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:	**Clinical Study Protocol, 18 October 2024**

CLINICAL STUDY PROTOCOL
ALN-AGT01-006
DATED 18 OCTOBER 2024

Protocol 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
Short Title:	A Study to Evaluate Zilebesiran in Japanese Patients with Mild to Moderate Hypertension
Compound:	Zilebesiran (ALN-AGT01)
IND Number:	143503
Protocol Date:	Original protocol, 12 January 2024 Amendment 1, 18 October 2024
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PI [redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

PI

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-006 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol 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

Short Title

A Study to Evaluate Zilebesiran in Japanese Patients with Mild to Moderate Hypertension

Compound

Zilebesiran (ALN-AGT01)

Phase

Phase 1/2

Study Center(s)

The study will be conducted at approximately 4 clinical study centers in Japan.

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_{last} and urine f_e 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

Objectives	Endpoints
• 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
• 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; AUC_{last}=AUC from the time of dosing to the last measurable concentration; C_{max}=maximum observed concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; f_e=fraction excreted; PD=pharmacodynamics; PK=pharmacokinetics; RAS = renin-angiotensin system; SBP=systolic blood pressure.

Study Design

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

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.

Eligible patients will be admitted to the site on Day -1, and patients who receive a dose of study drug on Day 1 will remain inpatient at the study site until discharge on Day 2. Patients will return to the clinical study site on an outpatient basis during the 6-month Double-blind (DB) Treatment period for safety, tolerability, efficacy, PD, and PK assessments.

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for 24-hour mean systolic blood pressure (SBP) ≥130 mmHg by ambulatory blood pressure monitoring (ABPM). After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure (eg, office SBP ≥140 mmHg, home blood pressure monitoring SBP >135 mmHg).[Williams 2018]

All patients will complete Safety/PD Follow-up visits at Months 9 and 12.

Number of Planned Patients

The planned enrollment for this study is 36 Japanese patients with mild to moderate hypertension. Each treatment arm will include 12 patients.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive, at time of initial informed consent) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications. Patients must have a 24-hour mean SBP ≥130 mmHg by ABPM, after a minimum of 3 weeks of washout if taking antihypertensive medication. Patients with secondary hypertension or clinically significant medical conditions or comorbidities that would interfere with study compliance or

data interpretation (including Type 1 diabetes mellitus or history of any cardiovascular event) will be excluded.

Study Drug, Dose, and Mode of Administration

Zilebesiran is an SC administered *N*-acetylgalactosamine-conjugated small interfering RNA targeting liver-expressed messenger RNA for angiotensinogen (AGT).

Patients randomized to receive zilebesiran will be administered 300 or 600 mg SC on Day 1 of the 6-month DB Treatment Period.

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered at the same dosing interval and volume as the study drug during the 6-month DB Treatment Period for patients randomized to placebo.

Duration of Treatment and Study Participation

The duration of treatment with zilebesiran is up to 6 months. The estimated total time on study for each patient is up to 14 months, including up to 2 months of screening, up to 6 months of treatment, and up to 6 months of safety follow-up.

Statistical Methods

The planned enrollment for this study is 36 patients, with 12 patients randomized to each of the 3 treatment arms. The sample size estimate is based on the percent change in AGT from baseline to Month 3 in Study ALN-AGT01-001. In Study ALN-AGT01-001, standard deviation (SD) for the percent change from baseline to Week 12 (Month 3) in the pooled zilebesiran arms was 42%. Assuming an SD of 0.42, the proposed sample size will provide more than 90% power to detect a 50% difference in percent AGT reduction at Month 3 between zilebesiran and placebo at a significance level of 0.05 (2-sided).

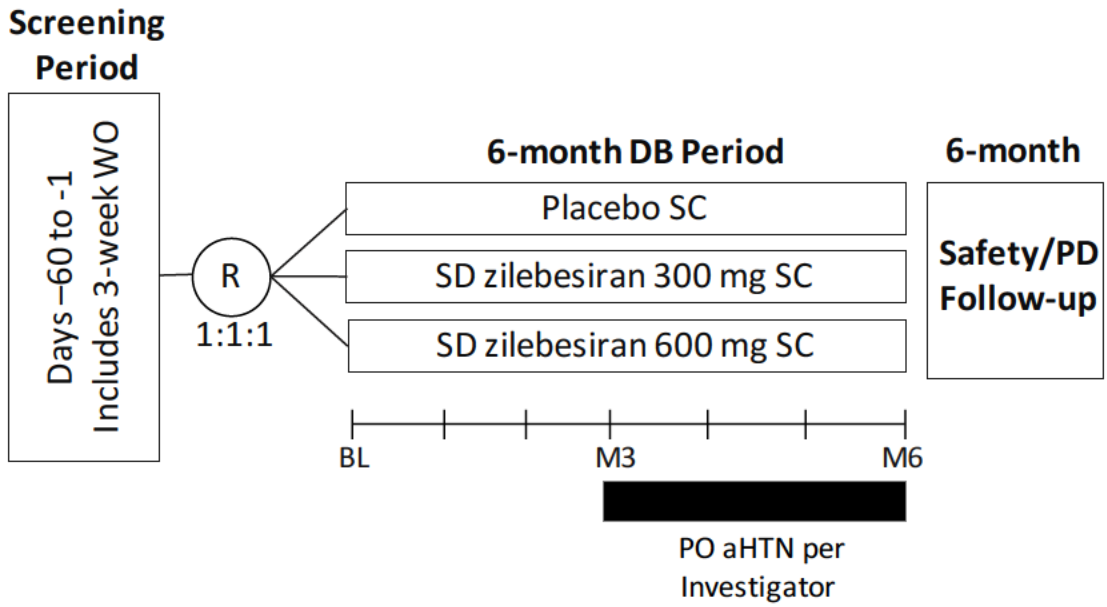
The populations (analysis sets) are defined as follows:

- **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.

Study Design Schema

Figure 1: Study Design



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.

Schedule of Assessments

Table 1: Schedule of Assessments

		Shading indicates inpatient visits															
		Screening Period		Treatment Period[a]												Safety/PD Follow-up	
				BL					M1	M2	M3	M4	M5	M6/EOT/ET	M9	M12/EOS
Study Day (±Visit Window)	**Note**	**D-60 to -2**	**D-1**	**D1**	**D2**	**D3**	**D8±3**	**D15±3**	**D29 ±5**	**D57 ±5**	**D85 ±7**	**D113 ±7**	**D141±7**	**D169±7**	**D253±14**	**D337±14**
Informed consent	Section 8.1.1	X														
Patient identification number	Section 3.4	X														
Demographics and medical history	Section 6.1	X														
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X	X													
Oral antihypertensive medication washout of a minimum of 3 weeks, if taking	Section 3.1	X														
Serum pregnancy test/FSH screening	Table 6; Section 6.5.5.3; FSH to confirm postmenopausal status if applicable	X														
HbA1c	Section 6.5.5	X														
Spot urine for albumin and creatinine	Section 6.5.5	X												X		
Full physical examination	Section 6.5.3	X		X										X		

Table 1: Schedule of Assessments

		Shading indicates inpatient visits															
		Screening Period		Treatment Period[a]												Safety/PD Follow-up	
				BL					M1	M2	M3	M4	M5	M6/EOT/ET	M9	M12/EOS
Study Day (±Visit Window)	**Note**	**D-60 to -2**	**D-1**	**D1**	**D2**	**D3**	**D8±3**	**D15±3**	**D29 ±5**	**D57 ±5**	**D85 ±7**	**D113 ±7**	**D141±7**	**D169±7**	**D253±14**	**D337±14**
Height, body weight, and BMI	Section 6.5.2; Height measured at Day 1 only			X										X		
Urine pregnancy test[b]	Table 6; Section 6.5.5.3 and Section 6.5.6.7			X										X		
Vital signs and office blood pressure[c]	Section 6.5.1 and Section 6.2.2	X		X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[c]	Section 6.2.1; Baseline ABPM recordings must be obtained within 1 week before randomization.	X									X			X		
HBPM[d]	Section 6.2.3	X				At least once per week										
24-h Holter ECG	Table 2; Section 6.5.4		X	X	X											
Single 12-lead ECG	Section 6.5.4	X												X		
Serum chemistry	Table 6; Section 6.5.5	X		X			X	X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation	Table 6; Section 6.5.5	X		X										X		

