifts from Baseline to Worst Post-Baseline in eGFR (mL/min/1.73m^2) during 6-month DB Period

Target population	:	Safety Analysis Set
Analysis Items	:	eGFR (mL/min/1.73m^2)
Content of analysis	:	・Create shift table for baseline to Worst post-baseline data by category. ・Category is as follows: >=90 (mL/min/1.73m^2), 60 to <90 (mL/min/1.73m^2), 45 to <60 (mL/min/1.73m^2), 30 to <45 (mL/min/1.73m^2), 15 to <30 (mL/min/1.73m^2), <15 (mL/min/1.73m^2), Missing, Total
Definition	:	・The denominator of proportions is the target population by groups.

12.4.5 Summary of Abnormalities in Worst Post-Baseline in Liver Function Tests

Target population	:	Safety Analysis Set
Analysis Items	:	Liver Function Tests
Content of analysis	:	・The number and percentages of patients by groups, analysis items and category. ・Category is as follow: ALT, AST, ALT or AST: <= ULN, > ULN & <= 3xULN, > 3xULN & <= 5xULN, > 5xULN & <= 10xULN, > 10xULN & <= 20xULN, > 20xULN, Missing Total Bilirubin: <=ULN, > ULN & <= 1.5xULN, > 1.5xULN <= 2xULN, > 2xULN <= 3xULN, > 3xULN <= 5xULN, > 5xULN, Missing Alkaline Phosphatase: <=ULN, >ULN & <=1.5xULN, >1.5xULN, Missing AST or ALT and Concurrent Total Bilirubin: (AST > 3xULN or ALT >3xULN) and Total Bilirubin > 2xULN
Definition	:	・The denominator of proportions is the target population by groups.

12.4.6 Mean (+/- SEM) of Laboratory Parameters for Liver Function Tests/eGFR/Potassium by Visit

Target population	:	Safety Analysis Set
Analysis Items	:	Liver Function Tests, eGFR, Potassium (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1

Content of analysis	:	・Trend diagram of Mean ± SEM of measurement value will be presented graphically by groups, analysis visit in 6-Month DB period and Safety/PD Follow-up

12.4.7 eDISH Plot of Post-baseline Peak ALT or AST versus Total Bilirubin/ALT versus Total Bilirubin/AST versus Total Bilirubin, Per Patient

Target population	:	Safety Analysis Set
Analysis Items	:	AST, ALT, Total Bilirubin
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・eDISH plot will be presented graphically by groups, patients. ・The target of the analysis are patients who have post-baseline data
Definition	:	・Peak value is defined as the highest data of analysis item.

12.4.8 Spaghetti Plot for Liver Function Tests during 6-Month DB Period

Target population	:	Safety Analysis Set
Analysis Items	:	Liver Function Tests (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and percent change from baseline of each analysis item by group, analysis visit in 6-Month DB period

12.4.9 Spaghetti plot for Potassium for Patients with Post Baseline >5.5 (mmol/L) during 6-Month DB Period

Target population	:	Safety Analysis Set
Analysis Items	:	Potassium (Refer to Appendix 2)
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg
Time of analysis	:	Refer to section 2.8.1
Content of analysis	:	・Spaghetti Plot for measurement value and percent change from baseline of analysis item by group, analysis visit in 6-Month DB period

12.5 Prior and Concomitant Medication, Prior and Concomitant Anti-hypertensive medication

12.5.1 Summary of Prior and Concomitant Medication, Prior and Concomitant Anti-hypertensive

medication

Target population	:	Safety Analysis Set
Group	:	Placebo, Zilebesiran 300 mg, Zilebesiran 600 mg, Total zilebesiran, Overall Total
Analysis Items	:	Prior medication, Concomitant medication, Prior Anti-hypertensive medication, Concomitant Anti-hypertensive medication.
Content of analysis	:	・The number and percentages of patients with at least one prior medication will be summarized by groups. ・For prior medications, the number and percentage of patients who took each medicine will be summarized by High level term and Preferred Term. ・Concomitant medication, Prior Anti-hypertensive medication, Concomitant Anti-hypertensive medication will be summarized as well as prior medication.
Definitions	:	・The denominator is the target population by groups.

