CLINICAL STUDY PROTOCOL
ALN-AGT01-003
DATED 20 JULY 2023

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication
Short Title:	Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)
Study Drug:	Zilebesiran (ALN-AGT01)
EudraCT Number:	2021-003776-13
IND Number:	143503
Protocol Date:	Original protocol, 25 August 2021 Amendment 1, 22 March 2022 Amendment 2, 22 September 2022 Amendment 3, 20 July 2023
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD PPD

SPONSOR PROTOCOL APPROVAL

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

_____

PPD

PPD

Alnylam Pharmaceuticals, Inc.

_____

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-003 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 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication

Short Title

Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)

Study Drug

Zilebesiran (ALN-AGT01)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 175 clinical study centers worldwide.

Objectives and Endpoints

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM • Time-adjusted change from baseline through Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6 Other Secondary Endpoints • Change in 24-hour mean SBP and DBP, assessed by ABPM • Change in office SBP and DBP

Objectives	Endpoints
	• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM • Change in serum AGT
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM control and response rates • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 36)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

Study Design

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

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

Patients who meet all inclusion/exclusion criteria after the Run-in period will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB treatment period as add-on therapy to their protocol-specified background antihypertensive medication.

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

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

Number of Planned Patients

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

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 should have a 24-hour mean systolic blood pressure (SBP) ≥130 mmHg and ≤160 mmHg by ambulatory blood pressure monitoring (ABPM) after at least 4 weeks of run-in on protocol-

specified background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

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

Patients randomized to receive zilebesiran will be administered 600 mg SC once during the 6-month DB treatment period. Before Amendment 3, patients who entered the OLE period received 600 mg zilebesiran SC at Month 6 after all predose assessments were conducted and once every 6 months during the OLE period. Upon implementation of Amendment 3, patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period but will not be eligible to enter the OLE period and receive a dose of study drug at Month 6. Patients in the OLE period will not receive any additional doses of study drug.

Reference Treatment, Dose, and Mode of Administration

Placebo (phosphate-buffered saline for SC administration) will be administered at the same dosing interval and volume as the study drug during the 6-month DB period.

Protocol-specified Background Antihypertensive Medication, Dose, and Mode of Administration

Patients will be randomized to 1 of the following protocol-specified background antihypertensive medications to be administered orally once daily during the Run-in and 6-month DB periods:

- Olmesartan: 40 mg (or 20 mg for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks.
- Amlodipine: 5 mg
- Indapamide: 2.5 mg

Duration of Treatment and Study Participation

The duration of treatment with zilebesiran is up to 36 months. The estimated total time on study for each patient is up to approximately 45 months, including up to 75 days in the Screening and Run-in periods, up to 36 months of treatment, and up to 12 months after the last dose of study drug in the Safety Follow-up period.

Statistical Methods

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period. Randomization on Day 1 will be stratified by race (black or all other races), baseline

blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

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

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

The populations (analysis sets) are defined as follows:

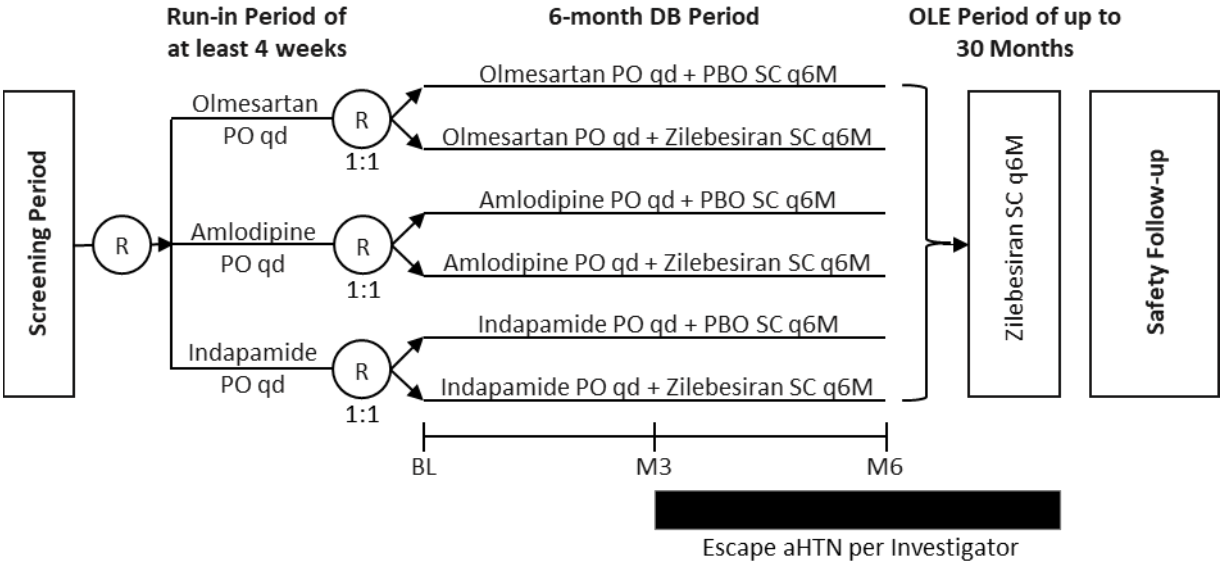
- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug. All by-treatment analyses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

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

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

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



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

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																				
			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]									Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Informed consent	Section 8.1.1	X																			
Assign patient identification no.	Section 3.4	X																			
Medical history	Section 6.1	X																			
Demographics	Section 6.1	X																			
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X	X	X																	
Serum pregnancy test/FSH screening	Table 6 and Sections 6.5.5.3 and 6.5.6.7; FSH to confirm post-menopausal state if applicable	X																			
Creatinine clearance	Section 6.5.5	X																			
Full physical exam	Section 6.5.3	X			X							X								X	
Height and BMI	Section 6.5.2; Height measured at Day 1 only				X				X			X			X	X	X	X	X	X	
Body weight	Section 6.5.2	X		X	X				X			X			X	X	X	X	X	X	

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		Shading indicates visits that must be performed at the site																				
			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]									Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Single 12-Lead ECG	Section 6.5.4	X			X							X				X	X	X	X	X	
Serum chemistry[c]	Table 6; Section 6.5.5	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X		X	X				X			X			X	X	X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicates for patients with abnormalities listed in Section 5.2.4	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Spot urine for albumin and creatinine[c]	Section 6.5.5	X		X	X				X			X				X	X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c[c]	Section 6.5.5.1	X		X	X				X			X				X				X	
Vital signs and office blood pressure[d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[e]	Section 6.2.1			X				X	X			X			X	X				X[h]	

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																				
			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]									Safety Follow-up
Study Visit (Month)		**Screening Period**	**Run-In Visit 1**	**Run-In Visit 2**	**D1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M12**	**M18**	**M24**	**M30**	**M36/EOT/ET**	**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-75 to -1**			**D1**	**D15±2**	**D29±2**	**D57±7**	**D85±7**	**D113±7**	**D141±7**	**D169±7**	**D197±7**	**D225±7**	**D253±7**	**D337±7**	**D505±14**	**D673±14**	**D841±14**	**D1009±14**	**±14**
HBPM[f]	Section 6.2.3			X	At least once per week																
Discontinue prior oral antihypertensive medications (if taking)	Section 3.1		X																		
Urine pregnancy test[b]	Table 6 and Sections 6.5.5.3 and 6.5.6.7		X		X							X				X	X	X	X	X	
RAAS biomarkers: renin concentration, aldosterone, AngI/II	Section 6.3; Only in patients randomized to receive olmesartan		X		X				X												
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X		X			X			X	X				X	
Randomization to protocol-specified background antihypertensive medication	Section 3.4; Randomization may occur on Run-in Visit 1 or 1 business day prior		X																		

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																				
			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]									Safety Follow-up
Study Visit (Month)		**Screening Period**	**Run-In Visit 1**	**Run-In Visit 2**		**W2**	**M1**	**M2**	**M3**	**M4**	**M5**											
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-75 to -1**			**D1**	**D15±2**	**D29±2**	**D57±7**	**D85±7**	**D113±7**	**D141±7**	**D169±7**	**D197±7**	**D225±7**	**D253±7**	**D337±7**	**D505±14**	**D673±14**	**D841±14**	**D1009±14**	**Q6M post last dose of study drug ±14**
Protocol-specified background antihypertensive medication administration	Section 5.3		Daily																			
Protocol-specified background antihypertensive medication pill count	Section 5.10			X	X		X	X	X	X	X	X										
Plasma for PK	Section 6.4 and Table 2				X							X										
Immunogenicity (ADA)	Section 6.5.5.2				X				X			X			X	X	X	X	X	X	X
Serum AGT	Section 6.3				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference and waist-to-hip ratio	Section 6.5.2				X							X				X	X	X	X	X		
Exploratory DNA sample (optional)	Section 6.6				X																	

Table 1: Schedule of Assessments

		Shading indicates visits that must be performed at the site																				
			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]									Safety Follow-up
Study Visit (Month)		**Screening Period**	**Run-In Visit 1**	**Run-In Visit 2**		**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M12**	**M18**	**M24**	**M30**	**M36/EOT/ET**	**Q6M post last dose of study drug**
Study Day (±Visit Window)	**See Section/Table for details; Notes**	**D-75 to -1**			**D1**	**D15±2**	**D29±2**	**D57±7**	**D85±7**	**D113±7**	**D141±7**	**D169±7**	**D197±7**	**D225±7**	**D253±7**	**D337±7**	**D505±14**	**D673±14**	**D841±14**	**D1009±14**	**±14**
Neurologic evaluation[g] and symptom-directed physical exam	Section 6.5.3															X	X	X	X		X
Randomization to zilebesiran or placebo	Section 3.4; Randomization may occur on Day 1 or 1 business day prior				X																
Study drug administration (zilebesiran or placebo)	Section 5.2.2				X							X				X	X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of protocol-specified background antihypertensive medication		Continuous																		
Concomitant medications	Section 5.9	Continuous																			

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; DB=double-blind; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone;

HbA1c=hemoglobin A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; No.=number; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin, aldosterone, and Ang I/II) should be performed before physical examinations and 12-lead ECGs.
- Run-in Visit 2 should occur at least 4 weeks after Run-in Visit 1.
- Patients may have been eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran beginning at the Month 6 visit and continue for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.
- Patients will be asked to perform Safety Follow-up visits once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed.

Footnotes:

[a] **All assessments, except for postdose PK sample collection (Table 2), are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

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

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

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

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

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

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

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

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±30 min)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±30 min)	X

Abbreviations: hh:mm=hour:minute; min=minutes; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates 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.

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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
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
HOMA	Homeostatic model assessment
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Abbreviation	Definition
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reactions
LFT	Liver function test
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measurements
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred term
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
THC	Delta-9-tetrahydrocannibinol
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing zilebesiran (ALN-AGT01), a subcutaneously (SC) administered investigational agent comprised of 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-AGT01-003 (KARDIA-2) is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety, and pharmacodynamics (PD) of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. Patients will be randomized to run-in on 1 of 3 protocol-specified antihypertensive medications open-label for at least 4 weeks (olmesartan, amlodipine, or indapamide). At the end of the Run-in period, patients with uncontrolled blood pressure will be randomized 1:1 to receive zilebesiran or placebo as add-on therapy to the protocol-specified background antihypertensive medication for 6 months during the double-blind (DB) period. After completion of the 6-month DB period, patients may have been eligible to participate in a separate zilebesiran open-label extension (OLE) study. Patients will discontinue their protocol-specified background antihypertensive medication at Month 6. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran (600 mg once every 6 months) for up to 30 additional months during the OLE period of this study (ALN-AGT01-003) until the separate OLE study was open and then transition. Upon implementation of Amendment 3, the OLE period of this study will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete end of treatment (EOT) assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean systolic blood pressure (SBP), assessed by ambulatory blood pressure monitoring (ABPM), from baseline to Month 3, relative to placebo. Secondary and exploratory objectives of the study include evaluating the add-on efficacy of zilebesiran on other measures of blood pressure response (including longer treatment durations, eg, up to 36 months) and evaluating the PD effect of zilebesiran, including reduction in circulating AGT concentration.

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; Services 2020]

The Sponsor is developing zilebesiran, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. 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-aldosterone system (RAAS) 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 (AngII).

Zilebesiran is being studied in the ongoing 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 in obese patients (Part D), and as a single dose of 800 mg co-administered for 2 weeks with 300 mg irbesartan (Part E). Preliminary data are available from Parts A, B, and E. Dose-dependent and durable reductions in circulating AGT were observed after single SC doses of zilebesiran, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Sustained reductions in serum AGT were observed for up to 6 months following a single dose of zilebesiran.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium. No patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in patients who received zilebesiran doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

Because most patients with hypertension eventually progress to require treatment with more than 1 antihypertensive class,[Williams 2018] it is anticipated that zilebesiran may be used together with other standard of care antihypertensive medication. This Phase 2 study will further quantify the antihypertensive effects of zilebesiran as add-on therapy in patients with hypertension not adequately controlled by a standard of care antihypertensive medication. The consistent and

durable PD effect of zilebesiran is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

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

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that zilebesiran may offer the benefit of sustained blood pressure reduction to patients with hypertension with infrequent administration (ie, once every 3 months or once every 6 months). The mean SBP reduction observed after single zilebesiran doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives.[Abraham 2015; Materson 1993] The blood pressure of patients will be closely monitored, and after Month 3, escape antihypertensive medications will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of zilebesiran, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with zilebesiran. 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, and escape antihypertensive medications are permitted to manage uncontrolled blood pressure following 3 months of add-on treatment with zilebesiran. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.8.1), hypertension (Section 5.8.2), renal dysfunction (Section 5.8.3), and hyperkalemia (Section 5.8.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from 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. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations. In addition to study drug, each patient will receive a protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). These agents are approved standard medications that will be dosed in accordance with local labeling.

While zilebesiran is designed to inhibit the RAAS, its site of action (AGT) in the RAAS is unique, and its tissue specificity for the liver is hypothesized to improve its renal safety profile relative to conventional RAAS blockade,[Mullick 2017; Uijl 2019] both in the context of monotherapy and when used together with a conventional RAAS blocker such as olmesartan. In the latter setting, zilebesiran is hypothesized to add antihypertensive benefit when added to a conventional RAAS blocker without the increased incidence of RAAS inhibitor-associated renal adverse effects that have been observed in prior trials of conventional dual RAAS blockade.[Makani 2013] Patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 or urine albumin:creatinine ≥ 300 mg/g will be exclusively assigned to the olmesartan cohort to ensure that patients with proteinuric chronic kidney disease or diabetes

continue the RAAS inhibition standardly recommended for their renal indication throughout the study.

This study's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS 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 highest risk to have events (eGFR <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, or poorly controlled diabetes) 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).

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

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM • Time-adjusted change from baseline through Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6 Other Secondary Endpoints • Change in 24-hour mean SBP and DBP, assessed by ABPM • Change in office SBP and DBP • Change in daytime and nighttime mean SBP and DBP, assessed by ABPM • Change in serum AGT
Exploratory	

Objectives	Endpoints
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM control and response rates • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 36)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

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

Run-in Period

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized as described in Section 3.4 to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US and Australia, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1).

Patients who do not tolerate run-in treatment or who do not meet eligibility for randomization at Day 1 will be withdrawn from the study and returned to their prior medication regimen in coordination with their usual health providers.

DB Period

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

Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the patient's protocol-specified background antihypertensive medication per Investigator judgement for elevated blood pressure as described in Table 4.

OLE Period

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

Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

During the OLE period of this study, Investigators will use escape antihypertensive medications as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring.

Patients will be considered as completing study drug if they received a dose of study drug at Day 1 and completed the Month 6 visit.

Safety Follow-up Period

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

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

An independent DMC will oversee the safety and overall conduct of this study, and an independent Clinical Event Adjudication Committee will review suspected renal events to adjudicate whether they meet criteria for acute kidney injury.

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

The duration of treatment with zilebesiran is up to 36 months. The estimated total time on study for each patient is up to approximately 45 months, including up to 75 days in the Screening and Run-in periods, up to 36 months of treatment, and up to 12 months after the last dose of study drug in the Safety Follow-up period.

3.2. Scientific Rationale for Study Design

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

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean SBP, assessed by ABPM, from baseline to Month 3, relative to placebo.