Table 1: Schedule of Assessments

		Shading indicates inpatient visits														
		Screening Period		Treatment Period[a]											Safety/PD Follow-up	
				BL					M1	M2	M3	M4	M5	M6/EOT/ET	M9	M12/EOS
Study Day (±Visit Window)	**Note**	**D-60 to -2**	**D-1**	**D1**	**D2**	**D3**	**D8±3**	**D15±3**	**D29 ±5**	**D57 ±5**	**D85 ±7**	**D113 ±7**	**D141±7**	**D169±7**	**D253±14**	**D337±14**
Liver function tests	Table 6; See Table 7 for additional LFTs indicated for patients with abnormalities listed in Section 5.7.5	X		X			X	X	X	X	X	X	X	X	X	X
Plasma PK	Table 2; Section 6.4			X	X	X										
Pooled urine PK	Table 2; Section 6.4			X												
Immunogenicity (ADA)	Table 6; Section 6.5.5.2			X					X		X			X		
Serum AGT	Section 6.3			X			X	X	X	X	X			X	X	X
RAS biomarkers: renin concentration, renin activity, and aldosterone	Blood samples should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position)			X					X	X	X			X		
Exploratory DNA sample (optional)	Section 6.6			X												
Optional research samples (urine, plasma, serum)	Section 6.6			X							X			X		

Table 1: Schedule of Assessments

		Shading indicates inpatient visits															
		Screening Period		Treatment Period[a]												Safety/PD Follow-up	
				BL					M1	M2	M3	M4	M5	M6/EOT/ET		M9	M12/EOS
Study Day (±Visit Window)	**Note**	**D-60 to -2**	**D-1**	**D1**	**D2**	**D3**	**D8±3**	**D15±3**	**D29 ±5**	**D57 ±5**	**D85 ±7**	**D113 ±7**	**D141±7**	**D169±7**		**D253±14**	**D337±14**
Symptom-directed physical exam	Section 6.5.3										X					X	X
Admission to inpatient unit	Section 3.1		X														
Randomization	Section 3.4; Randomization may occur on Day 1 or 1 business day prior			X													
Study drug administration	Section 5.2.2			X													
Adverse events	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of study drug	Continuous															
Concomitant medications	Section 5.8	Continuous															

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AE=adverse event; AGT=angiotensinogen; BL=baseline; BMI=body mass index; D=day; ECG=electrocardiogram; EOT=End of treatment; EOS=End of study; 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; PD=pharmacodynamics; PK=pharmacokinetics; RAS=renin-angiotensin system; SAE=serious adverse event.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAS biomarkers should be performed before 12-lead ECGs and physical examinations.
- In the Safety/PD Follow-up period, the frequency of HBPM assessments can be reduced after the first Safety/PD Follow-up visit per Investigator judgement.

Footnotes:

[a] **All Day 1 assessments, except for postdose PK sample collection and ECG extraction (Table 2), are to be performed prior to dosing unless otherwise noted.**

[b] When applicable, pregnancy test results must be known prior to dosing.

[c] Clinical laboratory assessments and blood pressure measurements taken for eligibility must be performed after a minimum of 3 weeks of washout. Office blood pressure must be measured before the patient takes oral antihypertensive medications (if applicable).

[d] An HBPM unit will be provided before the randomization visit to establish the HBPM baseline, and HBPM should be collected at least 3 times during the last week prior to Day 1. HBPM should be measured in the mornings at trough and at approximately the same time each day. HBPM measurements should be obtained upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed.

Table 2: Pharmacokinetic and Electrocardiogram Time Points

Study Day	Sampling Time (hh:mm)	24-hour Holter ECG Extraction[a]	Blood PK Sample	Pooled Urine for PK[b]
Day-1	Predose (-24 h)	X		
Day 1	Predose (-1 h)	X	X	X
	Predose (-40, -30, -20, and -10 min)	X		
	00:30 (±5 min)	X	X	00:01-06:00
	01:00 (±5 min)	X	X	
	02:00 (±5 min)	X	X	
	03:00 (±5 min)	X	X	
	04:00 (±5 min)	X	X	
	06:00 (±10 min)	X	X	6:01-12:00
	08:00 (±15 min)	X	X	
	12:00 (±15 min)	X	X	12:01-24:00
	16:00 (±15 min)	X	X	
Day 2	24:00 (±2 hours)	X	X	
Day 3	48:00 (±6 hours)		X	

Abbreviations: ECG=electrocardiogram; hh:mm=hour:minute; PK=pharmacokinetics.
Notes:

- The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 6.4 for additional information on PK assessments.
- Patients should be supine for at least 10 minutes before each ECG is obtained. See Section 6.5.4 for additional information on ECG assessments.
- Sampling time windows do not apply to pooled urine PK unless otherwise stated.

[a] On Day -1, 12-lead digital ECG data will be recorded using a 12-lead Holter monitor for a total of 1 hour (30 minutes before and after the 24-hour predose timepoint), and ECG data will be extracted within that window. Continuous 12-lead digital ECG data will be recorded on a 24-hour 12-lead Holter monitor starting on Day 1 (1 hour before dosing) through 24 hours postdose on Day 2. ECGs will be extracted from a 10-min window preceding the indicated time points.

[b] Patients will be asked to void their bladders immediately before dosing (within 1 hour [±10 min] predose), and an aliquot will be taken from this sample as the 0 h sample. At the end of each collection interval, patients will be asked to void their bladders for a final time (eg, void bladder at 06:00 h for the 00:01 to 06:00 h sample), and all urine collected during the interval will be pooled.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody
AE	Adverse event
AGT	Angiotensinogen
ALT	Alanine aminotransferase
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CPC	Clinical product complaint
CRO	Contract research organization
DB	Double-blind
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISR	Injection site reactions
LFT	Liver function test

Abbreviation	Definition
LS	least-squares
MAO	Monoamine oxidase
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred Term
QTcF	Fridericia-corrected QT interval
q3M	Every 3 months
q6M	Every 6 months
RAS	Renin-angiotensin system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
SD	Standard deviation
SGLT2	Sodium-glucose co-transporter 2
SOC	System Organ Class
siRNA	Small interfering RNA
THC	Tetrahydrocannibinol
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is co-developing (with F. Hoffmann-La Roche Ltd.) zilebesiran (ALN-AGT01), a subcutaneously (SC) administered investigational agent comprising a synthetic small interfering RNA (siRNA) covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand, which is designed to suppress liver production of angiotensinogen (AGT) and thereby reduce blood pressure in individuals with hypertension.

1.1. Study Rationale

Study ALN-AGT01-006 is a single dose, randomized, double-blind, placebo-controlled, parallel-group, Phase 1/2 study to evaluate the safety, tolerability, efficacy, pharmacodynamics (PD), and pharmacokinetics (PK) of zilebesiran administered SC in Japanese patients with mild to moderate hypertension.

The primary objective of the study is to evaluate the safety and tolerability of zilebesiran in Japanese patients, as assessed through adverse events (AEs), vital signs, electrocardiograms (ECGs), and clinical laboratory assessments. Secondary and exploratory objectives of the study include evaluating the efficacy of zilebesiran on blood pressure as assessed by ambulatory blood pressure monitoring (ABPM) and office blood pressure; evaluating the PD effect of zilebesiran, including reduction in circulating AGT concentration; and characterizing the PK of zilebesiran and its metabolite, AS(N-1)3′ zilebesiran.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Hypertension affects 30% to 45% of adults and is the strongest modifiable risk factor for cardiovascular disease, primarily strokes and myocardial infarction.[Olsen 2016; Williams 2018] The worldwide disease burden is profound, with a global prevalence of over 1 billion,[Kearney 2005; NCD Risk Factor Collaboration 2017] and approximately 9 million deaths attributed to hypertension annually.[Angell 2015]

Currently available pharmacologic therapies achieve target blood pressure in only a minority of patients, due in large part to physician inertia and patient nonadherence to daily oral medication.[Whelton 2018; Williams 2018] Low adherence to oral antihypertensives is associated with poor cardiovascular outcomes and is prevalent at all stages of disease.[Corrao 2011; Peacock 2017; Schulz 2016; van der Laan 2017] Thus, despite the availability of multiple efficacious agents, current rates of control are low, and the global burden of death and disability-adjusted life-years attributed to elevated blood pressure remains high.[Forouzanfar 2017; Muntner 2020] Development of new approaches to treat hypertension and to overcome the limitations of current therapies is a key unmet need.[Dzau 2019; McClellan 2019; US Department of Health and Human Services 2020]

The Sponsor is developing zilebesiran, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration to reduce the risk of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure for adult patients with hypertension at high risk of developing a major adverse cardiovascular event. RNAi is a naturally occurring cellular mechanism for regulation of gene expression, mediated through the binding of siRNA to its complementary messenger RNA (mRNA) sequence, leading to mRNA cleavage and subsequent

suppression of the synthesis and levels of the target protein. Zilebesiran contains an siRNA targeting *AGT* mRNA, conjugated to a GalNAc-containing ligand to facilitate delivery to the liver. Based on the mechanism of RNAi, zilebesiran is specifically designed to reduce the hepatic synthesis of AGT protein, the first substrate in the renin-angiotensin system (RAS) and the sole precursor of vasoactive angiotensin peptides.[Khanna 2017; Romero 2015] Because hepatocytes are the predominant source of circulating AGT, zilebesiran has been developed to reduce blood pressure by decreasing circulating AGT levels and the downstream effects of angiotensin II.