13. Listings to create

13.1 Listing of Screened Patient

13.2 Listing of Randomization

13.3 Listing of Patient Disposition

13.4 Listing of Protocol Deviations

13.5 Listing of Analysis Population

13.6 Listing of Demographics

13.7 Listing of Medical and Surgical History

13.8 Listing of Prior and Concomitant Medication

13.9 Listing of Concomitant Anti-hypertension Medication

13.10 Listing of Study Drug Administration

13.11 Listing of Patients Receiving Various Batches of Investigational Products

13.12 Listing of 24-Hour Mean ABPM

13.13 Listing of Individual Office Sitting BP Readings

13.14 Listing of Average Office BP

13.15 Listing of Individual HBPM Readings

13.16 Listing of Weekly Average of HBPM

13.17 Listing of Serum AGT

13.18 Listing of RAS Biomarkers

13.19 Listing of Adverse Events

13.20 Listing of Serious Adverse Events

13.21 Listing of Adverse Events of Clinical Interest

13.22 Listing of Adverse Events of Hepatic including AEs of LFT abnormalities

13.23 Listing of Adverse Events of Hyperkalemia

13.24 Listing of Adverse Events of Hypotension and Potential Hypotension

13.25 Listing of Adverse Events of Acute Renal Failure

13.26 Listing of Injection Site Reactions

13.27 Listing of Deaths

13.28 Listing of Vital Signs, Weight, Height and BMI

13.29 Listing of Pregnancy Test

13.30 Listing of Physical examination

13.31 Listing of 12-lead Electrocardiogram

13.32 Listing of 24-hour Holter Electrocardiogram

13.33 Listing of Hematology

13.34 Listing of Serum Chemistry

13.35 Listing of Liver Function Tests

13.36 Listing of Coagulation

13.37 Listing of Urinalysis

13.38 Listing of Laboratory Abnormalities

13.39 Listing of Liver Function Test Results for Patients with Abnormal LFT

13.40 Listing of Serum Chemistry Potassium Results for Patients with Post Baseline >5.5 (mmol/L)

13.41 Listing of Patients with 30% eGFR reduction from Baseline

13.42 Listing of Normal Ranges for Laboratory Parameters

13.43 Listing of Anti-drug Antibodies Test Results

13.44 Listing of individual Plasma Zilebesiran Pharmacokinetic Concentrations

13.45 Listing of individual Urine Zilebesiran Pharmacokinetic Concentrations

13.46 Listing of individual Plasma Zilebesiran Pharmacokinetic Parameters

13.47 Listing of individual Urine Zilebesiran Pharmacokinetic Parameters

14. Citations

Not applicable.

Appendix 1: Software, Dictionary

The following software and versions will be used.

	Software and Versions
OS	Microsoft Windows 10
Statistical analysis software	SAS 9.4 or later
Tabulation software	Microsoft Word 2016
WHO-Drug Dictionary	Version Global C3 Mar 2022
MedDRA	Version 25.0