Patients with hypertension often require treatment with multiple antihypertensive drugs to reach target blood pressure,[Williams 2018] and it is anticipated that zilebesiran may be administered to individuals on a background of other antihypertensive medications. Therefore, this study evaluates the effects of zilebesiran relative to placebo in patients whose blood pressure is not adequately controlled despite treatment with 1 of the 3 major drug classes recommended for initial treatment of hypertension by all clinical guidelines: RAAS inhibitors (ie, angiotensin

converting enzyme [ACE] inhibitors, angiotensin II-receptor blockers, or a direct renin inhibitor), diuretics, and calcium channel blockers (CCBs).[Whelton 2018; Williams 2018] Studying coadministration with olmesartan will assess if the synergistic antihypertensive effects recently observed in rodents treated with both an ARB and an AGT-targeting GalNAc-siRNA will translate into clinically significant blood pressure reduction in hypertensive patients given zilebesiran as an add-on to conventional RAAS inhibition.[Uijl 2019] In addition, it will examine the safety and tolerability of liver-specific AGT targeting during treatment with a conventional RAAS blocker (olmesartan). The newer-generation ARB olmesartan was selected because of its high potency relative to early-generation RAAS inhibitors,[Ojima 2011; White 2011] enabling a robust test for added efficacy when combined with zilebesiran. The maximum dose of olmesartan permitted per local labeling will be used to further increase the rigor of this efficacy evaluation. The thiazide-like diuretic indapamide was selected in accordance with recent guidelines that highlight the greater potency and durability of thiazide-like diuretics over other diuretics.[Burnier 2019] The long-acting dihydropyridine CCB amlodipine was selected given its extensive use in clinical practice and randomized controlled trials.[Dahlof 2005; Jamerson 2008; Julius 2004]

During the study, blood pressure will be monitored with both automated office blood pressure measurements and outpatient 24-hour ABPM (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). 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 home blood pressure monitoring (HBPM), to assess long-term blood pressure variability and 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] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), 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 at Month 3 and will continue throughout the remainder of the study (see Table 4). The term “escape antihypertensive medication” is used to refer to any oral antihypertensive medication initiated to control blood pressure after Day 1. Separate from these treat-to-target modifications, 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.

If a patient requires treatment with an oral escape antihypertensive medication before Month 6, a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already the protocol-specified background antihypertensive medication) should be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS.

After the 6-month DB period, protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide) will be discontinued, and patients may have been

eligible to participate in a separate zilebesiran OLE study. If an individual patient reached Month 6 prior to availability of the separate OLE study, they may have received open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months during the OLE period until the separate OLE study was open and then transition. Because many patients would have received zilebesiran for the first time at Month 6, office blood pressure and serum chemistries were monitored monthly from Month 6 to Month 9. Upon implementation of Amendment 3, the OLE period will be closed because a separate OLE study will not be conducted. Patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period and then enter the Safety Follow-up period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

During the OLE period, Investigators may use escape antihypertensive medications of permitted classes as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring and following current care guidelines.[Whelton 2018; Williams 2018] Olmesartan, amlodipine, and indapamide will be discontinued as protocol-specified background antihypertensive medication during the OLE period; however, patients may continue to receive amlodipine or indapamide as escape antihypertensive medication at the Investigator's discretion. The use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure should be avoided throughout the study.

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 RAAS inhibitors[McMurray 2016; Parving 2012].

3.3. Justification for Dose

The dose of zilebesiran in this study (600 mg once every 6 months) was selected on the basis of data from the Phase 1 Study 001, in which single zilebesiran doses up to 800 mg were found to have an acceptable safety profile, and dose-dependent, clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed at doses as low as 100 mg. An acceptable safety profile was also observed for a single zilebesiran dose of 800 mg under low-salt/high-salt conditions or co-administered for 2 weeks with 300 mg irbesartan once daily. The selected dose of 600 mg is predicted to result in a median serum AGT reduction of 94.9% at trough (Month 6), translating to a median SBP reduction of 11.6 mmHg as monotherapy.

The protocol-specified background antihypertensive medications are standard agents recommended in international and regional hypertension guidelines, and the selected regimens are standard doses used for their approved indication of hypertension.[Whelton 2018; Williams 2018] Indapamide will be dosed at 2.5 mg orally once daily, and amlodipine will be dosed at 5 mg orally once daily. The dose regimens for indapamide and amlodipine used in this study were selected on the basis of their common use in clinical care (when used both individually and combined with other classes of antihypertensives) and their expected efficacy, safety, and tolerability. Olmesartan will be dosed at the maximum dose allowed per local labeling: 40 mg

orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia; Olmetec Product Information, September 2020).[von Bergmann 2001]

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 should contact the Interactive Response Technology (IRT) to obtain a patient identification number.

The Investigator or designee will contact the IRT to randomize the patient at Run-in Visit 1 and again at Day 1 after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at each visit.

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

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 7.1. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

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

3.5. Blinding

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

Zilebesiran and placebo will be packaged identically. Because zilebesiran may be slightly visually distinguishable from placebo, the vials will be masked in such a way as to hide the identity of the study drug contained within. For administration, syringes will be masked by a site pharmacist or delegate prior to withdrawing the study drug from vial. See the Pharmacy Manual for additional details. The study drug will be administered under the supervision of the Investigator (see Section 5.2.2).

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. 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 (eTMF).

Refer to the IRT instructions for details on unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review the suspected renal events blinded to treatment assignment to adjudicate whether they meet diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the Safety Follow-up visits as described in Section 3.1.

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. Has hypertension as follows:
    a. Untreated hypertension (not taking antihypertensive medication), or
    b. Treated hypertension 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.

4. Seated office SBP at Run-in Visit 1 as follows:
    a. ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
    b. ≥145 mmHg and ≤180 mmHg for patients on antihypertensive medications
5. 24-hour mean SBP ≥130 mmHg and ≤160 mmHg by ABPM at Run-in Visit 2 after at least 4 weeks of run-in.
6. ≥80% adherence to the protocol-specified background antihypertensive medication during the Run-in period as assessed by pill count performed at Run-in Visit 2.

Informed Consent

7. 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, or aortic coarctation)
2. Orthostatic hypotension, 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) at screening or during the Run-in period

Laboratory Assessments

3. Has any of the following laboratory parameter assessments at screening or Run-in Visit 2:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (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. Potassium <lower limit of normal range or >5 mEq/L
    e. Sodium <lower limit of normal range
    f. eGFR <30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula; refer to Section 10.1)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days or 5 half-lives of the investigational agent, whichever is longer, prior to Run-in Visit 1 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.

5. Currently taking, taken within 30 days prior to first 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 should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to discontinue prior to Run-in Visit 1
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.
8. 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.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to first randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), direct renin inhibitor, CCB (including but not limited to significant peripheral edema), or thiazide/thiazide-like diuretic
12. History of multiple drug allergies or history of allergic reaction to any component of or excipient in the study drug
13. 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
14. Has known active human immunodeficiency virus infection; or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection.
15. History of clinically significant cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting or other cardiothoracic surgeries, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to first randomization
16. Known history of angioedema
17. Clinically significant valvular heart disease
18. New York Heart Association II to IV heart failure

19. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia/supraventricular tachycardia, or atrial fibrillation with rapid ventricular response in the 3 months prior to first randomization
20. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
21. History of renal transplantation
22. 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
23. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to either randomization
24. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability
25. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

26. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.11.1
27. Female patient is pregnant, planning a pregnancy, or breast-feeding

Alcohol or Nicotine Use and Substance Abuse

28. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
29. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
30. 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 Restrictions

31. Third shift, night shift, or 24-hour shift workers
32. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
33. Placed in an institution on the basis of an official or court order

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or 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 discontinue study drug or stop a

patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or 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

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.9.1) per Investigator discretion
- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and 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.

If a patient has an AE, including SAEs, and/or laboratory abnormalities that in the judgment of the investigator, taking into account the patient's overall status, requires interruption or discontinuation from treatment with study drug, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month DB period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 6 assessments) will be encouraged to remain on the study and complete assessments (excluding pharmacokinetic [PK] assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

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 before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents. If a patient still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 6-month DB period, every effort should be made to conduct the Month 6 visit assessments at an earlier time (see Table 1).

A patient considering stopping participation in the study during the OLE period should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

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. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process the patient's personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the Investigator at any time in writing or in any other form that may be locally required. Also, where allowed by local

law, the patient may object to the collection, storage, and use of the patient's personal data, informing the Investigator at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

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 even if study drug is discontinued.

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 center. The following actions must be taken if a patient fails to return to the clinic 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.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study after the second randomization at Day 1.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug and protocol-specified background antihypertensive medication supplied by the Sponsor 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 and protocol-specified background antihypertensive medication that have been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of zilebesiran SC and placebo SC 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 (phosphate-buffered saline for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to zilebesiran.

5.2.2. Dose and Administration

During the 6-month DB period, patients will be administered a single dose of 600 mg zilebesiran or placebo, at the same volume, as SC injection on Day 1. Before Amendment 3, patients who entered the OLE period received 600 mg zilebesiran SC at Month 6 after all predose assessments were conducted and once every 6 months during the OLE period. Upon implementation of Amendment 3, patients in the 6-month DB period will continue their planned visits through the end of the 6-month DB period but will not be eligible to enter the OLE period and receive a dose of study drug at Month 6. Patients in the OLE period will not receive any additional doses of study drug.

Study drug injections 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. If a local reaction around the injection site occurs, photographs may be obtained. 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 study drug withdrawal from the vial. A full description of the blinding procedure is included in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 85 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

If a patient misses a dose of study drug, the Investigator should discuss with the Medical Monitor whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

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

5.2.3. Dose Modifications

Dose modifications of study drug are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator, and the Medical Monitor should be contacted.

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
    a. If local laboratory results are obtained, confirm with a 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 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing 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	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • 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 biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

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

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.3. Protocol-specified Background Antihypertensive Medications

All patients will be randomized to receive 1 of the 3 following standard of care oral antihypertensive medications during a Run-in period of at least 4 weeks and will continue this

protocol-specified background antihypertensive medication through Month 6. Protocol-specified background antihypertensive medications will be supplied by the Sponsor.

- Olmesartan: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks (in this case, the patient must take the full olmesartan dose of 40 mg once daily for at least 4 weeks prior to reassessment at Run-in Visit 2).
- Amlodipine: 5 mg orally once daily
- Indapamide: 2.5 mg orally once daily

Protocol-specified antihypertensive medications may be downtitrated or temporarily discontinued per Investigator judgement for low blood pressure (see Section 5.8.1). At the Investigator's discretion, oral antihypertensive agents, including protocol-specified background antihypertensive medication, may be prophylactically held during intercurrent illness or volume depletion. Additional information on the protocol-specified background antihypertensive medications, including side effects, drug-drug interactions, and other important prescribing information can be found in the Pharmacy Manual.

5.4. Preparation, Handling, and Storage

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

Study drug will be stored at approximately 2 to 30°C until dose preparation. Protocol-specified background antihypertensive medication will be stored according to the storage instructions on the label. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the affected study drug or protocol-specified background antihypertensive medication 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 protocol-specified background antihypertensive medication and additional storage will be provided in the Pharmacy Manual.

5.5. Packaging and Labeling

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

5.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug and protocol-specified background antihypertensive medication supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug and protocol-specified background antihypertensive medication 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 and protocol-specified background antihypertensive medication. Used, partially used, and unused study drug and protocol-specified background antihypertensive medication will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.7. Clinical Product Complaints

5.7.1. Definition

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 nonmedical 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.

5.7.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.8. Monitoring for Potential Clinical Events

5.8.1. 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 (supine 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). Oral antihypertensives should be downtitrated/interrupted in reverse order to how they were added (ie, interrupt escape antihypertensive medications before protocol-specified background antihypertensive medications).
- 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 orthostatic intolerance syndromes 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.

5.8.2. 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 4.

Table 4: 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. • Until double-blind data are generated that demonstrate acceptable safety and added antihypertensive efficacy of zilebesiran when combined with olmesartan, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure will be avoided throughout the study. • If added, escape antihypertensives must be used per their labeled instructions and in accordance with current clinical guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of 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 (whichever agent is not already the protocol-specified background antihypertensive medication) as an escape antihypertensive medication.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already a protocol-specified background antihypertensive medication):</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added as an escape antihypertensive medication if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, other escape antihypertensive medications may also be added per Investigator judgement for persistent elevations in SBP above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018]

Study Period	Intervention
Month 6 to End of Study (OLE period)	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide) will be discontinued. • Patients who continued into the OLE period initiated open-label treatment with 600 mg zilebesiran once every 6 months. As many patients would have received zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be carefully monitored monthly from Month 6 to Month 9, and Investigators will be prepared to downtitrate or interrupt escape antihypertensive medications if low blood pressure develops (see Section 5.8.1). • If the Month 6 ABPM is in target (daytime mean SBP <135 mmHg), escape antihypertensive medications (if taken) may be downtitrated or interrupted per Investigator judgement to determine if the patient's blood pressure remains within target on zilebesiran treatment alone. • During the OLE period, oral antihypertensive medications may be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

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; OLE=open-label extension; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

5.8.3. 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 RAAS 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 or to ≤30 mL/min/1.73m^2, 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 or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeats tests, look

for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug and/or oral antihypertensives. Serum creatinine should be monitored at least weekly until improving.

5.8.4. 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 5 apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: 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 (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of open-label olmesartan (in patients randomized to receive it as their protocol-specified background antihypertensive medication) according to Investigator medical judgement • Consider interruption or delay of study drug administration, according to Investigator medical judgment • Apply all measures outlined for serum K^+ >5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

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).

The availability of patiromer and sodium zirconium cyclosilicate (ZS-9) will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos 2018; Weir 2015]

5.9. 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 other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for at least 4 days after each 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 5.9.1 and after consulting the Pharmacy Manual, which contains information on drug-drug interactions and other important prescribing information for the protocol-specified background antihypertensive medications. 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.

5.9.1. Prohibited Concomitant Medication

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

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors), except for olmesartan as protocol-specified background antihypertensive medication during the 6-month DB period
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi 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.

5.10. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff. Compliance with protocol-specified background antihypertensive medication will be assessed through pill count by study staff.

5.11. Other Requirements

5.11.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before the first dose of protocol-specified background antihypertensive medication, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

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 post-vasectomy 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, post-ovulation 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 (if applicable; see Section 3.1)

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 child-bearing 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, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

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 every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.11.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.11.3. 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.

5.11.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 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 sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.11.5. 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, are to be performed prior to dosing with protocol-specified background antihypertensive medication or study drug. Additional information on the collection of study assessments will be detailed in the study manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs (including blood pressure assessments), performing pill counts of protocol-specified background antihypertensive medications, and collection of weight (at the discretion and oversight of the Investigator). See further details in Section 10.3.

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 once is permitted with agreement 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 Run-in Visit 1 will be updated prior to administration of protocol-specified background antihypertensive medication.

6.1.1. Retesting

If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. Retesting of office blood pressure at Run-in Visit 1 is permitted once if in the Investigator's judgement, the result is not accurate due to a transient condition. Retesting of ABPM at Run-in Visit 2 is permitted once if the first ABPM is invalid. A valid ABPM recording must be obtained within 7 days prior to randomization for all patients. If a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening following agreement with the Medical Monitor. A patient will be re-consented if rescreening occurs outside of the Screening period. In this case, all screening procedures must be repeated. Patients who do not meet eligibility criteria after Run-in Visit 1 will not be rescreened.

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 Section 10.2. Office blood pressure assessments and ABPM initiation must be performed before administration of any oral antihypertensive medications and study drug (as applicable).

Patients taking oral antihypertensives prior to screening should discontinue these medications at Run-in Visit 1. The baseline ABPM and office blood pressure measured at Run-in Visit 2 must be taken within 7 days before Day 1. An HBPM unit will be provided before Run-in Visit 2 to establish the HBPM baseline, and HBPM should be collected at least 3 times during the last week prior to Day 1.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the ABPM Investigator Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.2.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.8.1 and Section 5.8.2, 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. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording. During the Run-in period, if a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

See further details in Section 10.2 and the ABPM Investigator 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) and should be at approximately the same time of day for each assessment; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

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 as detailed in Section 10.2 and the HBPM and OBPM Investigator Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral antihypertensive medications. HBPM is not required on days when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the HBPM and OBPM Investigator Manual.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT will be collected according to the Schedule of Assessments (Table 1). In addition, blood samples for determination of RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected only for patients randomized to receive olmesartan as protocol-specified background antihypertensive medication.

Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a regulated bioanalytical laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. 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 adjust dosing of zilebesiran or guide clinical management and will not be shared with sites until after study unblinding.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma 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 samples for PK analysis is in Table 2.

Plasma concentrations of zilebesiran and AS(N-1)3′ zilebesiran will be determined using a validated assay. 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, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination will be 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should 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, or as per DMC advice.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at Day 1 only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a study drug dosing visit, it should be conducted prior to dosing. 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 evaluation (see the Recommended Neurological Assessments for All Physical Examinations document for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

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, QT interval, and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should 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.

When ECG and blood sample collection for RAAS biomarkers (renin, aldosterone, and Ang I/II) 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, or as per DMC advice.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.4. 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, or as per DMC advice, 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. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

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. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. In patients randomized to receive olmesartan as the protocol-specified background antihypertensive medication, blood samples for RAAS 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	Chloride
Creatinine clearance (screening only)	
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
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

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 days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a regulated bioanalytical laboratory.

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 child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments 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 discontinued from study drug but will continue to be followed for safety. Patients who become 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 will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.11.1 for definition of postmenopausal state).

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 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA - quantitative
HAV antibody IgM	HHV-6 DNA viral load - quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
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 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

Abbreviations: CT=computed tomography; DNA=deoxyribonucleic acid; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a 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; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of zilebesiran.

  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.

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.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event 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 Treatment

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.

The relationship of each AE to the protocol-specified background antihypertensive medication should also be assessed by the Investigator.

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 treatment during the Run-in period regardless of their relationship to the study treatment through the end of study. Study treatment is defined as protocol-specified background antihypertensive medication or study drug (zilebesiran or placebo). Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before the Run-in period will be captured as medical history (see Section 6.1), while AEs that occur after study treatment, and baseline events that worsen after study treatment, 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 treatment through the end of study. 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 related. Each AE must be described in

detail: onset time and date, description of event, severity, relationship to study treatment, 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).

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 treatment.

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 treatment, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Immediately and no later than 24 hours after 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 the Investigator's best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study treatment, 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 with a suspected causal relationship to the study drug that occurs after the end of the study in a patient, 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 (see Section 3.1), 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 on the pregnancy reporting form. 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 90 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 participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor and Sponsor within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant 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 reporting instructions for overdose and other special situations 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.

Biological specimens 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, study participants 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 study unblinding for the analysis of the primary endpoints and secondary endpoints measured at Month 3. 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

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

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

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

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

The power is assessed by simulation based on the Mixed Model with Repeated Measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

7.2. Statistical Methodology

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug. All by-treatment analyses based on the Safety Analysis Set will be grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of zilebesiran and have at least 1 nonmissing postdose PK assessment.

- **PD Analysis Set**: All patients who received at least 1 full dose of study drug. All by-treatment analyses based on the PD Analysis Set will be grouped according to the treatment actually received.
- **All Zilebesiran Treated Set**: All patients who received any amount of zilebesiran, including patients who took zilebesiran during the 6-month DB period and patients who initially took placebo and then switched to zilebesiran after the Month 6 visit.

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

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

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, between Run-in Visit 2 and prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM. The primary hypothesis of the add-on effect of zilebesiran compared to placebo in patients receiving each of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine or indapamide) will be tested separately at a 2-sided significance level of 0.05 using MMRM. The MMRM model will include treatment, time, treatment-by-time, and race (black or all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM and screening eGFR as covariates.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM
- Time-adjusted change from baseline through Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD reduction after zilebesiran treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

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

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 classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term [by dose level and overall]. AEs, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by System Organ Class and PT for each treatment arm. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug. Adverse events collected during the Run-in period will be summarized.

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 post-baseline grade (or category) will be presented for

laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

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

7.2.10. Interim Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted after all patients complete the Month 3 visit or withdraw from the study prior to the Month 3 visit. No formal interim analysis is planned before the analysis at Month 3.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

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, 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 for approval before patients are enrolled under the amended protocol, and patients must be re-consented 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 study participant 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 end of study 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 participants 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 CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied 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 study 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. Formula 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.

Modification of Diet in Renal Disease Formula [Levey 2009]

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

10.2. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

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) should 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 ABPM Investigator Manual and the HBPM and OBPM Investigator Manual. Unless significant weight loss or gain occurs between visits, the patient should 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 should be used for all subsequent office blood pressure and HBPM readings. The ABPM should 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.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the ABPM Investigator Manual. 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. ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take

readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid (either during the Run-in Period or after the second randomization), the patient will be provided 1 opportunity to repeat the study within 7 days from the end time of the invalid ABPM. During the Run-in period, if a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medications, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. 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) use of cannabis or THC-containing substances should be avoided for at least 2 days prior to office blood pressure measurements.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.

- Follow the HBPM and OBPM Investigator Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction, so the staff will avoid interacting with you during this assessment. This assessment will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Measure standing blood pressure 1 to 3 minutes after standing using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and record their response.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the HBPM and OBPM Investigator Manual. Results and the remote method used will be recorded.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM 3 times during the week prior to the second randomization.

After Day 1, HBPM should be measured at least once per week and may be increased at the Investigator's discretion if more frequent measurement is warranted. Patients may select the day of the week that is most convenient for their personal schedule.

10.3. Procedures for Optional Home Healthcare Visits

Home healthcare may be allowed where applicable country and local regulations and infrastructure for home healthcare allow and will follow procedures that are in compliance with relevant local regulations and guidelines (eg, General Data Protection Regulation [EU no 2016/679], ICH E6[R2], and the Declaration of Helsinki). The use of home healthcare is optional and will not be utilized for visits at which study drug is administered or for visits that are required to be performed at the site (see Table 1).

The option for home healthcare aims to improve patient diversity, participation, engagement, and retention in the study by reducing patient burden and minimizing study-related travel to the site, allowing flexibility in the study visit schedule.

For clinical study sites where home healthcare is utilized, the Investigator will retain responsibility for oversight, patient safety, and conduct of the trial, and will be responsible for reviewing the qualifications of and approving each home healthcare professional, delegating responsibilities to the home healthcare professional in the site delegation log, providing instructions for home healthcare visits, communicating with the home healthcare professional at home visits as needed, and reviewing the source data files collected during the home healthcare visit. The home healthcare professional will be trained on the protocol and other relevant study documents and procedures and will be responsible for conducting vital sign assessments (including blood pressure assessments), collecting blood and urine samples, collecting weight, performing pill counts of protocol-specified background antihypertensive medications, and documenting and notifying the site study team of any suspected or potential AE symptoms or changes to concomitant medications. The home healthcare professional will be responsible for providing source documentation of the visit to the study site.

10.4. Amendment History

10.4.1. Amendment 3 Summary of Changes

The primary purpose of this amendment is to close the OLE period of the study, and to provide instructions for patients to complete the study. Patients who completed the 6-month DB period may have been eligible to enter a separate OLE study to continue to receive zilebesiran. If the separate OLE study was not yet available at the time patients completed the 6-month DB period, they could have entered the optional OLE period of the study to continue receiving zilebesiran uninterrupted and then transition to the separate OLE study when it opened. The Sponsor has made the decision not to conduct a separate OLE study; therefore, the OLE period is no longer needed. Upon implementation of this amendment, patients in the 6-month DB period will enter safety follow-up following completion of the 6-month DB period. Patients will not receive a dose of study drug at Month 6. Patients who are already in the OLE period will not receive any additional doses of study drug. Patients should complete all planned assessments at Months 7, 8, and 9. For visits at Month 12 or later, patients should complete EOT assessments in lieu of their scheduled visit assessments and enter the Safety Follow-up period.

Section(s)	Description of Change	Brief Rationale
Synopsis, Figure 1, Table 1, Table 4, Sections 1.1, 3.1, 3.2, 3.8, and 5.2.2	Closed the OLE period and provided instructions for patients to complete the study.	A separate OLE study will not be conducted; therefore, the OLE period of the study is not required after the end of the 6-month DB period. Instructions are provided for how patients should complete the study.
Sections 3.5 and 7	Removed the reference to database lock for the Month 3 analysis.	To clarify that a database lock will not be performed for the interim analysis at Month 3 and that Month 3 interim analysis results will not be shared with blinded team members.
Sections 6 and 10.3	Added details on the home healthcare process.	To incorporate revisions requested by a Regulatory Agency or Ethics Committee.
Section 6.5.6.4	Clarified that SAEs should be reported to the Sponsor immediately.	To incorporate revisions requested by a Regulatory Agency or Ethics Committee.
Section 6.5.6.4	Added wording on collecting SAEs with a suspected causal relationship to study drug that occur after a patient withdraws from the study or after the end of the study.	To align with Article 41 of Regulation (EU) No 536/2014 of the European Parliament and of the Council.
Throughout the document	Minor updates (typographical, editorial, administrative) were made.	To ensure clarity, accuracy, and consistency.

10.4.2. Amendment 2 Summary of Changes

10.4.2.1. Rationale for Protocol Amendment

The primary purposes for this protocol amendment are to extend the duration of the study to allow patients to continue to receive zilebesiran until a separate open-label extension study is initiated and to increase the number of patients randomized into the Run-in period to 1800.

Several additional changes are being implemented as outlined below.

- Allowed for patients with a valid ambulatory blood pressure monitoring (ABPM) at Run-in Visit 2 that meets inclusion criteria to repeat ABPM once if the assessment

was obtained outside the 7-day window prior to randomization into the Double-blind period.

- Clarified that the inclusion criterion for ABPM is inclusive of 130 mmHg
- Revised the timing of repeat ABPM measurements from 4 days to 7 days
- Clarified that retesting of office blood pressure at Run-in Visit 1 is permitted once if the Investigator believes that the result is not accurate due to a transient condition
- Revised the serum potassium cutoff in the recommended interventions for hyperkalemia to align with the normal range of potassium
- Increased the number of clinical study centers
- Clarified timing of age determination for eligibility
- Clarified the timing of blood sample collections for renin-angiotensin-aldosterone system (RAAS) biomarkers in relation to electrocardiograms (ECGs)
- Added exclusion criterion for patients placed in an institution on the basis of an official or court order to align with local requirements in some countries
- Removed references to legal guardian throughout the protocol because inclusion criterion 7 requires that the patient provide written informed consent
- Revised the duration of rest required before vital sign collection to align with automated processes on the machines used to collect this information
- Removed the reference that ECG recordings will be archived because these are not being archived
- Clarified that creatinine clearance is required during screening only to determine the dose of olmesartan for patients enrolled at sites outside of the US and Australia who are randomized to receive olmesartan as protocol-specified background antihypertensive medication
- Clarified that home blood pressure monitoring (HBPM) is not required on days when ABPM is being performed
- Clarified that medications, supplements, or other substances that may be associated with increases in LFT abnormalities or with blood pressure abnormalities may be used as needed after approval by the Investigator and Medical Monitor
- Specified the titles of study manuals
- Added forehead scan as a method of temperature collection to reflect site standard practice
- Clarified that patients should return to their usual care during the Safety Follow-up period

A detailed summary of changes is provided in Section 10.4.2.2. The following changes are not detailed: administrative changes, changes associated with administrative letters (between

protocol amendments 1 and 2), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

10.4.2.2. Protocol Amendment 2 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Extended the duration of the study.

The primary change occurs in Section 3.1, Study Design

Revised text:

OLE Period

After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to ~~12~~ **30** additional months until the separate OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into that OLE study at Month 6, 12, ~~or~~ 18**, 24, 30, or 36** (first visit after the separate OLE study is open).

The duration of treatment with zilebesiran is up to ~~18~~ **36** months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately ~~20~~**39** months, including up to ~~2 months~~**75 days** of the Screening and Run-in periods, and up to ~~18~~ **36** months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months **after the last dose of study drug**.

Section(s) also reflecting this change:

- Synopsis
- Figure 1, Study Design
- Table 1, Schedule of Assessments
- Section 1.1
- Section 2
- Section 3.2

Purpose: Increased the number of patients randomized into the Run-in period.

The primary change occurs in Section 3.1, Study Design

Revised text: The planned enrollment for this study is approximately ~~800~~ **1800** patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

Section(s) also reflecting this change:

- Synopsis

Purpose: Allowed for patients with a valid ABPM at Run-in Visit 2 that meets inclusion criteria to repeat ABPM once if the assessment was obtained outside the 7-day window prior to randomization into the Double-blind period.

The primary change occurs in Section 6.1.1, Retesting

Revised text: If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. **Retesting of office blood pressure at Run-in Visit 1 is permitted once if in the Investigator's judgement, the result is not accurate due to a transient condition.** Retesting of ABPM at Run-in Visit 2 is permitted **once if the first ABPM is invalid. A valid ABPM recording must be obtained within 7 days prior to randomization for all patients. If a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure**~~once, with eligibility assessed by the second ABPM result~~.

Section(s) also reflecting this change:

- Section 6.2.1
- Section 10.2

Purpose: Clarified that the inclusion criterion for ABPM is inclusive of 130 mmHg.

The primary change occurs in Section 4.1, Inclusion Criteria (criterion 5)

Revised text: 5. 24-hour mean SBP ~~>~~≥130 mmHg and ≤160 mmHg by ABPM at Run-in Visit 2 after at least 4 weeks of run-in.

Section(s) also reflecting this change:

- Synopsis

Purpose: Revised the timing of repeat ABPM measurements from 4 days to 7 days.

The primary change occurs in Section 10.2, Measurement of Blood Pressure

Revised text: After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid (either during the Run-in Period or after the second randomization), the patient will be provided 1 opportunity to repeat the study within ~~4~~ **7** days **from the end time of the invalid ABPM**. **During the Run-in period, if a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.**~~If the second ABPM recording is also invalid during screening, the patient is a run-in failure.~~

Purpose: Clarified that retesting of office blood pressure at Run-in Visit 1 is permitted once if the Investigator believes that the result is not accurate due to a transient condition.

The primary change occurs in Section 6.1.1, Retesting

Revised text: If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. **Retesting of office blood pressure at Run-in Visit 1 is permitted once if in the Investigator's judgement, the result is not accurate due to a transient condition.** Retesting of ABPM at Run-in Visit 2 is permitted **once if the first ABPM is invalid. A valid ABPM recording must be obtained within 7 days prior to randomization for all patients. If a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure**~~once, with eligibility assessed by the second ABPM result~~.

Purpose: Revised the serum potassium cutoff in the recommended interventions for hyperkalemia.

The primary change occurs in Table 5, Recommended Interventions for Hyperkalemia

Revised text:

Table 5: 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 (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of open-label olmesartan (in patients randomized to receive it as their protocol-specified background antihypertensive medication) according to Investigator medical judgement • Consider interruption or delay of study drug administration, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ~~≥~~>5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

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).

Purpose: Increased the number of clinical study sites.

The primary change occurs in the Synopsis

Revised text: The study will be conducted at approximately ~~120~~ **175** clinical study centers worldwide.

Purpose: Clarified timing of age determination for eligibility.

The primary change occurs in Section 4.1, Inclusion Criteria (criterion 1)

Revised text: 1. Age 18 to 75 years, inclusive**, at time of initial informed consent**

Section(s) also reflecting this change:

- Synopsis

Purpose: Clarified the timing of blood sample collections for RAAS biomarkers in relation to ECGs.

The primary change occurs in Section 6.5.4, Electrocardiogram

Revised text: When ECG and blood sample collection **for RAAS biomarkers (renin, aldosterone, and Ang I/II)** 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.

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments

Purpose: Added exclusion criterion for patients placed in an institution on the basis of an official or court order.

The primary change occurs in Section 4.2, Exclusion Criteria (criterion 33)

Added text: **33. Placed in an institution on the basis of an official or court order**

Purpose: Removed references to legal guardian throughout the protocol.

The primary change occurs in Section 4.3.2.1, Patient Stops Participation in the Study

Revised text:

4.3.2.1 Patient ~~or Legal Guardian~~ Stops Participation in the Study

A patient ~~or their legal guardian~~ may stop participation in the study at any time. A patient ~~or legal guardian~~ considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient ~~or legal guardian~~ consents. If a patient ~~or legal guardian~~ still chooses to discontinue study drug and stop participation in all follow-up prior to the

completion of the 6-month DB period, every effort should be made to conduct the Month 6 visit assessments at an earlier time (see Table 1).