Zilebesiran has been studied in the completed Phase 1 Study ALN-AGT01-001 (hereafter referred to as Study 001) in patients with hypertension as single ascending doses of 10 to 800 mg (Part A), as a single dose of 800 mg under low-salt or high-salt conditions (Part B), as 2 doses of 800 mg administered every 3 months (q3M) in obese patients (Part D), and as a single dose of 800 mg co-administered for 2 weeks with 300 mg irbesartan (Part E). Dose-dependent and durable reductions in circulating AGT were observed after single SC doses of zilebesiran in Part A, accompanied by clinically significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP). The effects of zilebesiran on serum AGT were unaffected by altered sodium intake or coadministration of irbesartan.

In Study 001, most AEs were mild or moderate in severity, and there were no severe or serious adverse events (SAEs) considered by the Investigator to be related to study drug. There were no clinically significant elevations in serum creatinine or serum potassium. No patient required medication therapy for low blood pressure. Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN) were observed in 2 (2.3%) of 88 patients who received zilebesiran at doses as high as 800 mg. The associated AEs were not considered related to study drug by the Investigator. Laboratory results returned to within the normal range during the study, and there were no associated symptoms or hyperbilirubinemia. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

Zilebesiran is being studied in the ongoing Phase 2 Studies ALN-AGT01-002 (KARDIA-1; hereafter referred to as Study 002) and ALN-AGT01-003 (KARDIA-2; hereafter referred to as Study 003). Data from Study 002 showed that all doses of zilebesiran (single doses of 150, 300, and 600 mg and 2 doses of 300 mg each 3 months apart) resulted in statistically significant reductions in 24-hour mean SBP assessed by ABPM and office SBP at Months 3 and 6 of the 6-month placebo-controlled double-blind (DB) period. The least-squares (LS) mean reductions at Month 3 were >14 mmHg for 24-hour mean SBP assessed by ABPM and >9 mmHg for office SBP compared to placebo across all doses. Similar results were observed for 24-hour mean DBP assessed by ABPM and office DBP. Tonic blood pressure control was demonstrated by consistent 24-hour mean SBP reductions throughout the dosing period, including during daytime and nighttime, particularly in the 300 and 600 mg dose groups. All doses of zilebesiran led to substantial sustained reductions in serum AGT levels, with median reductions of >96% observed at Month 6 for the 300 and 600 mg every 6 months (q6M) dose groups. The 300 and 600 mg dose groups had a greater magnitude of reduction in serum AGT that was less variable toward the end of the dosing interval relative to the 150 mg q6M dosing regimen.

In Study 002, most AEs were mild or moderate in severity, and there were no severe AEs or SAEs considered by the Investigator to be related to study drug during the 6-month placebo-controlled DB period. A total of 24 (7.9%) zilebesiran patients and 5 (6.7%) placebo patients had at least 1 potential hypotension AE. Most events were transient and resolved without intervention. Hyperkalemia was reported in 19 (6.3%) zilebesiran patients and 1 (1.3%) placebo patient. Most events of hyperkalemia were mild, not serious, resolved during the study, and were considered by the Investigator to be related to study drug. Serum potassium >5.5 mmol/L was observed in 17 (5.6%) zilebesiran patients and 0 placebo patients, and serum potassium >6.0 mmol/L was observed in 2 (0.7%) zilebesiran patients. The majority of patients with serum potassium >5.5 mmol/L had elevations at a single time point with serum potassium returning to the normal range without intervention in most patients. A total of 7 zilebesiran patients and 0 placebo patients had ALT or AST elevations >3×ULN. Most elevations returned to within normal range during the study without an interruption in study drug dosing. A ≥30% decline from baseline in estimated glomerular filtration rate (eGFR) in at least 1 time point was observed in 16 (5.3%) zilebesiran patients and 2 (2.7%) placebo patients. In most cases, the decline in eGFR reversed while on treatment, and there was no dose-dependent trend.

This Phase 1/2 study, ALN-AGT01-006, will evaluate the safety, tolerability, efficacy, PD, and PK of zilebesiran in Japanese patients with mild to moderate hypertension.

A detailed description of the chemistry, pharmacology, efficacy, and safety of zilebesiran is provided in the Investigator's Brochure.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits

Clinical data available from Studies 001 and 002 indicate that zilebesiran may offer the benefit of sustained blood pressure reduction to patients with hypertension with infrequent administration (ie, once q3M or once q6M). The mean SBP reduction observed after single doses of ≥100 mg zilebesiran and multiple doses of 300 or 800 mg zilebesiran exceed 10 mmHg, which is comparable to the effect of conventional antihypertensives.[Abraham 2015; Materson 1993]

Due to the potent and durable PD effects of GalNAc-siRNAs, zilebesiran has demonstrated the unique benefit of tonic blood pressure control (ie, consistent BP control over a 24-hour period, day after day) in both studies.

1.3.2. Possible Risks and Risk Mitigation

Given the mechanism of action and mode of administration of zilebesiran, possible risks include liver transaminase elevations, ISRs, hypotension, hyperkalemia, and renal dysfunction. Based upon the disease population, there is also a risk of blood pressure elevation. Because eligible patients have mild to moderate primary hypertension, the likelihood of disease progression during the course of the study is low. This study has exclusion criteria intended to minimize these risks, as well as frequent monitoring for laboratory and blood pressure abnormalities. Furthermore, the duration of the placebo period is limited, blood pressure will be closely monitored, and escape antihypertensive medications are permitted to manage uncontrolled blood pressure following 3 months of treatment with zilebesiran or placebo.

Detailed guidance is provided to Investigators for liver transaminase elevations (Section 5.7.5), hypotension (Section 5.7.1), hypertension (Section 5.7.2), renal dysfunction (Section 5.7.3), and hyperkalemia (Section 5.7.4).

1.3.3. Overall Benefit/Risk Conclusion

Efficacy data from Studies 001 and 002 show that zilebesiran leads to sustained reductions in serum AGT and blood pressure.

Based on safety data from the completed Study 001, zilebesiran has an acceptable safety profile in patients with hypertension as a monotherapy or with the addition of conventional antihypertensives in patients who were inadequately controlled on zilebesiran alone. Zilebesiran also had an acceptable safety profile in Study 002 in patients with hypertension when administered as single or multiple SC doses ranging from 150 to 600 mg based on available data. These data support that the possible risks of treatment are low and can be managed through the proposed monitoring and safety mitigations.

The benefit/risk assessment is positive and supports the evaluation of zilebesiran in this Phase 1/2 study in Japanese patients with mild to moderate hypertension.

Information about the known and expected benefits and risks of zilebesiran may also be found in the current edition of the Investigator's Brochure.

2. 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_{last} and urine f_e of zilebesiran and its metabolite AS(N-1)3′ zilebesiran

Objectives	Endpoints
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
• 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; AUC_{last}=AUC from the time of dosing to the last measurable concentration; C_{max}=maximum observed concentration; DBP=diastolic blood pressure; ECG=electrocardiogram; f_e=fraction excreted; PD=pharmacodynamics; PK=pharmacokinetics; RAS = renin-angiotensin system; SBP=systolic blood pressure.

3. INVESTIGATIONAL PLAN

3.1. Summary of 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. A schematic of the study design is provided in Figure 1.

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, as described in Section 3.4, to receive a single dose of 300 or 600 mg zilebesiran or placebo.

The planned enrollment for this study is 36 Japanese patients with mild to moderate hypertension. Each treatment arm will include 12 patients.

Eligible patients will be admitted to the site on Day -1, and patients who receive a dose of study drug on Day 1 will remain inpatient at the study site until discharge on Day 2. Patients will return to the clinical study site on an outpatient basis during the 6-month DB Treatment Period for safety, tolerability, efficacy, PD, and PK assessments, as outlined in the Schedule of Assessments (Table 1).

At Month 3, conventional oral antihypertensives may be added per Investigator judgement for 24-hour mean SBP ≥130 mmHg by ABPM. After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure (eg, office SBP ≥140 mmHg, home blood pressure monitoring [HBPM] SBP >135 mmHg).[Williams 2018]

All patients will complete Safety/PD Follow-up visits and complete assessments as described in Table 1 at Months 9 and 12.

The estimated duration of study participation, inclusive of screening and safety/PD follow-up, is 14 months.

3.2. Scientific Rationale for Study Design

Study ALN-AGT01-006 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 in Japanese patients with mild to moderate hypertension. The primary objective of the study is to evaluate the safety and tolerability of zilebesiran in Japanese patients, as assessed through AEs, vital signs, ECGs, and clinical laboratory assessments.

This study will also quantify the antihypertensive effects of zilebesiran in Japanese patients with mild to moderate hypertension at doses that showed clinically and statistically significant placebo-corrected reductions in 24-hour mean SBP by ABPM in prior studies in the broader population of adult patients with hypertension.