Appendix 2: The list of Unit and Display digit for quantitative item

Assessment Classification	Item name	Unit	Display digit
Efficacy			
ABPM, OBP, HBPM	Systolic blood pressure	[mmHg]	1
	Diastolic blood pressure	[mmHg]	1
Pharmacodynamic (PD)			
	Serum AGT	[ng/mL]	1
Biomarker Evaluation			
	Plasma renin concentration	[ng/mL]	
	Plasma renin activity	NA	1
	Aldosterone/Renin Activity	NA	1
	Aldosterone serum	NA	1
Pharmacokinetics			
Concentrations	Plasma zilebesiran concentrations	[ng/mL]	1
	Urine zilebesiran concentrations	[ng/mL]	1
	Metabolite plasma AS(N-1)3′ zilebesiran concentration	[ng/mL]	1
	Metabolite urine AS(N-1)3′ zilebesiran concentration	[ng/mL]	1
Pharmacokinetics parameters, Metabolite	AUC_{0-24}	[ng*h/mL]	3 significant figures
	AUC_{0-last}	[ng*h/mL]	3 significant figures
	AUC_{0-inf}	[ng*h/mL]	3 significant figures
	$AUC_{\%extrap}$	[%]	3 significant figures
	C_{max}	[ng/mL]	3 significant figures
	T_{max}	[h]	3 significant figures
	$T_{1/2}$	[h]	3 significant figures
	CL/F	[L/h]	3 significant figures
	Vz/F	[L]	3 significant figures
	λ z	[1/h]	3 significant figures
	MRCMAX	NA	3 significant figures
	MRAUC	NA	3 significant figures
Pooled urine Pharmacokinetic Parameters, Metabolite Urine	Ae	[mg]	3 significant figures
	fe	[%]	3 significant figures
	CL_R	[L/h]	3 significant figures
Safety			
Vital sign	Height	[cm]	0.1
	Weight	[kg]	0.1
	BMI	[kg/m^2]	0.1
	Body Temperature	[^oC]	0.1

Assessment Classification	Item name	Unit	Display digit
ECG	Heart Rate	[beats/min]	1
	Respiratory Rate	[beats/min]	1
	ECG Ventricular rate	[beats/min]	1
	RR Interval	[msec]	1
	PR Interval	[msec]	1
	QRS Duration	[msec]	1
	QT Interval	[msec]	1
	QTcF Interval	[msec]	1
	ECG Mean Heart Rate	[beats/min]	1
	QTcB Interval	[msec]	1
Laboratory test			
Hematology	Basophils	[%]	0.1
	Basophils (Absolute Ct)	[10^9/L]	0.01
	Nucleated Red Blood Cell, % (Sysmex)	[%]	0.1
	Eosinophils	[%]	0.1
	Eosinophils (Absolute Ct)	[10^9/L]	0.01
	Immature Granulocytes	[%]	0.1
	Immature Granulocytes/Leukocytes	[10^9/L]	0.01
	Hematocrit	[%]	0.1
	Hemoglobin	[g/L]	0.1
	Platelets	[$\times 10^4/\mu$L]	0.1
	Lymphocytes	[%]	1
	Lymphocytes/Leukocytes	10^9/L	0.01
	Ery. Mean Corpuscular Hemoglobin	[pg]	0.1
	Ery. Mean Corpuscular HGB Concentration	[g/dL]	0.1
	Ery. Mean Corpuscular Volume	[fL]	0.1
	Monocytes	[%]	0.1
	Monocytes/Leukocytes	[10^9/L]	0.01
	Mean Platelet Volume	[fL]	0.1
	Neutrophil	[%]	0.1
	Neutrophils/Leukocytes	[10^9/L]	0.01
	Erythrocytes	[10^{12}/L]	0.01
	Nucleated Erythrocytes	[10^9/L]	0.01
	Erythrocytes Distribution Width	[%]	0.1
	Leukocytes	[10^9/L]	0.01
Serum Chemistry	Sodium	[mmol/L]	1
	Triglycerides	[mg/dL]	1
	Urea Nitrogen	[mg/dL]	1
	Urate	[mg/dL]	0.1
	Protein	[g/dL]	0.1
	Glucose	[mmol/L]	1
	Creatinine	[mg/dL]	0.1
	eGFR	[mL/min/1.73 m^2]	1