Sections also reflecting this change:

- Section 4.3
- Section 4.3.3
- Section 6.1
- Section 6.5.6.2
- Section 8.1.1
- Section 8.1.2

Purpose: Revised the duration of rest required before vital sign collection.

The primary change occurs in Section 6.5.1, Vital Signs

Revised text: 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured in the seated position, after the patient has rested comfortably for approximately ~~10~~ **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.

Purpose: Removed the reference that ECG recordings will be archived.

The primary change occurs in Section 6.5.4, Electrocardiogram

Revised text: 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, or as per DMC advice. ~~Recordings will be archived according to the Study Manual.~~

Purpose: Clarified that creatinine clearance is required during screening only.

The primary change occurs in Table 6, Clinical Laboratory Assessments

Revised text:

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	Chloride
Creatinine clearance **(screening only)**	
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
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	

Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments

Purpose: Clarified that HBPM is not required on days when ABPM is being performed.

The primary change occurs in Section 6.2.3, HBPM

Revised text: The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral antihypertensive medications. HBPM is not required ~~at times~~**on days** when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the **HBPM and OBPM Investigator** ~~Study~~ Manual.

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments

Purpose: Clarified that medications, supplements, or other substances that may be associated with increases in LFT abnormalities or with blood pressure abnormalities may be used as needed after approval by the Investigator and Medical Monitor.

The primary change occurs in Section 5.9.1, Prohibited Concomitant Medication

Revised text: 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**.

Purpose: Specified the titles of study manuals.

The primary change occurs in Section 10.2, Measurement of Blood Pressure

Revised text: 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) should 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 ~~Study Manual~~ **ABPM Investigator Manual and the HBPM and OBPM Investigator Manual**. Unless significant weight loss or gain occurs between visits, the patient should use the same cuff/bladder size throughout the study.

Section(s) also reflecting this change:

- Sections 6.2, 6.2.1, 6.2.2, and 6.2.3
- Section 6.5.3

Purpose: Added forehead scan as a method of temperature collection.

The primary change occurs in Section 6.5.1, Vital Signs

Revised text: 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured in the seated position, after the patient has rested comfortably for approximately ~~10~~ **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.

Purpose: Clarified that patients should return to their usual care during the Safety Follow-up period.

The primary change occurs in Section 3.1, Summary of Study Design

Revised text:

Safety Follow-up Period

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

Purpose: Administrative changes, changes associated with administrative letters (since the original protocol was finalized), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

10.4.3. Amendment 1 Summary of Changes

10.4.3.1. Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to reduce patient burden by removing or modifying procedures that are not considered necessary for analysis of primary or secondary efficacy endpoints or for safety; and by providing clarifications and updates to inclusion/exclusion criteria and concomitant medications to better take into account common characteristics of patients with mild-to-moderate hypertension.

Changes to Procedures:

- Clarified that 3 measurements are sufficient to establish baseline for home blood pressure monitoring (HBPM). Removed the requirement to consider patients who do not establish baseline HBPM as run-in failures because evaluation of change in HBPM is an exploratory endpoint. Revised the frequency of HBPMs after randomization to at least once per week and clarified that they may be increased at the Investigator's discretion if more frequent measurement is warranted.
- Removed 24-hour ambulatory blood pressure monitoring (ABPM) at Month 18 and during the safety follow-up period because office blood pressures and HBPM will be sufficient to monitor safety
- Removed 24-hour urine samples for assessment of sodium status
- Clarified the extended hepatic panel required in patients who experience elevated transaminases
- Clarified that patients did not have to avoid over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) before laboratory assessments

Changes to Eligibility Criteria and Concomitant Medications:

- Removed limitations on the allowable classes and doses of prior antihypertensive medication because these were not meant to be limiting, and patients will be discontinuing their prior antihypertensives and starting the protocol specified background antihypertensive
- Clarified that patients who are currently taking beta blockers may be enrolled if beta blockers can be discontinued prior to the Run-in period
- Clarified that over-the-counter NSAIDs are permitted because low-dose aspirin is commonly used in this population as a cardioprotectant and should not have an additional effect on blood pressure. Doses of aspirin ≤100 mg daily are not expected to have a significant effect on blood pressure. In addition, the period in which patients should avoid NSAIDs before office blood pressure and ABPM assessments was revised to 2 days because the effects of these medications are expected to be washed out within 2 days.
- Clarified that patients are allowed to be on sodium-glucose co-transporter 2 (SGLT2) inhibitors as long as patients are on a stable dose prior to and during the study treatment period. This change was made because SGLT2 inhibitors may be

commonly used in this population, and stable doses of SGLT2 inhibitors are not expected to have an additional appreciable effect on blood pressure.

- Revised and simplified the exclusion criterion for diabetes mellitus as this is not expected to have a significant effect on blood pressure
- Clarified that patients with mild-to-moderate obstructive sleep apnea are eligible if they are on continuous positive airway pressure therapy because these patients would not be expected to have spikes in nighttime blood pressure
- Clarified that patients who are in follow-up for a coronavirus-19 vaccine study for approved or investigational agents are allowed to be enrolled because follow-up procedures for these studies are not expected to impact patient safety in this study
- Removed exclusions on cannabis use and clarified that use of cannabis or delta-9-tetrahydrocannibinol-containing substances should be avoided when possible and for at least 2 days before ABPM and office blood pressure measurements
- Removed the exclusion criterion for being unable or unwilling to perform HBPM as specified as it is redundant with the inclusion criteria specifying that the patient is willing and able to comply with the study requirements, which includes procedures
- Clarified that physicians should refer to recommended target per treatment guidelines when considering the addition of oral antihypertensive medication for persistent elevations in blood pressure
- Clarified the duration of medication restrictions during the study

Several additional changes are being implemented as outlined below.

- Defined key secondary and other secondary endpoints to account for the implementation of a hierarchical testing procedure in this study. Modified exploratory endpoints to better reflect the objectives of the study
- Modified analysis sets to better reflect the analysis methods of the study
- Increased number of clinical study centers worldwide to approximately 120
- Clarified dosing of study drug during the study to be consistent with other parts of the protocol
- Corrected the definition of permanent sterilization
- Clarified that analysis of urinalysis measures protein, which includes albumin

A detailed summary of changes is provided in Section 10.4.3.2. 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.

10.4.3.2. Protocol Amendment 1 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 1 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Clarified the criteria for establishing baseline for HBPM, removed the requirement to consider patients who do not establish baseline HBPM as run-in failures, and revised the frequency of HBPM measurements after randomization.

The primary change occurs in Section 10.2, Measurement of Blood Pressure

Revised text: To establish baseline, each patient ~~must~~**should** measure HBPM ~~daily at least 1~~ **3 times during the** week prior to the second randomization. ~~If adequate baseline HBPM data are not collected during the Run-in Period, the patient is a run-in failure.~~

After Day 1, HBPM should be measured at least ~~3 times~~**once** per week **and may be increased at the Investigator's discretion if more frequent measurement is warranted**. Patients may select the ~~3~~ day~~s~~ of the week that ~~are~~**is** most convenient for their personal schedule.

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments
- Section 3.2
- Section 5.8.1
- Sections 6.2 and 6.2.3
- Section 10.2

Purpose: Removed 24-hour ABPMs at Month 18 and during the safety follow-up period.

The primary change occurs in Table 1, Schedule of Assessments

Change: The "X" was removed from the ABPM row under the Safety Follow-up column, and the following footnote was added to the "X" in the ABPM row under the M18/EOT/ET column.

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

Purpose: Removed 24-hour urine samples.

The primary change occurs in Section 6.5.5, Clinical Laboratory Assessments

Revised text: Spot urine collections for albumin and creatinine should be obtained in the morning. ~~A 24-hour urine collection for sodium and creatinine will be performed at time points listed in the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.~~

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments
- Section 6.6

Purpose: Clarified the extended hepatic panel required in patients who experience elevated transaminases.

The primary change occurs in Table 7, Hepatic Assessments in Patients Who Experience Elevated Transaminases

Revised text:

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, ~~HBsAb,~~ HBc antibody IgM	Parvovirus B19 DNA - quantitative
HAV antibody IgM	HHV-6 DNA viral load - quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
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 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

Purpose: Clarified that patients did not have to avoid NSAIDs before laboratory assessments.

The primary change occurs in Section 6.5.5, Clinical Laboratory Assessments

Revised text: Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. ~~Consecutive (daily) use of over-the-counter NSAIDs should be avoided for at least 7 days prior to laboratory assessments.~~ In patients randomized to receive olmesartan as the protocol-specified background antihypertensive medication, blood samples for RAAS 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.

Purpose: Removed limitations on the allowable classes and doses of prior antihypertensive medication.

The primary change occurs in Section 4.1, Inclusion Criteria (criterion 3b)

Revised text: Treated hypertension on stable therapy with up to 2 antihypertensive medications~~ that include the following classes: an ACE inhibitor, ARB, renin inhibitor, CCB, thiazide diuretic, and/or thiazide-like diuretic~~. Stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening~~, and the doses have to be at least half of the maximally approved daily doses per local labeling.~~**.**

Section(s) also reflecting this change:

- Synopsis

Purpose: Clarified that patients who are currently taking beta blockers may be enrolled if beta blockers can be discontinued prior to the Run-in period.

The primary change occurs in Section 4.2, Exclusion Criteria (criterion 6)

Revised text: **Currently taking beta blockers and unable to discontinue prior to Run-in Visit 1**

Purpose: Clarified that over-the-counter NSAIDs are permitted and revised the washout period to 2 days.

The primary change occurs in Section 5.9, Concomitant Medications and Procedures

Revised text: ~~Occasional use of~~**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 ~~7~~**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.

Section(s) also reflecting this change:

- Section 4.2
- Sections 6.2.1 and 6.2.2
- Section 10.2

Purpose: Clarified that patients are allowed to be on SGLT2 inhibitors as long as patients are on a stable dose prior to and during the study treatment period.

The primary change occurs in Section 5.9, Concomitant Medications and Procedures

Revised text: **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.**

Section(s) also reflecting this change:

- Section 4.2

Purpose: Revised exclusion criterion for diabetes mellitus.

The primary change occurs in Section 4.2, Exclusion Criteria (criterion 13)

Revised text: Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >~~8~~**9**.0%), ~~newly diagnosed Type 2 diabetes mellitus (within 6 months prior to first randomization),~~ or laboratory evidence of diabetes during screening (~~fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or~~ HbA1c ≥~~6.5~~**7.0**%) without known diagnosis of diabetes

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Purpose: Clarified that patients with mild-to-moderate obstructive sleep apnea are eligible if they are on continuous positive airway pressure therapy.

The primary change occurs in Section 4.2, Exclusion Criteria (criterion 1)

Revised text: Secondary hypertension (including, but not limited to, due to **known history of** moderate-to-severe obstructive sleep apnea **not treated** with ~~or without receiving nasal~~ continuous positive airway pressure therapy, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, **or** aortic coarctation~~, or other cause of secondary hypertension~~)

Purpose: Clarified that patients who are in follow-up for a coronavirus-19 vaccine study for approved or investigational agents are allowed to be enrolled.

The primary change occurs in Section 4.2, Exclusion Criteria (criterion 4)

Revised text: Received an investigational agent within the last 30 days or 5 half-lives of the investigational agent, whichever is longer, prior to Run-in Visit 1 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.**

Purpose: Removed exclusions on cannabis use and clarified that use of cannabis or delta-9-tetrahydrocannibinol-containing substances should be avoided when possible and for at least 2 days before ABPM and office blood pressure measurements.

The primary change occurs in Section 5.9, Concomitant Medications and Procedures

Revised text: **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.**

Section(s) also reflecting this change:

- Section 4.2
- Section 5.11
- Sections 6.2.1 and 6.2.2
- Section 10.2

Purpose: Removed the exclusion criterion for being unable or unwilling to perform HBPM.

The primary change occurs in Section 4.2, Exclusion Criteria (previous criterion 33)

Revised text: ~~Unable or unwilling to perform HBPM as specified~~

Purpose: Clarified that physicians should refer to recommended target treatment guidelines when considering the addition of oral antihypertensive medication for persistent elevations in blood pressure.

The primary change occurs in Table 4, Recommended Interventions for Potentially Clinically Significant Blood Pressure Elevation

Revised text:

Table 4: 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. • Until double-blind data are generated that demonstrate acceptable safety and added antihypertensive efficacy of zilebesiran when combined with olmesartan, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure will be avoided throughout the study. • If added, escape antihypertensives must be used per their labeled instructions and in accordance with current clinical guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of 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 (whichever agent is not already the protocol-specified background antihypertensive medication) as an escape antihypertensive medication.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already a protocol-specified background antihypertensive medication):</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic **may**~~should~~ be added as an escape antihypertensive medication if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF.

Study Period	Intervention
	• After Month 3, other escape antihypertensive medications may also be added per Investigator judgement for persistent elevations in SBP above **recommended** target **per treatment guidelines** (**eg**, ~~target defined as~~ office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018]
Month 6 to End of Study (OLE period)	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide) will be discontinued. • Patients who continue into the OLE period will initiate open-label treatment with 600 mg zilebesiran once every 6 months. As many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be carefully monitored monthly from Month 6 to Month 9, and Investigators will be prepared to downtitrate or interrupt escape antihypertensive medications if low blood pressure develops (see Section 5.8.1). • If the Month 6 ABPM is in target (daytime mean SBP <135 mmHg), escape antihypertensive medications (if taken) may be downtitrated or interrupted per Investigator judgement to determine if the patient's blood pressure remains within target on zilebesiran treatment alone. • During the OLE period, oral antihypertensive medications may be added per Investigator judgement for persistent elevations in blood pressure above **recommended** target **per treatment guidelines** (**eg**, ~~target defined as~~ office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

Section(s) also reflecting this change:

- Section 3.2

Purpose: Clarified the duration of medication restrictions during the study.

The primary change occurs in Section 5.9.1, Prohibited Concomitant Medication

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

Section(s) also reflecting this change:

- Section 4.2

Purpose: Defined key secondary and other secondary endpoints and modified exploratory endpoints.

The primary change occurs in Section 2, Objectives and Endpoints

Revised text:

Objectives	Endpoints
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	**Key Secondary Endpoints** • Change ~~in office SBP~~ from baseline ~~to~~**at** Month 3 • ~~Change in 24-hour mean SBP from baseline to Month 6, assessed by ABPM~~ • ~~Change~~ in office SBP ~~from baseline to Month 6~~ • ~~Change in 24-hour mean DBP from baseline to Months 3 and 6, assessed by ABPM~~ • ~~Change in office DBP from baseline to Months 3 and 6~~ • **Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM** • **Time-adjusted change from baseline through Month 6 in office SBP** • **Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6** **Other Secondary Endpoints** • **Change in 24-hour mean SBP and DBP, assessed by ABPM** • **Change in office SBP and DBP** • **Change in daytime and nighttime mean SBP and DBP, assessed by ABPM** • **Change in serum AGT**
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM **control and** response rates ~~(by blood pressure reduction)~~

Objectives	Endpoints
	~~• Office blood pressure and ABPM response rate (by blood pressure normalization)~~ • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 18)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM

Section(s) also reflecting this change:

- Synopsis

- Section 7.2.5

Purpose: Modified analysis sets.

The primary change occurs in Section 7.2.1, Populations to be Analyzed

Revised text:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be **grouped** according to the randomized treatment arm.
- Safety Analysis Set: All patients who received any amount of study drug**.** ~~,~~ **All by-treatment analyses based on the Safety Analysis Set will be** grouped according to the treatment actually received.
- PK Analysis Set: All patients who received at least 1 full dose of ~~study drug~~**zilebesiran** and have at least 1 **nonmissing** postdose ~~blood sample for~~ PK ~~parameters and have evaluable PK data~~**assessment**.
- PD Analysis Set: All patients who received at least 1 full dose of study drug**. All by-treatment analyses based on the PD Analysis Set** ~~and who have an evaluable baseline and at least 1 evaluable post-baseline PD measurement~~ will be ~~included in the PD analyses~~**grouped according to the treatment actually received**.
- **All Zilebesiran Treated Set: All patients who received any amount of zilebesiran, including patients who took zilebesiran during the 6-month DB period and patients who initially took placebo and then switched to zilebesiran after the Month 6 visit.**

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

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

Section(s) also reflecting this change:

- Synopsis

Purpose: Increased number of clinical study centers worldwide to approximately 120.

The primary change occurs in the Synopsis

Revised text: The study will be conducted at approximately ~~80~~**120** clinical study centers worldwide.