Patients will discontinue prior antihypertensive medications (if taking) for a minimum of 3 weeks prior to study drug administration. During the study, blood pressure will be monitored with both automated office blood pressure measurements and outpatient 24-hour ABPM. In addition to having greater precision, ABPM can assess short-term blood pressure variability and circadian patterns (including potential restoration of the normal nocturnal blood pressure dipping pattern that is lost in 24% to 35% of hypertensive patients). More frequent (at least once per week) measurements will be collected through a third method, oscillometric HBPM, to provide close safety monitoring for potential hypotension (or hypertension) while not in the clinic.

As recommended by current guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E12A Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000), the 6-month DB period is designed as a randomized, placebo-controlled, parallel-group study. To adhere to best ethical standards for the treatment of patients with hypertension, the use of oral antihypertensive medications per Investigator judgement to maintain blood pressure within target is permitted starting Month 3 through the remainder of the study (Table 3). Because zilebesiran acts on the RAS, the use of conventional RAS inhibitors (angiotensin II-receptor blocker [ARB], angiotensin converting enzyme [ACE] inhibitors, or direct renin inhibitors) as escape medications for high blood pressure are prohibited throughout this study.

Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) will be appropriately treated with escape antihypertensive medication regardless of its timing relative to study drug administration. “Escape antihypertensive medication” is used to refer to any oral antihypertensive medication initiated to control blood pressure after Day 1. If a patient requires treatment with an oral escape antihypertensive medication before Month 6, a

calcium channel blocker and/or thiazide/thiazide-like diuretic should be used because there is extensive experience combining these classes with antihypertensive drugs that impact the RAS. After the 6-month DB period, Investigators may use escape antihypertensive medications of their choice to control blood pressure, guided by continued blood pressure monitoring and following current care guidelines.[Umemura 2019; Whelton 2018; Williams 2018]

While the tissue specificity of zilebesiran for the liver is hypothesized to improve tolerability relative to current oral antihypertensives [Mullick 2017; Uijl 2019], the protocol's monitoring plan is designed to meet the standards set by prior studies of conventional RAS inhibitors.[McMurray 2016; Parving 2012] The risk of renal safety events is further mitigated in this study by its eligibility criteria, which exclude patients who are at increased risk to have events (eGFR <60 mL/min/1.73m^2, baseline serum potassium >5 mmol/L, Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus, or severely increased albuminuria) and those who may have decreased tolerance for renal safety events (patients with clinically significant heart failure, valvular heart disease, or recent history of cardiovascular event).

3.3. Justification for Dose

Zilebesiran will be administered as a single dose of 300 or 600 mg SC in this study. These doses of zilebesiran have been selected for further evaluation in a planned Phase 2 study that will inform the doses selected for the Phase 3 program.

These doses were selected based on data from Study 001 and Study 002 that showed robust and durable reduction in serum AGT at these dose levels. Single and multiple doses of zilebesiran up to 800 mg in Study 001 and up to 600 mg in Study 002 were found to have acceptable safety profiles and lead to clinically meaningful reductions in 24-hour mean SBP by ABPM.

- In Study 001 Part A, single ascending doses of zilebesiran from 10 to 800 mg showed dose-dependent reductions in serum AGT and 24-hour mean SBP assessed by ABPM. Zilebesiran also demonstrated an acceptable safety profile at all dose levels. Based on Study 001 results, zilebesiran dose regimens of 150 mg q6M, 300 mg q6M, 600 mg q6M, and 300 mg q3M zilebesiran were selected to be evaluated in Study 002.
- In Study 002, a single dose of 300 or 600 mg zilebesiran (q6M regimens) showed clinically and statistically significant reductions in 24-hour mean SBP by ABPM compared to placebo at Month 3 (LS mean reductions of 16.7 mmHg for 300 mg and 15.7 mmHg for 600 mg) that were sustained through Month 6 (LS mean reductions of 14.5 mmHg for 300 mg and 14.2 mmHg for 600 mg). A dose-dependent reduction from baseline in serum AGT over time was observed across all the zilebesiran dose levels.
- For the proposed dose levels in this study, median reductions in serum AGT were 98.1% and 98.8% at Month 3 and 96.1% and 97.8% at Month 6 for the zilebesiran 300 and 600 mg doses, respectively. A log-linear relationship between reductions in serum AGT and change from baseline in 24-hour mean SBP by ABPM was observed in Study 002 leveraging data from all doses. Both regimens had acceptable safety profiles.

Accordingly, dose levels of 300 and 600 mg were selected for Japanese patients in this study to generate safety, tolerability, efficacy, PD, and PK data to facilitate demonstration of comparability of systemic exposure and PD (serum AGT) in Japanese patients with non-Japanese patients at therapeutic dose levels used in ongoing studies and planned to be used in subsequent studies. Changes in blood pressure will also be evaluated to assess whether blood pressure reduction in Japanese patients is within the range of blood pressure reduction observed in non-Japanese patients.

3.4. Method of Assigning Patients to Treatment Groups

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. After the patient signs the Informed Consent Form (ICF) and before proceeding with screening procedures, the Investigator or designee will contact the interactive response technology (IRT) to obtain a patient identification number.

The Investigator or designee will contact the IRT to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria. Patients will be randomized 1:1:1 to the 300 mg zilebesiran, 600 mg zilebesiran, or placebo arm using the IRT.

3.5. Blinding

The Investigators, site personnel, contract research organization (CRO) staff, and patients will be blinded to study drug treatment until the end of the study. CRO staff who will have responsibilities for the planned analyses will be unblinded at the time of those analyses. The Sponsor, unblinded site pharmacist or delegate, and CRO unblinded clinical research associate and their escalation contact (eg, clinical trial manager) will be unblinded to study drug assignment.

Because zilebesiran may be visually distinguishable from placebo, the syringe will be masked by the unblinded site pharmacist prior to transferring the syringe to any blinded healthcare professional. See the Pharmacy Manual for additional details. The study drug will be administered under the supervision of the Investigator.

3.5.1. Emergency Unblinding

If a treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may make the decision to break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken will be maintained in the electronic trial master file.

Refer to the IRT instructions for details on unblinding.

3.6. Definition of End of Study for an Individual Patient

The end of study (EOS) for a patient is defined as the patient's last visit in 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.

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Age 18 to 75 years, inclusive, at time of initial informed consent.
2. Male or female.

Patient and Disease Characteristics

3. The patient must have been born in Japan, and their biological parents and grandparents must have been of Japanese origin.
4. Has untreated hypertension or newly diagnosed with hypertension (not taking antihypertensive medication) or is on stable therapy with up to 2 antihypertensive medications. Stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening.
5. Mean sitting SBP of >130 and ≤165 mmHg by automated office blood pressure measurement, without antihypertensive medication, after washout (if applicable). Patients previously taking medication for hypertension must be without antihypertensives for a minimum of 3 weeks prior to office blood pressure measurement.
6. 24-hour mean SBP ≥130 mmHg by ABPM. Patients previously taking medication for hypertension must be without antihypertensives for a minimum of 3 weeks prior to ABPM.[Ito 2015; Kario 2014; White 2011]
7. The patient, as judged by the Investigator, can safely discontinue background antihypertensive therapy for a minimum of 3 weeks prior to the DB Treatment Period.
8. 12-lead ECG within normal limits or with no clinically significant abnormalities in the opinion of the Investigator, with a Fridericia-corrected QT interval (QTcF) <450 msec in males or <470 msec in females.

Informed Consent

9. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Secondary hypertension (including, but not limited to, due to known history of moderate-to-severe obstructive sleep apnea not treated with continuous positive airway pressure therapy, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, and aortic coarctation).
2. Mean sitting DBP >105 mmHg by automated office blood pressure measurement.
3. History of orthostatic hypotension or orthostatic hypotension during screening, defined as a fall of ≥20 mmHg SBP or ≥10 mmHg DBP within approximately 1 to 3 minutes of standing up from a seated position by office blood pressure that is symptomatic (such as dizziness, weakness, lightheadedness, or syncope).

Laboratory Assessments

4. Has any of the following laboratory parameter assessments after a minimum of 3 weeks of washout during screening:
    a. ALT or AST >2× ULN.
    b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN.
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed).
    d. Elevated serum potassium >5 mmol/L.
    e. Serum sodium <130 mmol/L.
    f. eGFR of <60 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula with a Japanese coefficient of 0.808; Section 10.1).[Levey 2006; Matsuo 2009]

Prior/Concomitant Therapy

5. Received an investigational agent within the last 30 days before randomization or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional Regulatory Authorities is not considered investigational. Patients who are in follow-up for a coronavirus disease 2019 vaccine (authorized or investigational) study are allowed.
6. Currently taking, taken within 30 days prior to randomization, or anticipated to receive during the study treatment period any medication or herbal supplement known to significantly affect blood pressure (with the exception of medications for the treatment of essential hypertension). Patients who require medications such as monoamine oxidase (MAO) inhibitors that are associated with hypertensive crisis are excluded.[Whelton 2018]
7. Currently taking beta blockers and unable to undergo a washout at least 3 weeks prior to randomization.

8. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on SGLT2 inhibitors must be on a stable dose for at least 30 days prior to screening with no anticipated changes during the study treatment period.
9. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening are permitted. Paracetamol/acetaminophen for analgesia will be allowed.
10. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period.
11. Currently taking, taken within 6 months prior to randomization, or anticipated to receive an RNAi therapeutic or antisense oligonucleotide other than zilebesiran (approved or investigational) during the study.

Medical Conditions

12. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), or direct renin inhibitor.
13. Medical condition, other than hypertension, that requires treatment with a RAS inhibitor.
14. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to GalNAc.
15. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >9.0%), or laboratory evidence of diabetes during screening (HbA1c ≥7.0%) without known diagnosis of diabetes.
16. History of severely increased albuminuria (urine albumin:creatinine ratio >300 mg/g or >300 mg/day) or laboratory results consistent with this diagnosis upon screening.
17. Has known human immunodeficiency virus or known current or chronic hepatitis C virus or hepatitis B virus infection.
18. History of any cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to randomization.
19. Clinically significant valvular heart disease.
20. New York Heart Association II to IV heart failure.
21. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia in the 3 months prior to randomization.
22. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period.
23. History of renal transplantation or under immunosuppressive therapy.
24. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.

25. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to randomization.
26. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability.
27. Has planned major surgery or general anesthesia during the study.

Contraception, Pregnancy, and Breastfeeding

28. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.10.1.
29. Female patient is pregnant, planning a pregnancy, or breastfeeding.

Alcohol Use

30. Known history of alcohol abuse or alcohol dependency, within the last 12 months before screening.
31. History of substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator.
32. Unwilling or unable to abstain from use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within 30 minutes prior to office blood pressure measurements.

Other

33. Third shift or night shift workers.
34. Blood pressure cannot be accurately assessed by study blood pressure instruments provided by the Sponsor (eg, due to cuff size limitations).

4.3. Removal from Study Drug or Assessment

Patients are free to stop protocol procedural assessments, or participation in the study as a whole, at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any stopping of the patient's participation in the study must be fully documented in the electronic Case Report Form (eCRF) and be followed up by the Investigator.

Declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Discontinuation of study drug is not applicable because this is a single dose study.

Patients who decline procedural assessments should not be automatically removed from study. In general, patients will be encouraged to remain on the study to complete the remaining assessments through the End of treatment (EOT) visit so that their experience is captured in the final analyses. They will also be asked to complete safety follow-up visits once q3M per the safety follow-up schedule (see Table 1); see Section 3.1.

If this occurs, the Investigator must discuss with the patient the options for continuation of the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study should be informed that the patient can decline procedural assessments and remain in the study to complete their study assessments through the Month 12 visit, including safety follow-up, or alternatively may complete any minimal assessments for which the patient consents, as described in Section 4.3.1. If a patient still chooses to stop participation in all follow-up, every effort should be made to conduct the early termination assessments at an earlier time (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study.

Patients may exercise further privacy rights with respect to the collection and processing of their data in accordance with Section 4.3.2.2.

4.3.2.2. Withdrawal of Consent to Collect and Process the Patient's Personal Data or Exercise of Other Patient's Privacy Rights

The patient may exercise their privacy rights to collect, use, share, store and destroy their personal data and biological samples, in compliance with applicable local law. These details are provided in the ICF.

The Sponsor has appropriate processes and policies in place to handle personal data breaches according to applicable privacy and data protection laws.

If a patient stops participation in the study, the patient may request the destruction of samples taken, and any such destruction should follow the patient's rights as detailed in the ICF. The Investigator must document any such request in the source documents and eCRF and notify the Sponsor accordingly.

If the patient withdraws consent, where applicable, the Sponsor may retain and continue to use any data collected before such withdrawal of consent as detailed in the ICF. The Investigator must document any such request in the source documents and eCRF and notify the Sponsor accordingly.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study site. The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who stop participation in the study.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of zilebesiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Zilebesiran will be supplied as a sterile solution for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (commercially available sodium chloride 0.9% w/v for SC administration) and will be sourced by sites and prepared by the site pharmacist.

5.2.2. Dose and Administration

Patients will be administered a single dose of 300 or 600 mg zilebesiran or placebo as an SC injection on Day 1. To maintain the blind, the volume of study drug administered will be identical. Study drug injection will be administered by qualified clinical study center staff under the supervision of the Investigator or designee. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. Detailed instructions for study drug administration are found in the Pharmacy Manual.

To maintain the blind, the syringes are to be masked by the site pharmacist or designee prior to transferring the syringe to any blinded healthcare professional. A full description of the blinding procedure is included in the Pharmacy Manual.

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided in Section 6.5.6.8.

5.2.3. Dose Modifications

Dose modifications are not permitted.

5.3. Preparation, Handling, and Storage

Staff at each clinical study center will be responsible for preparing zilebesiran or placebo doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored at approximately 2°C to 30°C until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the affected study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.4. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.5. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.6. Clinical Product Complaints

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically non-medical in nature; however, it is possible that study drug complaints could be associated with an AE. Examples of a CPC include, but are not limited to, illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

AEs that may be associated with a CPC must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs, including reporting timeframe, will be provided in the Pharmacy Manual.

5.7. Monitoring for Potential Clinical Events

5.7.1. Monitoring and Approach for Potential Hypotension

Hypotension is an obligate risk of antihypertensive medications. In addition to office blood pressure monitoring, outpatient blood pressure will be monitored weekly with HBPM to ensure the early detection of potential hypotension. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure.

The following management recommendations for hypotension are provided:

- Patients who experience low blood pressure that is associated with symptoms should promptly seek medical evaluation at the clinical study site or another hospital setting. Clinical study site evaluation for low blood pressure should include the assessment of orthostatic blood pressure (seated to standing).
- The Investigator should consider downtitration or interruption of oral antihypertensives (if taking) if confirmed office SBP <90 mmHg or if clinical symptoms, such as lightheadedness or dizziness, develop coupled with a significantly lower SBP compared to prior visits (ie, SBP <100 mmHg).
- Clinically significant events discovered during the course of a patient's general medical care should be promptly communicated to the site and evaluated by the Investigator, especially if hypotension is noted. Patients will carry Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved patient cards to facilitate this physician-to-physician communication.
- If hypotension is confirmed, serum electrolytes and creatinine should be measured and any oral antihypertensive(s) should be downtitrated or interrupted per Investigator judgement as outlined above.
- The frequency of blood pressure and laboratory monitoring (serum electrolytes and creatinine) should be increased during intercurrent illnesses that predispose patients to dehydration (eg, vomiting or diarrhea that persists for more than 24 hours) or when symptoms consistent with decreased effective circulating volume (eg, presyncopal symptoms, unexplained falls, decreased urine output) manifest, even if a patient's recent blood pressure measurements have been normal.
- Hypotension that warrants direct evaluation at the site should be communicated to the Medical Monitor within 24 hours. In addition, other clinical events consistent with potential hypotension (eg, unexplained presyncope, syncope, or falls) should be communicated to the Medical Monitor within 24 hours of the site being notified.
- Management of persistent hypotension may include increased salt intake or, if unresponsive, standard treatments for hypotension, such as fludrocortisone or midodrine.
- Low blood pressure that requires medical treatment (including intravenous fluid support) or other clinical events consistent with potential hypotension (see above) should be recorded as AEs.

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, or any significantly lower SBP compared to prior visits that requires clinical intervention must be recorded as an AE of clinical interest (Section 6.5.6.1).

5.7.2. Monitoring and Approach for Clinically Significant Blood Pressure Elevation

In addition to office blood pressure monitoring, outpatient blood pressure will be monitored frequently with HBPM to ensure the early detection of potential significant elevations. Whenever possible, management decisions will be based on blood pressure measurements confirmed by office blood pressure. The recommended interventions for potentially clinically significant blood pressure elevation are presented in Table 3.

Table 3: Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Study Period	Intervention
Throughout study	• Whenever possible, management decisions should be based on blood pressure measurements confirmed by office blood pressure. • Any confirmed event of severe hypertension (office SBP ≥180 mmHg and/or office DBP ≥120 mmHg) should be appropriately treated regardless of its timing relative to study drug administration. • Because zilebesiran acts on the RAS, the use of conventional RAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape medications for high blood pressure is prohibited throughout this study. • If added, oral antihypertensives must be used per their labeled instructions and in accordance with current care guidelines.[Umemura 2019; Whelton 2018; Williams 2018]
Day 1 to Month 3	Intervene if clinically significant blood pressure elevation: • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient receives study drug. • After Week 6, patients who develop office SBP >160 mmHg and increased >10 mmHg from their baseline office SBP that persists for ≥24 hours on 2 consecutive measurements or that is accompanied by hypertensive symptoms should be evaluated by the clinical study site. Severely symptomatic patients should be evaluated at the clinical study site or another hospital setting within 24 hours. • If persistent hypertension is confirmed (without the identification of a specific treatable cause) and the Investigator deems it to be a clinically significant change, treatment may be initiated at the medical discretion of the Investigator using a CCB and/or a thiazide/thiazide-like diuretic.
Months 3 to 6	Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic: • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added if the 24-hour mean SBP is ≥130 mmHg by ABPM. • After Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure (eg, systolic office blood pressure ≥140 mmHg or systolic HBPM >135 mmHg).[Williams 2018]
Safety Follow-up period	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s).