Assessment Classification	Item name	Unit	Display digit
	Choriogonadotropin Beta	[IU/L]	0.1
	Potassium	[mmol/L]	0.1
	Phosphate	[mmol/L]	0.1
	Albumin	[g/L]	0.01
	Calcium	[mmol/L]	0.1
	Bicarbonate	[mEq/L]	1
	Chloride	[mEq/L]	1
Liver Function Tests	AST	[U/L]	1
	ALT	[U/L]	1
	GGT	[U/L]	1
	ALP	[U/L]	1
	Direct Bilirubin	[mg/dL]	0.01
	Total Bilirubin	[mg/dL]	0.01
Urinalysis	pH	[pH]	1
	Specific gravity	NA	0.001
	Bacteria	[/HPF]	1
	Color	NA	1
	Granular Casts	[/LPF]	1
	Hyaline Casts	[/LPF]	1
	RBC Casts	[/LPF]	1
	Waxy Casts	[/LPF]	1
	WBC Casts	[/LPF]	1
	Amorphous Crystals	[/HPF]	1
	Calcium Carbonate Crystals	[/HPF]	1
	Calcium Oxalate Crystals	[/HPF]	1
	Calcium Phosphate Crystals	[/HPF]	1
	Cystine Crystals	[/HPF]	1
	Leucine Crystals	[/HPF]	1
	Triple Phosphate Crystals	[/HPF]	1
	Tyrosine Crystals	[/HPF]	1
	Uric Acid Crystals	[/HPF]	1
	Renal Epithelial Cells	[/HPF]	1
	Squamous Epithelial Cells	[/HPF]	1
	Transitional Epithelial Cells	[/HPF]	1
	Ketones	[mg/dL]	1
	Albumin	NA	1
	Urinary Glucose	[mg/dL]	1
	Urinary protein	[mg/dL]	1
	Nitrite	NA	1
	Leukocytes Esterase	NA	1
	Erythrocytes	[/HPF]	1
	Specimen Appearance	NA	1
	Urinary Blood	NA	1
	Urinary Mucus	NA	1
	Urobilinogen	[mg/dL]	1
	Leukocytes	[/HPF]	1

Assessment Classification	Item name	Unit	Display digit
	Yeast Cells	NA	1
Coagulation	Activated Partial Thromboplastin Time	[s]	0.1
	Prothrombin Time	[s]	0.1
	Prothrombin Time - INR	NA	0.1
Glycemic Assessment	Hemoglobin A1C	[%]	0.1
FSH	Follicle Stimulating Hormone	[IU/L]	0.1

Appendix 3: The list of AE terms for Hyperkalemia and Potentially related to hypotension

AE type	AE Preferred Terms
Hyperkalemia	Hyperkalemia
	Blood potassium increased
	Blood potassium abnormal

AE type	AE Preferred Terms	Final Classification
Potential Hypotension	Arterial pressure NOS decreased	Narrow (FMQ)
	Blood pressure decreased	Narrow (FMQ)
	Blood pressure diastolic decreased	Narrow (FMQ)
	Blood pressure systolic decreased	Narrow (FMQ)
	Diastolic hypotension	Narrow (FMQ)
	Hypotension	Narrow (FMQ)
	Hypotension aggravated	Narrow (FMQ)
	Hypotension NOS	Narrow (FMQ)
	Hypotension on induction	Narrow (FMQ)
	Hypotension postural aggravated	Narrow (FMQ)
	Hypotensive anaesthesia procedure	Narrow (FMQ)
	Hypotensive transfusion reaction	Narrow (FMQ)
	Intraoperative hypotension	Narrow (FMQ)
	Neonatal hypotension	Narrow (FMQ)
	Orthostatic hypotension	Narrow (FMQ)
	Postoperative hypotension	Narrow (FMQ)
	Postural hypotension	Narrow (FMQ)
	Procedural hypotension	Narrow (FMQ)
	Blood pressure abnormal	Broad (FMQ)
	Blood pressure ambulatory abnormal	Broad (FMQ)
	Blood pressure ambulatory decreased	Broad (FMQ)
	Blood pressure diastolic abnormal	Broad (FMQ)
	Blood pressure orthostatic abnormal	Broad (FMQ)
	Blood pressure orthostatic decreased	Broad (FMQ)
	Blood pressure systolic abnormal	Broad (FMQ)
	Blood pressure systolic inspiratory decreased	Broad (FMQ)
	Dehydration	Broad (FMQ)
	Haemorrhagic adrenal infarction	Broad (FMQ)
	Hypovolaemia	Broad (FMQ)
	Procedural shock	Broad (FMQ)
	Orthostatic intolerance	Additional
	Dizziness	Additional
	Dizziness exertional	Additional
	Dizziness postural	Additional
	Presyncope	Additional
	Syncope	Additional
	Hypotensive crisis	Additional
	Mean arterial pressure decreased	Additional