Purpose: Clarified dosing of study drug during the study.

The primary change occurs in Section 5.2.2, Dose and Administration

Revised text: During the 6-month DB period, patients will be administered **a single dose of** 600 mg zilebesiran or placebo, at the same volume, as SC ~~injections once every 6 months. During~~**injection on Day 1. Patients who enter** the OLE period~~, all patients~~ will receive 600 mg zilebesiran SC **at Month 6 after all predose assessments are conducted and** once every 6 months **during the OLE period**.

Purpose: Corrected the definition of permanent sterilization

The primary change occurs in Section 5.11.1, Contraception

Revised text: Females of child-bearing 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 ~~tubal occlusion~~**oophorectomy**, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

Purpose: Clarified that analysis of urinalysis measures protein, which includes albumin.

The primary change occurs in Table 6, Clinical Laboratory Assessments

Revised text:

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	Chloride

Creatinine clearance	
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~~**Protein**	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
~~Protein~~	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	

Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Purpose: Administrative changes, changes associated with administrative letters (since the original protocol was finalized), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-AGT01-003
DATED 22 SEPTEMBER 2022

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication
Short Title:	Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)
Study Drug:	Zilebesiran (ALN-AGT01)
EudraCT Number:	2021-003776-13
IND Number:	143503
Protocol Date:	Original protocol, 25 August 2021 Amendment 1, 22 March 2022 Amendment 2, 22 September 2022
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD PPD

SPONSOR PROTOCOL APPROVAL

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

_____

PPD

PPD

Alnylam Pharmaceuticals, Inc.

_____

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-003 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 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication

Short Title

Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)

Study Drug

Zilebesiran (ALN-AGT01)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 175 clinical study centers worldwide.

Objectives and Endpoints

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM • Time-adjusted change from baseline through Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6 Other Secondary Endpoints • Change in 24-hour mean SBP and DBP, assessed by ABPM • Change in office SBP and DBP

Objectives	Endpoints
	• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM • Change in serum AGT
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM control and response rates • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 36)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

Study Design

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

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

Patients who meet all inclusion/exclusion criteria after the Run-in period will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB treatment period as add-on therapy to their protocol-specified background antihypertensive medication.

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

After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may be eligible to participate in a separate zilebesiran open-label extension (OLE) study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months until the separate OLE study is open and then transition.

Number of Planned Patients

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

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 should have a 24-hour mean systolic blood pressure (SBP) ≥130 mmHg and ≤160 mmHg by ambulatory blood pressure monitoring (ABPM) after at least 4 weeks of run-in on protocol-specified background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

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

Patients randomized to receive zilebesiran will be administered 600 mg SC once during the 6-month DB treatment period; all patients will receive 600 mg SC once every 6 months during the OLE period.

Reference Treatment, Dose, and Mode of Administration

Placebo (phosphate-buffered saline for SC administration) will be administered at the same dosing interval and volume as the study drug during the 6-month DB period.

Protocol-specified Background Antihypertensive Medication, Dose, and Mode of Administration

Patients will be randomized to 1 of the following protocol-specified background antihypertensive medications to be administered orally once daily during the Run-in and 6-month DB periods:

- Olmesartan: 40 mg (or 20 mg for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks.
- Amlodipine: 5 mg
- Indapamide: 2.5 mg

Duration of Treatment and Study Participation

The duration of treatment with zilebesiran is up to 36 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 39 months, including up to 75 days of the Screening and Run-in periods, and up to 36 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months.

Statistical Methods

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period. Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

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

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

The populations (analysis sets) are defined as follows:

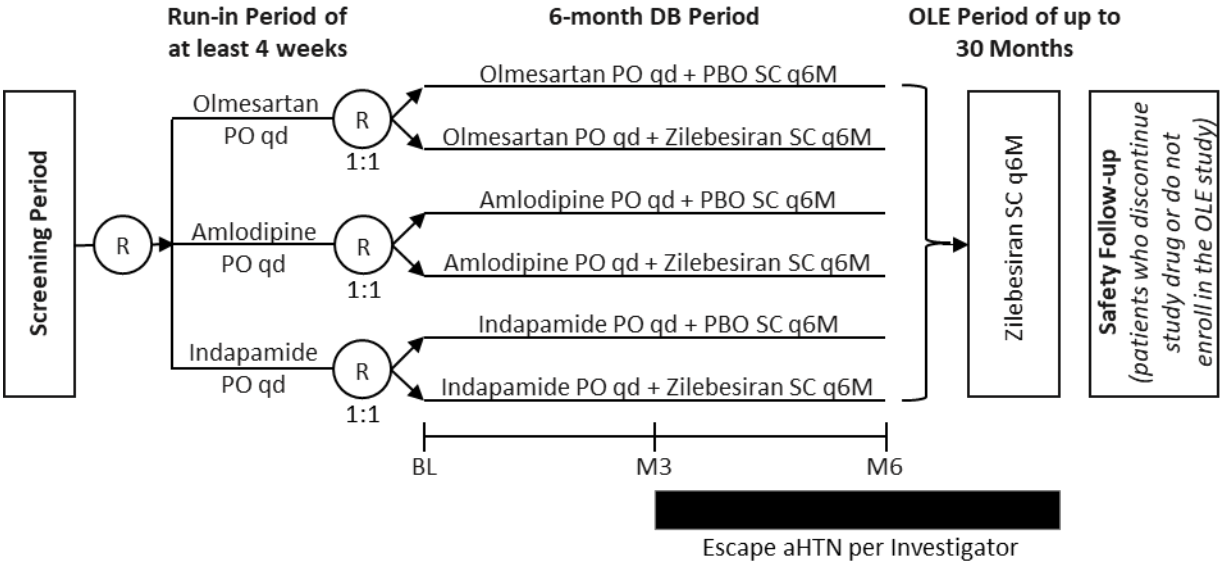
- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug. All by-treatment analyses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

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

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

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medication; BL=baseline; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); qd=once daily; q6M=once every 6 months; R=randomization; SC=subcutaneous.

Note: Patients may be eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran once every 6 months in the OLE period for up to 30 additional months until the OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into the separate OLE study at Month 6, 12, 18, 24, 30, or 36 (first visit after the separate OLE study is open).

Patients who were previously taking antihypertensives at screening should discontinue these medications at Run-in Visit 1.

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]								Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Informed consent	Section 8.1.1	X																			
Assign patient identification no.	Section 3.4	X																			
Medical history	Section 6.1	X																			
Demographics	Section 6.1	X																			
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X	X	X																	
Serum pregnancy test/FSH screening	Table 6 and Sections 6.5.5.3 and 6.5.6.7; FSH to confirm post-menopausal state if applicable	X																			
Creatinine clearance	Section 6.5.5	X																			
Full physical exam	Section 6.5.3	X			X							X								X	
Height and BMI	Section 6.5.2; Height measured at Day 1 only				X				X			X			X	X	X	X	X	X	
Body weight	Section 6.5.2	X		X	X				X			X			X	X	X	X	X	X	
Single 12-Lead ECG	Section 6.5.4	X			X							X				X	X	X	X	X	

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]								Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Serum chemistry[c]	Table 6; Section 6.5.5	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X		X	X				X			X			X	X	X	X	X	X	X
LFTs[c]	Table 6; See Table 7 for additional LFTs indicates for patients with abnormalities listed in Section 5.2.4	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Spot urine for albumin and creatinine[c]	Section 6.5.5	X		X	X				X			X				X	X	X	X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c[c]	Section 6.5.5.1	X		X	X				X			X				X				X	
Vital signs and office blood pressure[d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[e]	Section 6.2.1			X				X	X			X			X	X				X[h]	
HBPM[f]	Section 6.2.3			X	At least once per week																

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]								Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2	D1	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Discontinue prior oral antihypertensive medications (if taking)	Section 3.1		X																		
Urine pregnancy test[b]	Table 6 and Sections 6.5.5.3 and 6.5.6.7		X		X							X				X	X	X	X	X	
RAAS biomarkers: renin concentration, aldosterone, AngI/II	Section 6.3; Only in patients randomized to receive olmesartan		X		X				X												
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X		X			X			X	X				X	
Randomization to protocol-specified background antihypertensive medication	Section 3.4; Randomization may occur on Run-in Visit 1 or 1 business day prior		X																		
Protocol-specified background	Section 5.3		Daily																		

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]								Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
antihypertensive medication administration																					
Protocol-specified background antihypertensive medication pill count	Section 5.10			X	X		X	X	X	X	X	X									
Plasma for PK	Section 6.4 and Table 2				X							X									
Immunogenicity (ADA)	Section 6.5.5.2				X				X			X			X	X	X	X	X	X	X
Serum AGT	Section 6.3				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference and waist-to-hip ratio	Section 6.5.2				X							X				X	X	X	X	X	
Exploratory DNA sample (optional)	Section 6.6				X																
Neurologic evaluation[g] and symptom-directed physical exam	Section 6.5.3															X	X	X	X		X

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]								Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18	M24	M30	M36/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-75 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	D673±14	D841±14	D1009±14	±14
Randomization to zilebesiran or placebo	Section 3.4; Randomization may occur on Day 1 or 1 business day prior				X																
Study drug administration (zilebesiran or placebo)	Section 5.2.2				X							X				X	X	X	X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of protocol-specified background antihypertensive medication		Continuous																		
Concomitant medications	Section 5.9	Continuous																			

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

Notes:

- When scheduled at the same time points and where feasible, the assessments of vital signs and blood sample collections for RAAS biomarkers (renin, aldosterone, and Ang I/II) should be performed before physical examinations and 12-lead ECGs.
- Run-in Visit 2 should occur at least 4 weeks after Run-in Visit 1.
- Patients may be eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran beginning at the Month 6 visit and continue for up to 30 additional months until the separate OLE study is open and then transition at Month 12, 18, 24, 30, or 36 (first visit after the separate OLE study is open). Patients who rollover at Month 6 should complete all assessments scheduled for the Month 6 visit except for study drug administration. Patients who rollover at Month 12 should complete the EOT visit instead of the assessments scheduled at Month 12.
- Patients who discontinue study drug at any time during the study or do not enroll in the separate OLE study will be asked to perform Safety Follow-up visits once every 6 months after the last dose of study drug until serum AGT levels return to ≥50% of their individual mean baseline level (if known) or 12 months after the last dose of study drug, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.
- Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6. If a patient discontinues study drug after the Month 6 visit, EOT/ET assessments should be performed.

Footnotes:

[a] **All assessments, except for postdose PK sample collection (Table 2), are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**
[b] When applicable, pregnancy test results must be known prior to dosing with study drug at dosing visits.
[c] Laboratory assessments at Day 1 do not need to be repeated, per Investigator discretion, if they were collected within 7 days before Day 1 at Run-in Visit 2.
[d] Office blood pressure must be measured before the patient takes oral antihypertensive medications or study drug (as applicable).
[e] ABPM recordings associated with study drug dosing visits should be obtained within 7 days before the visit and results reviewed before dosing.
[f] HBPM should be measured at least 3 times during the week prior to the second randomization to establish baseline. After Day 1, HBPM should be measured at least once per week in the morning upon waking and may be increased at the Investigator's discretion if more frequent measurement is warranted. HBPM is not required on days when ABPM is being assessed. In the Safety Follow-up period, the frequency of HBPM assessments can be reduced after the first Safety Follow-up visit per Investigator judgement.
[g] Neurological evaluation will also be performed as part of the full physical examination.
[h] ABPM should only be performed as part of ET assessments if the patient discontinues the study prior to Month 12 and has not had an ABPM within the last 3 months. ABPM should not be performed at Month 36.

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±30 min)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±30 min)	X

Abbreviations: hh:mm=hour:minute; min=minutes; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates 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.

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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
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
HOMA	Homeostatic model assessment
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Abbreviation	Definition
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reactions
LFT	Liver function test
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measurements
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred term
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
THC	Delta-9-tetrahydrocannibinol
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing zilebesiran (ALN-AGT01), a subcutaneously (SC) administered investigational agent comprised of 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-AGT01-003 (KARDIA-2) is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety, and pharmacodynamics (PD) of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. Patients will be randomized to run-in on 1 of 3 protocol-specified antihypertensive medications open-label for at least 4 weeks (olmesartan, amlodipine, or indapamide). At the end of the Run-in period, patients with uncontrolled blood pressure will be randomized 1:1 to receive zilebesiran or placebo as add-on therapy to the protocol-specified background antihypertensive medication for 6 months during the double-blind (DB) period. After completion of the 6-month DB period, patients may be eligible to participate in a separate zilebesiran open-label extension (OLE) study. If an individual patient reaches Month 6 prior to availability of the OLE study, they may discontinue their protocol-specified background antihypertensive medication and receive open-label zilebesiran (600 mg once every 6 months) for up to 30 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean systolic blood pressure (SBP), assessed by ambulatory blood pressure monitoring (ABPM), from baseline to Month 3, relative to placebo. Secondary and exploratory objectives of the study include evaluating the add-on efficacy of zilebesiran on other measures of blood pressure response (including longer treatment durations, eg, up to 36 months) and evaluating the PD effect of zilebesiran, including reduction in circulating AGT concentration.

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 and Krousel-Wood 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 and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing zilebesiran, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. 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-aldosterone system (RAAS) 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 (AngII).

Zilebesiran is being studied in the ongoing 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 in obese patients (Part D), and as a single dose of 800 mg co-administered for 2 weeks with 300 mg irbesartan (Part E). Preliminary data are available from Parts A, B, and E. Dose-dependent and durable reductions in circulating AGT were observed after single SC doses of zilebesiran, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Sustained reductions in serum AGT were observed for up to 6 months following a single dose of zilebesiran.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium. No patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in patients who received zilebesiran doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

Because most patients with hypertension eventually progress to require treatment with more than 1 antihypertensive class,[Williams 2018] it is anticipated that zilebesiran may be used together with other standard of care antihypertensive medication. This Phase 2 study will further quantify the antihypertensive effects of zilebesiran as add-on therapy in patients with hypertension not adequately controlled by a standard of care antihypertensive medication. The consistent and durable PD effect of zilebesiran is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

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

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that zilebesiran may offer the benefit of sustained blood pressure reduction to patients with hypertension with infrequent administration (ie, once every 3 months or once every 6 months). The mean SBP reduction observed after single zilebesiran doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives.[Abraham 2015; Materson 1993] The blood pressure of patients will be closely monitored, and after Month 3, escape antihypertensive medications will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of zilebesiran, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with zilebesiran. 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, and escape antihypertensive medications are permitted to manage uncontrolled blood pressure following 3 months of add-on treatment with zilebesiran. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.8.1), hypertension (Section 5.8.2), renal dysfunction (Section 5.8.3), and hyperkalemia (Section 5.8.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from 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. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations. In addition to study drug, each patient will receive a protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). These agents are approved standard medications that will be dosed in accordance with local labeling.

While zilebesiran is designed to inhibit the RAAS, its site of action (AGT) in the RAAS is unique, and its tissue specificity for the liver is hypothesized to improve its renal safety profile relative to conventional RAAS blockade,[Mullick 2017; Uijl 2019] both in the context of monotherapy and when used together with a conventional RAAS blocker such as olmesartan. In the latter setting, zilebesiran is hypothesized to add antihypertensive benefit when added to a conventional RAAS blocker without the increased incidence of RAAS inhibitor-associated renal adverse effects that have been observed in prior trials of conventional dual RAAS blockade.[Makani 2013] Patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 or urine albumin:creatinine $\geq$300mg/g will be exclusively assigned to the olmesartan cohort to ensure that patients with proteinuric chronic kidney disease or diabetes continue the RAAS inhibition standardly recommended for their renal indication throughout the study.

This study's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS 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 highest

risk to have events (eGFR <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, or poorly controlled diabetes) 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).

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

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

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

Objectives	Endpoints
	• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 36)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

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

Run-in Period

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized as described in Section 3.4 to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US and Australia, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1).

Patients who do not tolerate run-in treatment or who do not meet eligibility for randomization at Day 1 will be withdrawn from the study and returned to their prior medication regimen in coordination with their usual health providers.

DB Period

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

Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the patient's protocol-specified background antihypertensive medication per Investigator judgement for elevated blood pressure as described in Table 4.

OLE Period

After the 6-month DB period, protocol-specified background antihypertensive medications will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months until the separate OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into that OLE study at Month 6, 12, 18, 24, 30, or 36 (first visit after the separate OLE study is open).