Abbreviations: ABPM=ambulatory blood pressure monitoring; ACE=angiotensin converting enzyme; ARB=angiotensin II-receptor blocker; CCB=calcium channel blocker; DBP=diastolic blood pressure; eCRF=electronic case report form; HBPM=home blood pressure monitoring; RAS=renin-angiotensin system; SBP=systolic blood pressure.

5.7.3. Monitoring and Approach for Potential Renal Dysfunction

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of eGFR through the anticipated onset of initial zilebesiran PD. Based upon the renal dysfunction associated with conventional RAS inhibitors,[McMurray 2016; Parving 2012] the following guidelines apply throughout the study:

- If an individual patient experiences a decrease in eGFR by ≥30% from baseline, the Investigator should obtain confirmatory repeat tests, contact the Sponsor, and look for potentially reversible causes of renal dysfunction such as:
  - NSAIDs, antibiotics, or other treatments known to impair renal function
  - Recent exposure to intravenous contrast agents
  - Hypovolemia
  - Hypotension
  - Urinary infection
  - Urinary tract obstruction
- If an individual patient experiences a decrease in eGFR by ≥40% from baseline, the Investigator should obtain confirmatory repeat tests, look for potentially reversible causes of renal dysfunction. Serum creatinine should be monitored at least weekly until improving.
- If a patient is on oral antihypertensive medications, the Investigator should consider whether these should be interrupted, especially during intercurrent illness or volume depletion.

Clinically significant renal function decline, defined as a decrease in eGFR by ≥30% from baseline and to eGFR <60 mL/min/1.73m^2 must be reported as an AE of clinical interest (Section 6.5.6.1).

5.7.4. Monitoring and Approach for Potential Hyperkalemia

The Schedule of Assessments (Table 1) includes frequent laboratory monitoring of serum electrolytes (at least monthly through the anticipated onset of zilebesiran PD). The guidelines in Table 4 apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 4: Recommended Interventions for Hyperkalemia

Serum K^+ >5.2 and <5.5 mmol/L	Serum K^+ ≥5.5 and <6.0 mmol/L	Serum K^+ ≥6.0 mmol/L
• Confirm potassium concentration in a non-hemolyzed sample. • Reinforce low-potassium diet and restriction of food/drinks with high potassium content. • Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia[a]. Consider reduction in dose or discontinuation of these agents only if clinically acceptable. • Repeat K^+ measurement within 3 to 5 days. • If K^+ remains >5.2 and <5.5 mmol/L, regularly monitor K^+ levels to ensure stability.	• Confirm potassium concentration in a non-hemolyzed sample. • Apply all measures outlined for serum K^+ >5.2 and <5.5 mmol/L. • Repeat K^+ measurement after 2 to 3 days. • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with a potassium binder.	• Confirm potassium concentration in a non-hemolyzed sample. • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with a potassium binder. • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L.

Abbreviations: NSAID=nonsteroidal anti-inflammatory drug.

[a] This list is not meant to be exhaustive: potassium-sparing diuretics (eg, amiloride and triamterene), potassium supplements (eg, potassium chloride), salt substitutes, NSAIDs, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, herbal supplements (eg, Noni juice, alfalfa [*Medicago sativa*], dandelion [*Taraxacum officinale*], horsetail [*Equisetum arvense*], nettle [*Urtica dioica*], milkweed, lily of the valley, Siberian ginseng, hawthorn berries).

Any potassium elevation >5.5 mmol/L that has been confirmed by a second measurement (serum or plasma) or that requires clinical intervention must be reported as an AE of clinical interest (Section 6.5.6.1).

5.7.5. Liver Function Test Criteria for Monitoring

1. Liver function test (LFT) results (Table 6) are to be obtained and reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN:
   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. If an alternative cause is found, provide appropriate care.
   c. If an alternative cause is not found, perform assessments per Table 5 and Table 7.
3. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by either clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, the Investigator

should monitor the patient closely, including following the elevations (at minimum weekly) until satisfactory resolution, or the Investigator deems the elevations to be chronic or stable. If elevation persists for ≥2 months, the Investigator must discuss with the Medical Monitor.

4. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by either clinical symptoms or by elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 5.

Table 5: Monitoring Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3×ULN, with No Alternative Cause Identified

Transaminase Level	Action
>3× to 5×ULN	• Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor
>5×ULN	• Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to every 2 weeks until satisfactory resolution • If elevation persists for ≥2 months, must discuss with the Medical Monitor

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function test(s); ULN=upper limit of normal.
Note: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.8. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1). Concomitant medications include all prescription medications, herbal preparations, over-the-counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. For permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for 4 days after the dose of study drug.

Patients receiving low-dose aspirin (defined as ≤100 mg per day) for at least 30 days prior to screening and during the study treatment period are allowed. Occasional use of other systemic over-the-counter NSAIDs is allowed. However, given their association with increased blood pressure, they should be avoided when possible and for at least 2 days prior to ABPM and office blood pressure assessments, and alternative analgesics (acetaminophen, topical NSAIDs) should be considered.[Whelton 2018] When used, the dosing of systemic NSAIDs should be at the lower end of the labeled range and for the shortest duration possible.

Patients receiving SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin) should be on a stable dose for at least 30 days prior to screening and during the study treatment period. These medications should not be initiated or discontinued, if possible, during the study treatment period.

Patients receiving stable doses of tamsulosin, alfuzosin, or silodosin for at least 30 days prior to screening are allowed.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional Regulatory Authorities.

Use of cannabis or delta-9-tetrahydrocannibinol (THC)-containing substances (including by smoking, vaping, dabbing, or ingesting/edibles) should be avoided when possible and for at least 2 days prior to ABPM and office blood pressure assessments.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.8.2. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.8.1. Oral Antihypertensive Medication

Individual initiation and modification of oral antihypertensive medications per Investigator judgement are permitted throughout the study if required to treat clinically significant blood pressure elevation (Section 5.7.2). In addition, after Month 3, oral antihypertensive medications may also be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines.[Umemura 2019; Williams 2018] All oral antihypertensive medication that are dosed once daily should be taken in the morning.

Serum electrolytes and creatinine should be measured at a central or local laboratory approximately 2 weeks after any antihypertensive addition or dose titration.

5.8.2. Prohibited Concomitant Medication

Conventional RAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) are prohibited throughout the study.

The following medications, treatments, and supplements are prohibited throughout the study treatment period (until the EOT visit):

- Beta blockers
- Prescription NSAIDs.
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol).
- Any nucleotide therapeutic (other than zilebesiran).
- Medications, herbal supplements (including Ma Huang and St. John's wort), or other substances (such as licorice) that are associated with increases in LFT abnormalities or with blood pressure abnormalities are prohibited. This includes certain stimulants (eg, amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine), MAO inhibitors, atypical antipsychotics (eg, clozapine, olanzapine), diet pills (eg, phenylpropanolamine, sibutramine), and nasal decongestants (eg, phenylephrine hydrochloride, pseudoephedrine, naphazoline hydrochloride), unless individually approved by both the Investigator and the Medical Monitor.

- Medications, herbal medicines, over-the-counter medications, or supplements known to cause hyperkalemia are prohibited unless individually approved by both the Investigator and the Medical Monitor. This includes potassium-sparing diuretics, potassium supplements, cyclo-oxygenase-2 inhibitors, trimethoprim and trimethoprim-containing combination products, mineralocorticoid receptor antagonists, Noni juice, alfalfa, dandelion, horsetail, nettle, milkweed, lily of the valley, Siberian ginseng, and hawthorn berries.

All concomitant medications must be reviewed and approved by the Investigator, with particular attention to avoiding drugs that may affect blood pressure.

5.9. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff.

5.10. Other Requirements

5.10.1. Contraception

Females of childbearing potential must be willing to use a highly effective method of contraception from 14 days before first dose and throughout study participation, including through safety follow-up.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.*
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable*, injectable*, or transdermal* hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods, if they start heterosexual relationships during the study and through safety follow-up.

* Contraceptive methods currently not approved for use in Japan.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of childbearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral oophorectomy, hysterectomy, or bilateral salpingectomy). A

postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause. Per Investigator's discretion, a high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.