During the OLE period of this study, Investigators will use escape antihypertensive medications as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring.

Safety Follow-up Period

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

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration)

through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

An independent DMC will oversee the safety and overall conduct of this study, and an independent Clinical Event Adjudication Committee will review suspected renal events to adjudicate whether they meet criteria for acute kidney injury.

The planned enrollment for this study is approximately 1800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

The duration of treatment with zilebesiran is up to 36 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 39 months, including up to 75 days of the Screening and Run-in periods, and up to 36 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months after the last dose of study drug.

3.2. Scientific Rationale for Study Design

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

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean SBP, assessed by ABPM, from baseline to Month 3, relative to placebo.

Patients with hypertension often require treatment with multiple antihypertensive drugs to reach target blood pressure,[Williams 2018] and it is anticipated that zilebesiran may be administered to individuals on a background of other antihypertensive medications. Therefore, this study evaluates the effects of zilebesiran relative to placebo in patients whose blood pressure is not adequately controlled despite treatment with 1 of the 3 major drug classes recommended for initial treatment of hypertension by all clinical guidelines: RAAS inhibitors (ie, angiotensin converting enzyme [ACE] inhibitors, angiotensin II-receptor blockers, or a direct renin inhibitor), diuretics, and calcium channel blockers (CCBs).[Whelton 2018; Williams 2018] Studying coadministration with olmesartan will assess if the synergistic antihypertensive effects recently observed in rodents treated with both an ARB and an AGT-targeting GalNAc-siRNA will translate into clinically significant blood pressure reduction in hypertensive patients given zilebesiran as an add-on to conventional RAAS inhibition.[Uijl 2019] In addition, it will examine the safety and tolerability of liver-specific AGT targeting during treatment with a conventional RAAS blocker (olmesartan). The newer-generation ARB olmesartan was selected because of its high potency relative to early-generation RAAS inhibitors,[Ojima 2011; White 2011] enabling a robust test for added efficacy when combined with zilebesiran. The maximum dose of olmesartan permitted per local labeling will be used to further increase the rigor of this efficacy evaluation. The thiazide-like diuretic indapamide was selected in accordance with recent guidelines that highlight the greater potency and durability of thiazide-like diuretics over other diuretics.[Burnier 2019] The long-acting dihydropyridine CCB amlodipine was selected given its

extensive use in clinical practice and randomized controlled trials.[Dahlof 2005; Jamerson 2008; Julius 2004]

During the study, blood pressure will be monitored with both automated office blood pressure measurements and outpatient 24-hour ABPM (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). 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 home blood pressure monitoring (HBPM), to assess long-term blood pressure variability and 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] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), 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 at Month 3 and will continue throughout the remainder of the study (see Table 4). The term “escape antihypertensive medication” is used to refer to any oral antihypertensive medication initiated to control blood pressure after Day 1. Separate from these treat-to-target modifications, 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.

If a patient requires treatment with an oral escape antihypertensive medication before Month 6, a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already the protocol-specified background antihypertensive medication) should be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS.

After the 6-month DB period, protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide) will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 30 additional months until the separate OLE study is open and then transition. Because many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be monitored monthly from Month 6 to Month 9.

During the OLE period, Investigators may use escape antihypertensive medications of permitted classes as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring and following current care guidelines.[Whelton 2018; Williams 2018] Olmesartan, amlodipine, and indapamide will be discontinued as protocol-specified background antihypertensive medication during the OLE period; however, patients may continue to receive amlodipine or indapamide as escape antihypertensive medication at the Investigator’s discretion. The use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure should be avoided throughout the study.

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 RAAS inhibitors[McMurray 2016; Parving 2012].

3.3. Justification for Dose

The dose of zilebesiran in this study (600 mg once every 6 months) was selected on the basis of data from the Phase 1 Study 001, in which single zilebesiran doses up to 800 mg were found to have an acceptable safety profile, and dose-dependent, clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed at doses as low as 100 mg. An acceptable safety profile was also observed for a single zilebesiran dose of 800 mg under low-salt/high-salt conditions or co-administered for 2 weeks with 300 mg irbesartan once daily. The selected dose of 600 mg is predicted to result in a median serum AGT reduction of 94.9% at trough (Month 6), translating to a median SBP reduction of 11.6 mmHg as monotherapy.

The protocol-specified background antihypertensive medications are standard agents recommended in international and regional hypertension guidelines, and the selected regimens are standard doses used for their approved indication of hypertension.[Whelton 2018; Williams 2018] Indapamide will be dosed at 2.5 mg orally once daily, and amlodipine will be dosed at 5 mg orally once daily. The dose regimens for indapamide and amlodipine used in this study were selected on the basis of their common use in clinical care (when used both individually and combined with other classes of antihypertensives) and their expected efficacy, safety, and tolerability. Olmesartan will be dosed at the maximum dose allowed per local labeling: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia; Olmetec Product Information, September 2020).[von Bergmann 2001]

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 should contact the Interactive Response Technology (IRT) to obtain a patient identification number.

The Investigator or designee will contact the IRT to randomize the patient at Run-in Visit 1 and again at Day 1 after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at each visit.

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

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 7.1. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be

randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

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

3.5. Blinding

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

Zilebesiran and placebo will be packaged identically. Because zilebesiran may be slightly visually distinguishable from placebo, the vials will be masked in such a way as to hide the identity of the study drug contained within. For administration, syringes will be masked by a site pharmacist or delegate prior to withdrawing the study drug from vial. See the Pharmacy Manual for additional details. The study drug will be administered under the supervision of the Investigator (see Section 5.2.2).

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. 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 (eTMF).

Refer to the IRT instructions for details on unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review the suspected renal events blinded to treatment assignment to adjudicate whether they meet

diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

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

- has completed at least the Month 6 visit and enrolled in the separate OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the separate OLE study.

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. Has hypertension as follows:
   a. Untreated hypertension (not taking antihypertensive medication), or
   b. Treated hypertension 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.
4. Seated office SBP at Run-in Visit 1 as follows:
   a. ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
   b. ≥145 mmHg and ≤180 mmHg for patients on antihypertensive medications
5. 24-hour mean SBP ≥130 mmHg and ≤160 mmHg by ABPM at Run-in Visit 2 after at least 4 weeks of run-in.
6. ≥80% adherence to the protocol-specified background antihypertensive medication during the Run-in period as assessed by pill count performed at Run-in Visit 2.

Informed Consent

7. 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, or aortic coarctation)
2. Orthostatic hypotension, 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) at screening or during the Run-in period

Laboratory Assessments

3. Has any of the following laboratory parameter assessments at screening or Run-in Visit 2:
   a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (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. Potassium <lower limit of normal range or >5 mEq/L
   e. Sodium <lower limit of normal range
   f. eGFR <30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula; refer to Section 10.1)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days or 5 half-lives of the investigational agent, whichever is longer, prior to Run-in Visit 1 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.
5. Currently taking, taken within 30 days prior to first 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 should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to discontinue prior to Run-in Visit 1
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.

8. 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.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to first randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), direct renin inhibitor, CCB (including but not limited to significant peripheral edema), or thiazide/thiazide-like diuretic
12. History of multiple drug allergies or history of allergic reaction to any component of or excipient in the study drug
13. 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
14. Has known active human immunodeficiency virus infection; or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection.
15. History of clinically significant cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting or other cardiothoracic surgeries, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to first randomization
16. Known history of angioedema
17. Clinically significant valvular heart disease
18. New York Heart Association II to IV heart failure
19. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia/supraventricular tachycardia, or atrial fibrillation with rapid ventricular response in the 3 months prior to first randomization
20. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
21. History of renal transplantation
22. 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
23. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to either randomization
24. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability

25. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

26. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.11.1
27. Female patient is pregnant, planning a pregnancy, or breast-feeding

Alcohol or Nicotine Use and Substance Abuse

28. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
29. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
30. 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 Restrictions

31. Third shift, night shift, or 24-hour shift workers
32. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
33. Placed in an institution on the basis of an official or court order

4.3. Removal from Study Drug or Assessment

Patients are free to discontinue study drug and/or 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 discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or 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

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.9.1) per Investigator discretion
- AE
- Non-adherence to treatment regimen

- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and 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.

If a patient has an AE, including SAEs, and/or laboratory abnormalities that in the judgment of the investigator, taking into account the patient's overall status, requires interruption or discontinuation from treatment with study drug, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month DB period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 6 assessments) will be encouraged to remain on the study and complete assessments (excluding pharmacokinetic [PK] assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months after the last dose of study drug (whichever is earlier); see Section 3.1.

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 before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents. If a patient still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 6-month DB period, every effort should be made to conduct the Month 6 visit assessments at an earlier time (see Table 1).

A patient considering stopping participation in the study during the OLE period should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

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. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process the patient's personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the Investigator at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of the patient's personal data, informing the Investigator at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

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 even if study drug is discontinued.

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 center. The following actions must be taken if a patient fails to return to the clinic 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.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study after the second randomization at Day 1.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug and protocol-specified background antihypertensive medication supplied by the Sponsor 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 and protocol-specified background antihypertensive medication that have been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of zilebesiran SC and placebo SC 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 (phosphate-buffered saline for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to zilebesiran.

5.2.2. Dose and Administration

During the 6-month DB period, patients will be administered a single dose of 600 mg zilebesiran or placebo, at the same volume, as SC injection on Day 1. Patients who enter the OLE period will receive 600 mg zilebesiran SC at Month 6 after all predose assessments are conducted and once every 6 months during the OLE period.

Study drug injections 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. If a local reaction around the injection site occurs, photographs may be obtained. 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 study drug withdrawal from the vial. A full description of the blinding procedure is included in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 85 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

If a patient misses a dose of study drug, the Investigator should discuss with the Medical Monitor whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

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

5.2.3. Dose Modifications

Dose modifications of study drug are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator, and the Medical Monitor should be contacted.

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
    a. If local laboratory results are obtained, confirm with a 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 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing 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	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • 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 biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

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

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.3. Protocol-specified Background Antihypertensive Medications

All patients will be randomized to receive 1 of the 3 following standard of care oral antihypertensive medications during a Run-in period of at least 4 weeks and will continue this

protocol-specified background antihypertensive medication through Month 6. Protocol-specified background antihypertensive medications will be supplied by the Sponsor.

- Olmesartan: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min at screening enrolled at sites outside of the US or Australia, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks (in this case, the patient must take the full olmesartan dose of 40 mg once daily for at least 4 weeks prior to reassessment at Run-in Visit 2).
- Amlodipine: 5 mg orally once daily
- Indapamide: 2.5 mg orally once daily

Protocol-specified antihypertensive medications may be downtitrated or temporarily discontinued per Investigator judgement for low blood pressure (see Section 5.8.1). At the Investigator's discretion, oral antihypertensive agents, including protocol-specified background antihypertensive medication, may be prophylactically held during intercurrent illness or volume depletion. Additional information on the protocol-specified background antihypertensive medications, including side effects, drug-drug interactions, and other important prescribing information can be found in the Pharmacy Manual.

5.4. Preparation, Handling, and Storage

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

Study drug will be stored at approximately 2 to 30°C until dose preparation. Protocol-specified background antihypertensive medication will be stored according to the storage instructions on the label. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the affected study drug or protocol-specified background antihypertensive medication 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 protocol-specified background antihypertensive medication and additional storage will be provided in the Pharmacy Manual.

5.5. Packaging and Labeling

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

5.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug and protocol-specified background antihypertensive medication supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug and protocol-specified background antihypertensive medication 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 and protocol-specified background antihypertensive medication. Used, partially used, and unused study drug and protocol-specified background antihypertensive medication will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.7. Clinical Product Complaints

5.7.1. Definition

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 nonmedical 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.

5.7.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.8. Monitoring for Potential Clinical Events

5.8.1. 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 (supine 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). Oral antihypertensives should be downtitrated/interrupted in reverse order to how they were added (ie, interrupt escape antihypertensive medications before protocol-specified background antihypertensive medications).
- 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 orthostatic intolerance syndromes 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.

5.8.2. 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 4.

Table 4: 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. • Until double-blind data are generated that demonstrate acceptable safety and added antihypertensive efficacy of zilebesiran when combined with olmesartan, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure will be avoided throughout the study. • If added, escape antihypertensives must be used per their labeled instructions and in accordance with current clinical guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of 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 (whichever agent is not already the protocol-specified background antihypertensive medication) as an escape antihypertensive medication.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already a protocol-specified background antihypertensive medication):</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added as an escape antihypertensive medication if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, other escape antihypertensive medications may also be added per Investigator judgement for persistent elevations in SBP above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018]

Study Period	Intervention
Month 6 to End of Study (OLE period)	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide) will be discontinued. • Patients who continue into the OLE period will initiate open-label treatment with 600 mg zilebesiran once every 6 months. As many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be carefully monitored monthly from Month 6 to Month 9, and Investigators will be prepared to downtitrate or interrupt escape antihypertensive medications if low blood pressure develops (see Section 5.8.1). • If the Month 6 ABPM is in target (daytime mean SBP <135 mmHg), escape antihypertensive medications (if taken) may be downtitrated or interrupted per Investigator judgement to determine if the patient's blood pressure remains within target on zilebesiran treatment alone. • During the OLE period, oral antihypertensive medications may be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

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; OLE=open-label extension; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

5.8.3. 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 RAAS 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 or to ≤30 mL/min/1.73m^2, 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 or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeats tests, look

for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug and/or oral antihypertensives. Serum creatinine should be monitored at least weekly until improving.

5.8.4. 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 5 apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: 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 (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of open-label olmesartan (in patients randomized to receive it as their protocol-specified background antihypertensive medication) according to Investigator medical judgement • Consider interruption or delay of study drug administration, according to Investigator medical judgment • Apply all measures outlined for serum K^+ >5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

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).

The availability of patiromer and sodium zirconium cyclosilicate (ZS-9) will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.9. 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 other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for at least 4 days after each 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 5.9.1 and after consulting the Pharmacy Manual, which contains information on drug-drug interactions and other important prescribing information for the protocol-specified background antihypertensive medications. 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.

5.9.1. Prohibited Concomitant Medication

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

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors), except for olmesartan as protocol-specified background antihypertensive medication during the 6-month DB period
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi 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.

5.10. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff. Compliance with protocol-specified background antihypertensive medication will be assessed through pill count by study staff.

5.11. Other Requirements

5.11.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before the first dose of protocol-specified background antihypertensive medication, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

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 post-vasectomy 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, post-ovulation 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 (if applicable; see Section 3.1)

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 child-bearing 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, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

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 every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.11.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.11.3. 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.

5.11.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 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 sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.11.5. 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, are to be performed prior to dosing with protocol-specified background antihypertensive medication or study drug. Additional information on the collection of study assessments will be detailed in the study manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs (at the discretion and oversight of the Investigator).

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 once is permitted with agreement 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 Run-in Visit 1 will be updated prior to administration of protocol-specified background antihypertensive medication.

6.1.1. Retesting

If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. Retesting of office blood pressure at Run-in Visit 1 is permitted once if in the Investigator's judgement, the result is not accurate due to a transient condition. Retesting of ABPM at Run-in Visit 2 is permitted once if the first ABPM is invalid. A valid ABPM recording must be obtained within 7 days prior to randomization for all patients. If a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening following agreement with the Medical Monitor. A patient will be re-consented if rescreening occurs outside of the Screening period. In this case, all screening procedures must be repeated. Patients who do not meet eligibility criteria after Run-in Visit 1 will not be rescreened.

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 Section 10.2. Office blood pressure assessments and ABPM initiation must be performed before administration of any oral antihypertensive medications and study drug (as applicable).

Patients taking oral antihypertensives prior to screening should discontinue these medications at Run-in Visit 1. The baseline ABPM and office blood pressure measured at Run-in Visit 2 must be taken within 7 days before Day 1. An HBPM unit will be provided before Run-in Visit 2 to establish the HBPM baseline, and HBPM should be collected at least 3 times during the last week prior to Day 1.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the ABPM Investigator Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.2.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.8.1 and Section 5.8.2, 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. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording. During the Run-in period, if a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

See further details in Section 10.2 and the ABPM Investigator 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) and should be at approximately the same time of day for each assessment; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

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 as detailed in Section 10.2 and the HBPM and OBPM Investigator Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral antihypertensive medications. HBPM is not required on days when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the HBPM and OBPM Investigator Manual.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT will be collected according to the Schedule of Assessments (Table 1). In addition, blood samples for determination of RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected only for patients randomized to receive olmesartan as protocol-specified background antihypertensive medication.

Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a regulated bioanalytical laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. 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 adjust dosing of zilebesiran or guide clinical management and will not be shared with sites until after study unblinding.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma 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 samples for PK analysis is in Table 2.

Plasma concentrations of zilebesiran and AS(N-1)3′ zilebesiran will be determined using a validated assay. 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, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination will be 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should 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, or as per DMC advice.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at Day 1 only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a study drug dosing visit, it should be conducted prior to dosing. 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 evaluation (see the Recommended Neurological Assessments for All Physical Examinations document for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

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, QT interval, and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should 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.

When ECG and blood sample collection for RAAS biomarkers (renin, aldosterone, and Ang I/II) 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, or as per DMC advice.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.4. 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, or as per DMC advice, 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. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

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. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. In patients randomized to receive olmesartan as the protocol-specified background antihypertensive medication, blood samples for RAAS 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	Chloride
Creatinine clearance (screening only)	
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
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

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 days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a regulated bioanalytical laboratory.

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 child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments 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 discontinued from study drug but will continue to be followed for safety. Patients who become 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 will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.11.1 for definition of postmenopausal state).

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 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA - quantitative
HAV antibody IgM	HHV-6 DNA viral load - quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
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 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

Abbreviations: CT=computed tomography; DNA=deoxyribonucleic acid; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a 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; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of zilebesiran.

  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.

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.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event 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 Treatment

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.

The relationship of each AE to the protocol-specified background antihypertensive medication should also be assessed by the Investigator.

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 treatment during the Run-in period regardless of their relationship to the study treatment through the end of study. Study treatment is defined as protocol-specified background antihypertensive medication or study drug (zilebesiran or placebo). Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before the Run-in period will be captured as medical history (see Section 6.1), while AEs that occur after study treatment, and baseline events that worsen after study treatment, 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 treatment through the end of study. 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 related. Each AE must be described in

detail: onset time and date, description of event, severity, relationship to study treatment, 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).

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 within 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 treatment.

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 treatment, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 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 the Investigator's best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study treatment, 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.

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 Directive 2001/20/EC, 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 (see Section 3.1), 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 on the pregnancy reporting form. 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 90 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 participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor and Sponsor within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant 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 reporting instructions for overdose and other special situations 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.

Biological specimens 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, study participants 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 database lock and study unblinding for the analysis of the primary endpoints and secondary endpoints measured at Month 3. 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

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

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

- Indapamide cohort: 120 patients

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

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

The power is assessed by simulation based on the Mixed Model with Repeated Measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

7.2. Statistical Methodology

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

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

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

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

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, between Run-in Visit 2 and prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM. The primary hypothesis of the add-on effect of zilebesiran compared to placebo in patients receiving each of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine or indapamide) will be tested separately at a 2-sided significance level of 0.05 using MMRM. The MMRM model will include treatment, time, treatment-by-time, and race (black or all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM and screening eGFR as covariates.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM
- Time-adjusted change from baseline through Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD reduction after zilebesiran treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

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

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 classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term [by dose level and overall]. AEs, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by System Organ Class and PT for each treatment arm. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug. Adverse events collected during the Run-in period will be summarized.

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 post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

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

7.2.10. Interim Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted after all patients complete the Month 3 visit or withdraw from the study prior to the Month 3 visit. No formal interim analysis is planned before the analysis at Month 3.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

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, 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 for approval before patients are enrolled under the amended protocol, and patients must be re-consented 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 study participant 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 end of study 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 participants 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 CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied 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 study 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. Formula 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.

Modification of Diet in Renal Disease Formula [Levey 2009]

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

10.2. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

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) should 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 ABPM Investigator Manual and the HBPM and OBPM Investigator Manual. Unless significant weight loss or gain occurs between visits, the patient should 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 should be used for all subsequent office blood pressure and HBPM readings. The ABPM should 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.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the ABPM Investigator Manual. 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. ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take

readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid (either during the Run-in Period or after the second randomization), the patient will be provided 1 opportunity to repeat the study within 7 days from the end time of the invalid ABPM. During the Run-in period, if a valid ABPM recording that meets the inclusion criterion exceeds the 7-day window prior to randomization, 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 recording that meets the inclusion criterion is not obtained within the 7 days prior to randomization, the patient is a run-in failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medications, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. 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) use of cannabis or THC-containing substances should be avoided for at least 2 days prior to office blood pressure measurements.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.

- Follow the HBPM and OBPM Investigator Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction, so the staff will avoid interacting with you during this assessment. This assessment will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Measure standing blood pressure 1 to 3 minutes after standing using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and record their response.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the HBPM and OBPM Investigator Manual. Results and the remote method used will be recorded.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required on days when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM 3 times during the week prior to the second randomization.

After Day 1, HBPM should be measured at least once per week and may be increased at the Investigator's discretion if more frequent measurement is warranted. Patients may select the day of the week that is most convenient for their personal schedule.

CLINICAL STUDY PROTOCOL
ALN-AGT01-003
DATED 22 MARCH 2022

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication
Short Title:	Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)
Study Drug:	Zilebesiran (ALN-AGT01)
EudraCT Number:	2021-003776-13
IND Number:	143503
Protocol Date:	Original protocol, 25 August 2021 Amendment 1, 22 March 2022
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD PPD

SPONSOR PROTOCOL APPROVAL

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

_____

PPD

PPD

Alnylam Pharmaceuticals, Inc.

_____

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-003 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 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication

Short Title

Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)

Study Drug

Zilebesiran (ALN-AGT01)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 120 clinical study centers worldwide.

Objectives and Endpoints

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	Key Secondary Endpoints • Change from baseline at Month 3 in office SBP • Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM • Time-adjusted change from baseline through Month 6 in office SBP • Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6 Other Secondary Endpoints • Change in 24-hour mean SBP and DBP, assessed by ABPM • Change in office SBP and DBP

Objectives	Endpoints
	• Change in daytime and nighttime mean SBP and DBP, assessed by ABPM • Change in serum AGT
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM control and response rates • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 18)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

Study Design

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

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

Patients who meet all inclusion/exclusion criteria after the Run-in period will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB treatment period as add-on therapy to their protocol-specified background antihypertensive medication.

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

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

Number of Planned Patients

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications. Patients should have a 24-hour mean systolic blood pressure (SBP) >130 mmHg and ≤160 mmHg by ambulatory blood pressure monitoring (ABPM) after at least 4 weeks of run-in on protocol-specified background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

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

Patients randomized to receive zilebesiran will be administered 600 mg SC once during the 6-month DB treatment period; all patients will receive 600 mg SC once every 6 months during the OLE period.

Reference Treatment, Dose, and Mode of Administration

Placebo (phosphate-buffered saline for SC administration) will be administered at the same dosing interval and volume as the study drug during the 6-month DB period.

Protocol-specified Background Antihypertensive Medication, Dose, and Mode of Administration

Patients will be randomized to 1 of the following protocol-specified background antihypertensive medications to be administered orally once daily during the Run-in and 6-month DB periods:

- Olmesartan: 40 mg (or 20 mg for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks.
- Amlodipine: 5 mg
- Indapamide: 2.5 mg

Duration of Treatment and Study Participation

The duration of treatment with zilebesiran is up to 18 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 20 months, including up to 2 months of the Screening and Run-in periods, and up to 18 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months.

Statistical Methods

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period. Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

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

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

The populations (analysis sets) are defined as follows:

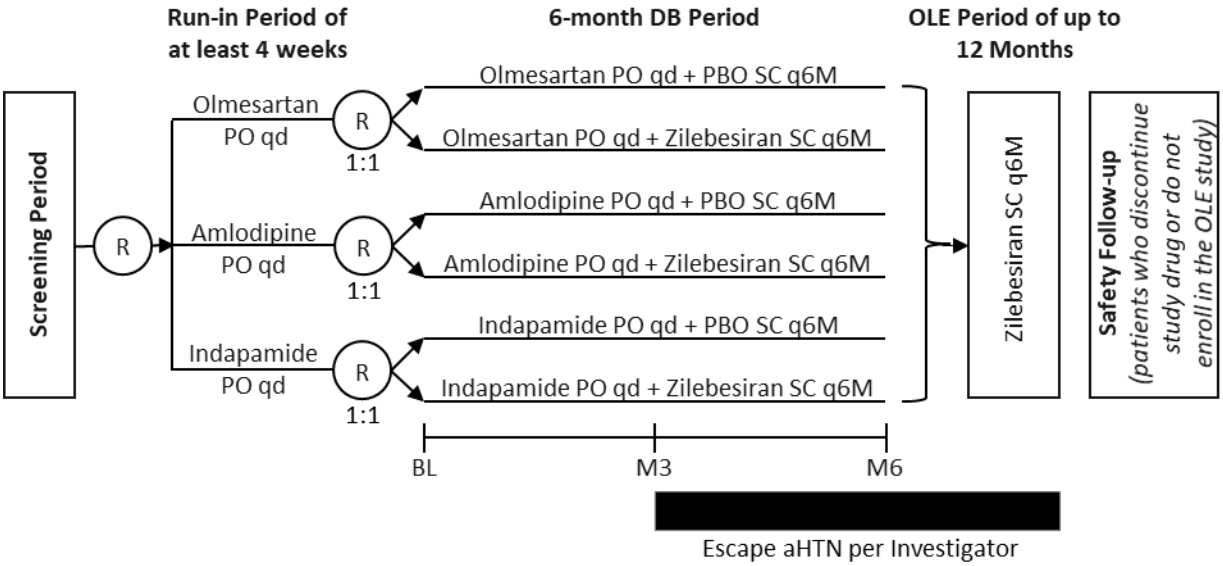
- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be grouped according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug. All by-treatment analyses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

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

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

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Figure 1: Study Design



Abbreviations: aHTN=antihypertensive medication; BL=baseline; DB=double-blind; M=month; OLE=open-label extension; PBO=placebo; PO=per os (oral); qd=once daily; q6M=once every 6 months; R=randomization; SC=subcutaneous.
Note: Patients may be eligible to participate in a separate zilebesiran OLE study upon completion of the Month 6 predose assessments. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran once every 6 months in the OLE period for up to 12 additional months until the OLE study is open and then transition. Once the separate OLE study is open for enrollment, eligible patients may rollover into the separate OLE study at Month 6, 12, or 18 (first visit after the separate OLE study is open). Patients who were previously taking antihypertensives at screening should discontinue these medications at Run-in Visit 1.

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
Informed consent	Section 8.1.1	X																
Assign patient identification no.	Section 3.4	X																
Medical history	Section 6.1	X																
Demographics	Section 6.1	X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X	X	X														
Serum pregnancy test/FSH screening	Table 6 and Sections 6.5.5.3 and 6.5.6.7; FSH to confirm post-menopausal state if applicable	X																
Full physical exam	Section 6.5.3	X			X							X					X	
Height, body weight, and BMI	Section 6.5.2; Height measured at Day 1 only				X				X			X			X	X	X	
Single 12-Lead ECG	Section 6.5.4	X			X							X				X	X	
Serum chemistry[c]	Table 6; Section 6.5.5	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X		X	X				X			X			X	X	X	X
LFTs[c]	Table 6; See Table 7 for	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
	additional LFTs indicates for patients with abnormalities listed in Section 5.2.4																	
Spot urine for albumin and creatinine[c]	Section 6.5.5	X		X	X				X			X				X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c[c]	Section 6.5.5.1	X		X	X				X			X				X	X	
Vital signs and office blood pressure[d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[e]	Section 6.2.1			X				X	X			X			X	X	X[h]	
HBPM[f]	Section 6.2.3			X	At least once per week													
Discontinue prior oral antihypertensive medications (if taking)	Section 3.1		X															
Urine pregnancy test[b]	Table 6 and Sections 6.5.5.3 and 6.5.6.7		X		X							X				X	X	
RAAS biomarkers: renin	Section 6.3; Only in patients		X		X				X									

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
concentration, aldosterone, AngI/II	randomized to receive olmesartan																	
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X		X			X			X	X	X	
Randomization to protocol-specified background antihypertensive medication	Section 3.4; Randomization may occur on Run-in Visit 1 or 1 business day prior		X															
Protocol-specified background antihypertensive medication administration	Section 5.3		Daily															
Protocol-specified background antihypertensive medication pill count	Section 5.10			X	X		X	X	X	X	X	X						
Plasma for PK	Section 6.4 and Table 2				X							X						
Immunogenicity (ADA)	Section 6.5.5.2				X				X			X			X	X	X	X
Serum AGT	Section 6.3				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference and waist-to-	Section 6.5.2				X							X				X	X	

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
hip ratio																		
Exploratory DNA sample (optional)	Section 6.6				X													
Neurologic evaluation[g] and symptom-directed physical exam	Section 6.5.3															X		X
Randomization to zilebesiran or placebo	Section 3.4; Randomization may occur on Day 1 or 1 business day prior				X													
Study drug administration (zilebesiran or placebo)	Section 5.2.2				X							X				X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of protocol-specified background antihypertensive medication		Continuous															
Concomitant medications	Section 5.9	Continuous																

Abbreviations: ABPM=ambulatory blood pressure monitoring; ADA=anti-drug antibodies; AGT=angiotensinogen; AE=adverse event; Ang=angiotensin; BMI=body mass index; D=day; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HbA1c=hemoglobin

A1C; HBPM=home blood pressure monitoring; ICF=informed consent form; LFT=liver function test; M=month; No.=number; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; Q6M=once every 6 months; RAAS=renin-angiotensin-aldosterone system; SAE=serious adverse event; W=week.

Notes:

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

Footnotes:

[a] **All assessments, except for postdose PK sample collection (Table 2), are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

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

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

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

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

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

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

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

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±30 min)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±30 min)	X

Abbreviations: hh:mm=hour:minute; min=minutes; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates 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.

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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
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
HOMA	Homeostatic model assessment
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
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measurements
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred term
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
THC	Delta-9-tetrahydrocannibinol
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing zilebesiran (ALN-AGT01), a subcutaneously (SC) administered investigational agent comprised of 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-AGT01-003 (KARDIA-2) is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety, and pharmacodynamics (PD) of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. Patients will be randomized to run-in on 1 of 3 protocol-specified antihypertensive medications open-label for at least 4 weeks (olmesartan, amlodipine, or indapamide). At the end of the Run-in period, patients with uncontrolled blood pressure will be randomized 1:1 to receive zilebesiran or placebo as add-on therapy to the protocol-specified background antihypertensive medication for 6 months during the double-blind (DB) period. After completion of the 6-month DB period, patients may be eligible to participate in a separate zilebesiran open-label extension (OLE) study. If an individual patient reaches Month 6 prior to availability of the OLE study, they may discontinue their protocol-specified background antihypertensive medication and receive open-label zilebesiran (600 mg once every 6 months) for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean systolic blood pressure (SBP), assessed by ambulatory blood pressure monitoring (ABPM), from baseline to Month 3, relative to placebo. Secondary and exploratory objectives of the study include evaluating the add-on efficacy of zilebesiran on other measures of blood pressure response (including longer treatment durations, eg, 6 months) and evaluating the PD effect of zilebesiran, including reduction in circulating AGT concentration.

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 and Krousel-Wood 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 and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing zilebesiran, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. 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-aldosterone system (RAAS) 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 (AngII).

Zilebesiran is being studied in the ongoing 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 in obese patients (Part D), and as a single dose of 800 mg co-administered for 2 weeks with 300 mg irbesartan (Part E). Preliminary data are available from Parts A, B, and E. Dose-dependent and durable reductions in circulating AGT were observed after single SC doses of zilebesiran, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Sustained reductions in serum AGT were observed for up to 6 months following a single dose of zilebesiran.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium. No patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in patients who received zilebesiran doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

Because most patients with hypertension eventually progress to require treatment with more than 1 antihypertensive class,[Williams 2018] it is anticipated that zilebesiran may be used together with other standard of care antihypertensive medication. This Phase 2 study will further quantify the antihypertensive effects of zilebesiran as add-on therapy in patients with hypertension not adequately controlled by a standard of care antihypertensive medication. The consistent and durable PD effect of zilebesiran is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

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

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that zilebesiran may offer the benefit of sustained blood pressure reduction to patients with hypertension with infrequent administration (ie, once every 3 months or once every 6 months). The mean SBP reduction observed after single zilebesiran doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives.[Abraham 2015; Materson 1993] The blood pressure of patients will be closely monitored, and after Month 3, escape antihypertensive medications will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of zilebesiran, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with zilebesiran. 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, and escape antihypertensive medications are permitted to manage uncontrolled blood pressure following 3 months of add-on treatment with zilebesiran. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.8.1), hypertension (Section 5.8.2), renal dysfunction (Section 5.8.3), and hyperkalemia (Section 5.8.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from 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. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations. In addition to study drug, each patient will receive a protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). These agents are approved standard medications that will be dosed in accordance with local labeling.