For male patients, no contraception is required.

Lastly, patients should also avoid ova and sperm donation through safety follow-up or until study completion, whichever is longer.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.5.3). Pregnancy testing will be performed before study drug dosing in the study (Table 1).

5.10.2. Alcohol Restrictions

Patients should abstain from alcohol consumption for 48 hours before each blood collection for clinical laboratory tests.

5.10.3. Tobacco and Nicotine Restrictions

Use of nicotine or tobacco-containing products (including, but not limited to, snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to office blood pressure measurements.

5.10.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit salt consumption to <6.0 g per day from screening through the end of the Treatment period. This direction should be provided at the start of the Screening period, and treatment-naïve patients should follow these recommendations for at least 1 week prior to screening assessments of blood pressure. This is the salt intake recommended in the Japanese Society of Hypertension Guidelines for hypertensive patients [Umemura 2019; Whelton 2018; Williams 2018].

5.10.5. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests and from any exercise for 30 minutes prior to office blood pressure measurements.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1. Study visits should be scheduled for the morning. All assessments, except for postdose PK sample collection and ECG extraction (Table 2), are to be performed prior to study drug dosing on Day 1. Additional information on the collection of study assessments will be detailed in the relevant study manual.

6.1. Screening Assessments

An ICF that has been approved by the appropriate IRB/IEC must be signed (in paper or electronic format per local regulations and institutional standards) by the patient before the screening procedures are initiated. All patients will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted once, with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

6.1.1. Retesting

If in the Investigator's judgement, screening assessment abnormalities are likely to be transient, then the assessments may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during screening provided that the patient can be evaluated for eligibility after a minimum of 3 weeks of antihypertensive washout (as applicable) and randomized within the allowed Screening period.

Retesting of office blood pressure during screening is permitted once if, in the Investigator's judgement, the result is not accurate due to a transient condition. Retesting of screening ABPM is permitted once, if the first screening ABPM is invalid. A valid screening ABPM recording must be obtained within 1 week prior to randomization for all patients. In circumstances where it is not possible to randomize an eligible patient within the 1-week window following a valid screening ABPM result that met the inclusion criterion, a single additional ABPM assessment is permitted, with no option for retesting in case of an invalid reading. Eligibility is assessed by the most recent ABPM result obtained. If a valid ABPM reading that meets the inclusion criterion is unable to be obtained within 1 week prior to randomization, the patient is a screen failure.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria will be allowed to return once for rescreening if, in the Investigator's judgement, they are likely to meet eligibility criteria (eg, prohibited medications that were subsequently discontinued) and in consultation with the Medical Monitor. A patient will be reconsented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

All blood pressure measurements (ABPM, office, and HBPM) must be taken at the times specified in the Schedule of Assessments (Table 1) using the standardized equipment provided by the Sponsor, according to the methods described in the relevant study manual. Office blood pressure assessments and ABPM initiation must be performed before administration of any oral antihypertensive medications and study drug (as applicable).

In patients taking oral antihypertensives, a washout of a minimum of 3 weeks (as applicable) must be completed prior to measurement of the baseline ABPM (for eligibility) and screening office blood pressure (for eligibility).

The appropriately sized cuff for each modality must be used for all assessments. The arm's circumference at midpoint (halfway between the acromion and olecranon) will be determined at screening with a metric tape measure and used to select the appropriately sized blood pressure cuff/bladder for each instrument as described in the relevant study manual. Unless significant weight loss or gain occurs between visits, the patient will use the same cuff/bladder size throughout the study.

At the first Screening visit only, office blood pressure will be measured in both arms to select the appropriate arm to use for office blood pressure and HBPM measurements. Unless a concomitant condition favors the use of a specific arm, the arm with the higher office SBP will be used for all subsequent office blood pressure and HBPM readings. The ABPM will be measured using the patient's nondominant arm. If the patient is ambidextrous, the same arm used for office blood pressure and HBPM readings should be used.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.7.1 and Section 5.7.2, respectively.

6.2.1. ABPM

The ABPM should be started prior to the morning dose of oral antihypertensive medication. Consecutive (daily) use of over-the-counter NSAIDs (other than aspirin ≤100 mg per day) and use of cannabis or THC-containing substances should be avoided for at least 2 days prior to ABPM measurements.

Validity will be assessed for all ABPMs. The baseline ABPM recording must be obtained within 1 week before randomization. In circumstances where it is not possible to randomize a patient within the 1-week window following a valid ABPM recording that met the inclusion criterion, a single additional ABPM recording is permitted, with no option for retesting in case of an invalid recording. Eligibility is assessed by the most recent ABPM recording obtained. If a valid ABPM recording that meets the inclusion criterion is unable to be obtained within 1 week prior to randomization, the patient is a screen failure.

If an invalid ABPM recording is obtained at any visit after randomization, the patient will be provided 1 opportunity to repeat the recording within the visit window.

See further details in the relevant study manual.

6.2.2. Office Blood Pressure

Office blood pressure must be measured in triplicate using the automated blood pressure device provided by the Sponsor at trough (prior to taking oral antihypertensives, if applicable) and at approximately the same time each day; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include both seated and standing measurements.

Exercise, caffeine, alcohol consumption, and use of nicotine or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) must be avoided within 30 minutes prior to blood pressure measurements. The use of inhaled short-acting beta agonists should be avoided within 6 hours prior to measuring blood pressure and/or heart rate. The use of phosphodiesterase type 5 inhibitors (eg, sildenafil, tadalafil, vardenafil, avanafil) should be avoided within 48 hours prior to measuring blood

pressure. Consecutive (daily) use of over-the-counter NSAIDs (other than aspirin ≤100 mg per day) and use of cannabis or THC-containing substances should be avoided for at least 2 days prior to blood pressure measurements.

The patient should be seated comfortably with the back supported and the feet flat on the floor, and measurements should be obtained after approximately 5 minutes of rest. A standing measurement should be obtained 1 to 3 minutes after the last seated measurement.

See further details in the relevant study manual.

6.2.3. HBPM

An HBPM unit will be provided during the Screening period to facilitate monitoring during the washout of prior oral antihypertensives (if taking) and to establish the HBPM baseline prior to randomization. To establish baseline, at least 3 recordings should be collected during the last week immediately prior to randomization.

For all measurements, HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The patient should be seated comfortably without distractions with the back supported and the feet flat on the floor.

See further details in the relevant study manual.

6.3. Pharmacodynamic Assessments

Blood samples for the assessment of AGT and RAS biomarkers (plasma renin concentration, renin activity, and aldosterone) will be collected according to the Schedule of Assessments (Table 1). Blood samples for PD assessments must be collected before study drug administration on Day 1 or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a central laboratory using a validated enzyme-linked immunosorbent assay for measurement of PD effect. RAS biomarkers may be analyzed using qualified assays. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

Results will not be used to guide clinical management and will not be shared with sites until after final database lock.

6.4. Pharmacokinetic Assessments

Blood and urine samples will be collected for the assessment of plasma and urine concentrations of zilebesiran and its primary metabolite AS(N-1)3′ zilebesiran at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood and urine samples for PK analysis is in Table 2.

Plasma and urine concentrations of zilebesiran and AS(N-1)3′ zilebesiran will be determined using validated assays. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight, ECG findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include office blood pressure, heart rate, body temperature, and respiratory rate. Vital signs are to be collected prior to administration of oral antihypertensive medications and study drug (as applicable). Vital signs should be measured before blood samples are drawn, where possible. Vital signs will be measured in the seated position, after the patient has rested comfortably for approximately 5 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, forehead, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute. Blood pressure is described in Section 6.2.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight and Height

Height will be measured in centimeters at Day 1 only. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1).

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose, and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.5.4. Electrocardiogram

The 12-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval, and QTcF will be obtained, as specified in the Schedule of Assessments (Table 1). Patients will be supine for at least 10 minutes before each ECG is obtained. The Investigator or qualified designee will review all single 12-lead ECGs to assess whether the

results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF.

Continuous 12-lead digital ECG data will be recorded on a 24-hour 12-lead Holter monitor for assessment of QTc interval as detailed in Table 1. Patients will rest supine 10 minutes before the ECG extraction at each nominal time point. The 12-lead ECGs will be extracted from the continuous recording at the nominal time points listed in Table 2. Continuous digital ECGs may not be read in real time and will only be analyzed at the end of the study.

When ECG and blood sample collection for RAS biomarkers (renin and aldosterone) occur at the same visit and where feasible, blood sample collection should occur first. ECGs should be performed at least 30 minutes after phlebotomy or other stressful assessments.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded in the eCRF. Additional ECGs may be collected at the discretion of the Investigator.

6.5.5. Clinical Laboratory Assessments

Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

Clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.7.5. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. While local laboratory results may be used for urgent clinical decisions, on the day of the assessments, all laboratory assessments specified in Table 6 that are performed at the clinic should also be sent in parallel to the central laboratory.

Blood samples collected for RAS biomarkers should be collected in the morning and in the seated/upright position (after blood pressure measurements and before any assessments collected in the supine position). Blood samples for laboratory evaluation should be collected after the completion of blood pressure assessments.

Spot urine collections for albumin and creatinine should be obtained in the morning.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 6: 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 (see Section 6.5.5.1)	
HbA1c	
Immunogenicity (see Section 6.5.5.2)	
Anti-drug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
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.

6.5.5.1. Glycemic Assessment

Blood samples for HbA1c will be collected as specified in the Schedule of Assessments (Table 1).

6.5.5.2. Immunogenicity

Blood samples will be collected to evaluate anti-drug antibodies (ADA). Blood samples for ADA testing must be collected before study drug administration (on Day 1) as specified in the Schedule of Assessments (Table 1).

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.3. Pregnancy Testing

A pregnancy test will be performed for females of childbearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1) and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant at screening are not eligible for study participation. Any woman with a positive urine pregnancy test, subsequently confirmed by a positive serum pregnancy test, during the study will be followed for safety. Patients determined to be pregnant while on study will be followed at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

A blood sample may be drawn at screening to measure the levels of follicle-stimulating hormone in order to confirm postmenopausal status in women suspected to be postmenopausal (see Section 5.10.1 for definition of postmenopausal state) at the Investigator's discretion.

6.5.5.4. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.7.5. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

The Investigator should consider testing for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are more typically observed in immunosuppressed individuals.

Monitoring for potential liver transaminase elevations is described in Section 5.7.5.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and Total	Anti-nuclear antibodies
HAV antibody IgM	Anti-smooth muscle antibodies
HCV antibody	Anti-LKM1 antibody
HCV RNA PCR – qualitative and quantitative	Anti-mitochondrial antibodies
HEV antibody IgM	Anti-SLA
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over-the-counter medications, supplements, and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic
Other potential causes of liver injury, including but not limited to MASH, hypoxic/ischemic hepatopathy, biliary tract disease, and metabolic disease (eg, Wilson disease)	

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MASH=metabolic dysfunction-associated steatohepatitis; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen.
Note:

- All laboratory assessments will be measured at the central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations 312.32, IND Safety Reporting, 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.

Serious Adverse Event

An SAE is any untoward medical occurrence that 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, 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/1.73m^2.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	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).
Severe:	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.

Worsening in severity should be documented in the medical record. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When an AE worsens throughout the course of the event, the maximum severity should be noted.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE 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.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the patient's EOS. Non-serious AEs will be followed until the patient's EOS. Events occurring after signing of the ICF and before study drug administration will be captured

as medical history (see Section 6.1), while AEs that occur after study drug administration and baseline events that worsen after study drug administration must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the patient's EOS. Refer to Section 6.5.6.4 for additional information regarding SAEs with a suspected causal relationship to study drug that occurs after a patient stops participation in the study or after the EOS. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to eCRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom[s], injection site location, follow-up actions taken, etc).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee immediately and no later than 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Immediately and no later than 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form.

Appropriate remedial measures should be taken by the Investigator using their best medical judgement to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study drug that occurs after a patient withdraws from the study, the Investigator shall report the SAE to the Sponsor or designee within 24 hours of first awareness of the event.

If the Investigator becomes aware of an SAE in a patient with a suspected causal relationship to the study drug that occurs after the end of the study, the Investigator shall report the SAE to the Sponsor within 24 hours of first awareness of the event using the paper SAE form.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Clinical Trials Regulation (EU) No 536/2014 (CTR), and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through safety follow-up, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded using the appropriate eCRF. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled to not breastfeed for 84 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Reporting of Overdose and Other Special Situations

An overdose is defined as any dose of study drug administered to the patient or taken by the patient that is >2× the assigned dose during a single administration.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, or misuse), the Investigator should:

- Notify the Sponsor or designee within 24 hours using the appropriate eCRF
- Closely monitor the patient for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with hypertension, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of zilebesiran.

Research samples will be collected at the intervals indicated in the Schedule of Assessments (Table 1). These specimens will be analyzed at a central laboratory. Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy, or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit) or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, patients will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before unblinding for the primary analysis of the 6-month DB period. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 36 patients, each treatment arm will include 12 patients. The sample size estimate is not based on the primary endpoint, which is a safety endpoint. Instead, sample size was estimated based on the secondary endpoint of percent change in AGT from baseline to Month 3 in Study 001. In Study 001, standard deviation (SD) for the percent change from baseline to Week 12 (Month 3) in the pooled zilebesiran arms was 42%. Assuming an SD of 0.42, the proposed sample size will provide more than 90% power to detect a 50% difference in percent AGT reduction at Month 3 between zilebesiran and placebo at a significance level of 0.05 (2-sided).

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the SAP. Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

Statistical analyses will be primarily descriptive in nature. No formal hypothesis testing will be conducted. Descriptive statistics (eg, n [non-missing observations], mean, SD, median, minimum, and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Analyses will be performed using SAS® (Version 9.4, or higher).

7.2.1. Analysis Populations

The populations (analysis sets) are defined as follows:

- **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.

7.2.2. Handling of Missing Data

In general, missing data will not be imputed.

7.2.3. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized for the Safety Analysis Set by dose level and overall.

7.2.4. Efficacy Analyses

Descriptive statistics will be provided for SBP and DBP summarizing the observed values and changes from baseline over time. Blood pressure analysis measured by ABPM, office blood pressure, and HBPM will be conducted using the Full Analysis Set.

7.2.5. Pharmacodynamic Analysis

Available PD data, including serum AGT, as well as exploratory biomarkers of the RAS pathway, will be summarized over time for all patients in the PD Analysis Set.

7.2.6. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using the PK Analysis Set. Plasma and urine concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran will be summarized using descriptive statistics. The calculation of PK parameters will be conducted using noncompartmental analysis.

Pharmacokinetic parameters include, but will not be limited to, maximum plasma concentration, time to maximum plasma concentration, elimination half-life, area under the concentration-time curve, apparent clearance, and apparent volume of distribution. Other parameters may be calculated, if deemed necessary.

7.2.7. Anti-drug Antibody Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during study will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.8. Safety Analyses

The primary endpoint is the frequency of patients with treatment-emergent AEs (hereafter referred to simply as AEs). Safety assessments also include vital signs, ECGs, clinical laboratory assessments, and physical exams. Extent of exposure will be summarized by dose level and overall.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical Classification System and Preferred Term (PT).

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. By-patient listings will be provided for deaths, SAEs, and AEs leading to withdrawal from study.

Descriptive statistics will be provided for clinical laboratory parameters, ECG, and vital signs summarizing the observed values and changes from baseline over time. Laboratory shift tables from baseline grade (or category) to worst postbaseline grade (or category) will be presented for laboratory parameters that are graded or categorized.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Interim Analysis

No interim analysis is planned.

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. All patients will be given a copy of the signed and dated ICF.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority (if needed) for approval before patients are enrolled under the amended protocol, and patients must be reconsented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, whichever is longer.

If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable Regulatory Authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The EOS is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and eCRFs to ensure overall quality and completeness of the data and to confirm study procedures comply with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC, or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

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10. APPENDICES

10.1. Formulae for Estimated Glomerular Filtration Rate Calculation

Estimated glomerular filtration rate (eGFR; in mL/min/1.73m^2) will be calculated from serum creatinine (SCr) based on the Modification of Diet in Renal Disease formula and using the Japanese coefficient of 0.808.[Matsuo 2009]

Modification of Diet in Renal Disease Formula [Levey 2006]

- Conventional units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (0.808, if Japanese)
- SI units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [µmol/L]/88.4)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female) × (0.808, if Japanese)

10.2. Amendment History

10.2.1. Amendment 1 Summary of Changes

The primary purpose of this amendment is to clarify planned analyses and unblinding around analyses.

The following changes are not detailed: administrative changes, changes associated with administrative letters (since the original protocol was finalized), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

Section(s)	Description of Change	Brief Rationale
Table 2, footnote a	Clarified that results from ECG monitoring will be read locally	Holter extraction ECGs are not read locally
5.6, 6.5.6.8	Clarified CPC reporting	The special situations form does not include CPC reporting
5.7.2	Removed the requirement of documenting the rationale for not adding oral antihypertensives for treat to target blood pressure in the eCRF	This field is not included in the eCRF because there is no plan to use this information for any analysis
6.5.5	Added triglycerides to the serum chemistry	To clarify that triglycerides are collected as part of the serum chemistry panel
6.5.5.4	Clarified follow-up testing for patients with ALT/AST elevations >3×ULN with no alternative cause	To provide an operational update on follow-up for patients with ALT/AST elevations due to changes in laboratory testing availability and provide additional guidance on potential alternative etiologies
7, 3.5	Modified language on timing of SAP finalization and clarified unblinding	To clarify timing and blinding procedures around the planned analyses