While zilebesiran is designed to inhibit the RAAS, its site of action (AGT) in the RAAS is unique, and its tissue specificity for the liver is hypothesized to improve its renal safety profile relative to conventional RAAS blockade,[Mullick 2017; Uijl 2019] both in the context of monotherapy and when used together with a conventional RAAS blocker such as olmesartan. In the latter setting, zilebesiran is hypothesized to add antihypertensive benefit when added to a conventional RAAS blocker without the increased incidence of RAAS inhibitor-associated renal adverse effects that have been observed in prior trials of conventional dual RAAS blockade.[Makani 2013] Patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 or urine albumin:creatinine $\geq$300mg/g will be exclusively assigned to the olmesartan cohort to ensure that patients with proteinuric chronic kidney disease or diabetes continue the RAAS inhibition standardly recommended for their renal indication throughout the study.

This study's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS 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

highest risk to have events (eGFR <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, or poorly controlled diabetes) 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).

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

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

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

Objectives	Endpoints
	• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 18)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

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

Run-in Period

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized as described in Section 3.4 to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1).

Patients who do not tolerate run-in treatment or who do not meet eligibility for randomization at Day 1 will be withdrawn from the study and returned to their prior medication regimen in coordination with their usual health providers.

DB Period

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

Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the patient's protocol-specified background antihypertensive medication per Investigator judgement for elevated blood pressure as described in Table 4.

OLE Period

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

During the OLE period of this study, Investigators will use escape antihypertensive medications as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring.

Safety Follow-up Period

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

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration)

through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

An independent DMC will oversee the safety and overall conduct of this study, and an independent Clinical Event Adjudication Committee will review suspected renal events to adjudicate whether they meet criteria for acute kidney injury.

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

The duration of treatment with zilebesiran is up to 18 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 20 months, including up to 2 months of the Screening and Run-in periods, and up to 18 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months.

3.2. Scientific Rationale for Study Design

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

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean SBP, assessed by ABPM, from baseline to Month 3, relative to placebo.

Patients with hypertension often require treatment with multiple antihypertensive drugs to reach target blood pressure,[Williams 2018] and it is anticipated that zilebesiran may be administered to individuals on a background of other antihypertensive medications. Therefore, this study evaluates the effects of zilebesiran relative to placebo in patients whose blood pressure is not adequately controlled despite treatment with 1 of the 3 major drug classes recommended for initial treatment of hypertension by all clinical guidelines: RAAS inhibitors (ie, angiotensin converting enzyme [ACE] inhibitors, angiotensin II-receptor blockers, or a direct renin inhibitor), diuretics, and calcium channel blockers (CCBs).[Whelton 2018; Williams 2018] Studying coadministration with olmesartan will assess if the synergistic antihypertensive effects recently observed in rodents treated with both an ARB and an AGT-targeting GalNAc-siRNA will translate into clinically significant blood pressure reduction in hypertensive patients given zilebesiran as an add-on to conventional RAAS inhibition.[Uijl 2019] In addition, it will examine the safety and tolerability of liver-specific AGT targeting during treatment with a conventional RAAS blocker (olmesartan). The newer-generation ARB olmesartan was selected because of its high potency relative to early-generation RAAS inhibitors,[Ojima 2011; White 2011] enabling a robust test for added efficacy when combined with zilebesiran. The maximum dose of olmesartan permitted per local labeling will be used to further increase the rigor of this efficacy evaluation. The thiazide-like diuretic indapamide was selected in accordance with recent guidelines that highlight the greater potency and durability of thiazide-like diuretics over other diuretics.[Burnier 2019] The long-acting dihydropyridine CCB amlodipine was selected given its

extensive use in clinical practice and randomized controlled trials.[Dahlof 2005; Jamerson 2008; Julius 2004]

During the study, blood pressure will be monitored with both automated office blood pressure measurements and outpatient 24-hour ABPM (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). 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 home blood pressure monitoring (HBPM), to assess long-term blood pressure variability and 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] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), 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 at Month 3 and will continue throughout the remainder of the study (see Table 4). The term “escape antihypertensive medication” is used to refer to any oral antihypertensive medication initiated to control blood pressure after Day 1. Separate from these treat-to-target modifications, 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.

If a patient requires treatment with an oral escape antihypertensive medication before Month 6, a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already the protocol-specified background antihypertensive medication) should be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS.

After the 6-month DB period, protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide) will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 12 additional months until the separate OLE study is open and then transition. Because many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be monitored monthly from Month 6 to Month 9.

During the OLE period, Investigators may use escape antihypertensive medications of permitted classes as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring and following current care guidelines.[Whelton 2018; Williams 2018] Olmesartan, amlodipine, and indapamide will be discontinued as protocol-specified background antihypertensive medication during the OLE period; however, patients may continue to receive amlodipine or indapamide as escape antihypertensive medication at the Investigator’s discretion. The use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure should be avoided throughout the study.

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 RAAS inhibitors[McMurray 2016; Parving 2012].

3.3. Justification for Dose

The dose of zilebesiran in this study (600 mg once every 6 months) was selected on the basis of data from the Phase 1 Study 001, in which single zilebesiran doses up to 800 mg were found to have an acceptable safety profile, and dose-dependent, clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed at doses as low as 100 mg. An acceptable safety profile was also observed for a single zilebesiran dose of 800 mg under low-salt/high-salt conditions or co-administered for 2 weeks with 300 mg irbesartan once daily. The selected dose of 600 mg is predicted to result in a median serum AGT reduction of 94.9% at trough (Month 6), translating to a median SBP reduction of 11.6 mmHg as monotherapy.

The protocol-specified background antihypertensive medications are standard agents recommended in international and regional hypertension guidelines, and the selected regimens are standard doses used for their approved indication of hypertension.[Whelton 2018; Williams 2018] Indapamide will be dosed at 2.5 mg orally once daily, and amlodipine will be dosed at 5 mg orally once daily. The dose regimens for indapamide and amlodipine used in this study were selected on the basis of their common use in clinical care (when used both individually and combined with other classes of antihypertensives) and their expected efficacy, safety, and tolerability. Olmesartan will be dosed at the maximum dose allowed per local labeling: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US; Olmetec Product Information, September 2020).[von Bergmann 2001]

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 should contact the Interactive Response Technology (IRT) to obtain a patient identification number.

The Investigator or designee will contact the IRT to randomize the patient at Run-in Visit 1 and again at Day 1 after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at each visit.

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

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 7.1. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be

randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

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

3.5. Blinding

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

Zilebesiran and placebo will be packaged identically. Because zilebesiran may be slightly visually distinguishable from placebo, the vials will be masked in such a way as to hide the identity of the study drug contained within. For administration, syringes will be masked by a site pharmacist or delegate prior to withdrawing the study drug from vial. See the Pharmacy Manual for additional details. The study drug will be administered under the supervision of the Investigator (see Section 5.2.2).

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. 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 (eTMF).

Refer to the IRT instructions for details on unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review the suspected renal events blinded to treatment assignment to adjudicate whether they meet

diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

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

- has completed at least the Month 6 visit and enrolled in the separate OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the separate OLE study.

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
2. Male or female

Patient and Disease Characteristics

3. Has hypertension as follows:
   a. Untreated hypertension (not taking antihypertensive medication), or
   b. Treated hypertension 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.
4. Office SBP at Run-in Visit 1 as follows:
   a. ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
   b. ≥145 mmHg and ≤180 mmHg for patients on antihypertensive medications
5. 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM at Run-in Visit 2 after at least 4 weeks of run-in.
6. ≥80% adherence to the protocol-specified background antihypertensive medication during the Run-in period as assessed by pill count performed at Run-in Visit 2.

Informed Consent

7. 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, or aortic coarctation)
2. Orthostatic hypotension, 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) at screening or during the Run-in period

Laboratory Assessments

3. Has any of the following laboratory parameter assessments at screening or Run-in Visit 2:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (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. Potassium <lower limit of normal range or >5 mEq/L
    e. Sodium <lower limit of normal range
    f. eGFR <30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula; refer to Section 10.1)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days or 5 half-lives of the investigational agent, whichever is longer, prior to Run-in Visit 1 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.
5. Currently taking, taken within 30 days prior to first 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 should be excluded.[Whelton 2018]
6. Currently taking beta blockers and unable to discontinue prior to Run-in Visit 1
7. Changes, such as initiation or discontinuation, of sodium-glucose co-transporter 2 (SGLT2) inhibitor therapy within 30 days prior to screening. Patients on a stable dose of SGLT2 therapy for at least 30 days prior to screening with no anticipated changes during the study treatment period are permitted.

8. 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.
9. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the study treatment period
10. Currently taking, taken within 6 months prior to first randomization, or anticipated to receive an RNAi therapeutic (approved or investigational) during the study

Medical Conditions

11. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), direct renin inhibitor, CCB (including but not limited to significant peripheral edema), or thiazide/thiazide-like diuretic
12. History of multiple drug allergies or history of allergic reaction to any component of or excipient in the study drug
13. 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
14. Has known active human immunodeficiency virus infection; or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection.
15. History of clinically significant cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting or other cardiothoracic surgeries, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to first randomization
16. Known history of angioedema
17. Clinically significant valvular heart disease
18. New York Heart Association II to IV heart failure
19. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia/supraventricular tachycardia, or atrial fibrillation with rapid ventricular response in the 3 months prior to first randomization
20. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
21. History of renal transplantation
22. 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
23. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to either randomization
24. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability

25. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

26. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.11.1
27. Female patient is pregnant, planning a pregnancy, or breast-feeding

Alcohol or Nicotine Use and Substance Abuse

28. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
29. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
30. 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 Restrictions

31. Third shift, night shift, or 24-hour shift workers
32. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or 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 discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or 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

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.9.1) per Investigator discretion
- AE
- Non-adherence to treatment regimen
- Pregnancy

- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and 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.

If a patient has an AE, including SAEs, and/or laboratory abnormalities that in the judgment of the investigator, taking into account the patient's overall status, requires interruption or discontinuation from treatment with study drug, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month DB period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 6 assessments) will be encouraged to remain on the study and complete assessments (excluding pharmacokinetic [PK] assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be

informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 6-month DB period, every effort should be made to conduct the Month 6 visit assessments at an earlier time (see Table 1).

A patient considering stopping participation in the study during the OLE period should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

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. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process the patient's personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the Investigator at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of the patient's personal data, informing the Investigator at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

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 even if study drug is discontinued.

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 center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study after the second randomization at Day 1.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug and protocol-specified background antihypertensive medication supplied by the Sponsor 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 and protocol-specified background antihypertensive medication that have been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of zilebesiran SC and placebo SC 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 (phosphate-buffered saline for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to zilebesiran.

5.2.2. Dose and Administration

During the 6-month DB period, patients will be administered a single dose of 600 mg zilebesiran or placebo, at the same volume, as SC injection on Day 1. Patients who enter the OLE period will receive 600 mg zilebesiran SC at Month 6 after all predose assessments are conducted and once every 6 months during the OLE period.

Study drug injections 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. If a local reaction around the injection site occurs, photographs may be obtained. 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 study drug withdrawal from the vial. A full description of the blinding procedure is included in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 85 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

If a patient misses a dose of study drug, the Investigator should discuss with the Medical Monitor whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

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

5.2.3. Dose Modifications

Dose modifications of study drug are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator, and the Medical Monitor should be contacted.

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a 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 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing 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	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • 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 biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

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

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.3. Protocol-specified Background Antihypertensive Medications

All patients will be randomized to receive 1 of the 3 following standard of care oral antihypertensive medications during a Run-in period of at least 4 weeks and will continue this

protocol-specified background antihypertensive medication through Month 6. Protocol-specified background antihypertensive medications will be supplied by the Sponsor.

- Olmesartan: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks (in this case, the patient must take the full olmesartan dose of 40 mg once daily for at least 4 weeks prior to reassessment at Run-in Visit 2).
- Amlodipine: 5 mg orally once daily
- Indapamide: 2.5 mg orally once daily

Protocol-specified antihypertensive medications may be downtitrated or temporarily discontinued per Investigator judgement for low blood pressure (see Section 5.8.1). At the Investigator's discretion, oral antihypertensive agents, including protocol-specified background antihypertensive medication, may be prophylactically held during intercurrent illness or volume depletion. Additional information on the protocol-specified background antihypertensive medications, including side effects, drug-drug interactions, and other important prescribing information can be found in the Pharmacy Manual.

5.4. Preparation, Handling, and Storage

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

Study drug will be stored at approximately 2 to 30°C until dose preparation. Protocol-specified background antihypertensive medication will be stored according to the storage instructions on the label. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the affected study drug or protocol-specified background antihypertensive medication 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 protocol-specified background antihypertensive medication and additional storage will be provided in the Pharmacy Manual.

5.5. Packaging and Labeling

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

5.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug and protocol-specified background antihypertensive medication supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug and protocol-specified background antihypertensive medication 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 and protocol-specified background antihypertensive medication. Used, partially used, and unused study drug and protocol-specified background antihypertensive medication will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.7. Clinical Product Complaints

5.7.1. Definition

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 nonmedical 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.

5.7.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.8. Monitoring for Potential Clinical Events

5.8.1. 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 (supine 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). Oral antihypertensives should be downtitrated/interrupted in reverse order to how they were added (ie, interrupt escape antihypertensive medications before protocol-specified background antihypertensive medications).
- 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 orthostatic intolerance syndromes 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.

5.8.2. 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 4.

Table 4: 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. • Until double-blind data are generated that demonstrate acceptable safety and added antihypertensive efficacy of zilebesiran when combined with olmesartan, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure will be avoided throughout the study. • If added, escape antihypertensives must be used per their labeled instructions and in accordance with current clinical guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of 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 (whichever agent is not already the protocol-specified background antihypertensive medication) as an escape antihypertensive medication.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already a protocol-specified background antihypertensive medication):</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic may be added as an escape antihypertensive medication if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, other escape antihypertensive medications may also be added per Investigator judgement for persistent elevations in SBP above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018]

Study Period	Intervention
Month 6 to End of Study (OLE period)	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide) will be discontinued. • Patients who continue into the OLE period will initiate open-label treatment with 600 mg zilebesiran once every 6 months. As many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be carefully monitored monthly from Month 6 to Month 9, and Investigators will be prepared to downtitrate or interrupt escape antihypertensive medications if low blood pressure develops (see Section 5.8.1). • If the Month 6 ABPM is in target (daytime mean SBP <135 mmHg), escape antihypertensive medications (if taken) may be downtitrated or interrupted per Investigator judgement to determine if the patient's blood pressure remains within target on zilebesiran treatment alone. • During the OLE period, oral antihypertensive medications may be added per Investigator judgement for persistent elevations in blood pressure above recommended target per treatment guidelines (eg, office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

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; OLE=open-label extension; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

5.8.3. 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 RAAS 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 or to ≤30 mL/min/1.73m^2, 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 or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeats tests, look

for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug and/or oral antihypertensives. Serum creatinine should be monitored at least weekly until improving.

5.8.4. 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 5 apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: 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 (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of open-label olmesartan (in patients randomized to receive it as their protocol-specified background antihypertensive medication) according to Investigator medical judgement • Consider interruption or delay of study drug administration, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

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).

The availability of patiromer and sodium zirconium cyclosilicate (ZS-9) will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.9. 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 other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for at least 4 days after each 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 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 5.9.1 and after consulting the Pharmacy Manual, which contains information on drug-drug interactions and other important prescribing information for the protocol-specified background antihypertensive medications. 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.

5.9.1. Prohibited Concomitant Medication

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

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors), except for olmesartan as protocol-specified background antihypertensive medication during the 6-month DB period
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi 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).
- 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.

5.10. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff. Compliance with protocol-specified background antihypertensive medication will be assessed through pill count by study staff.

5.11. Other Requirements

5.11.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before the first dose of protocol-specified background antihypertensive medication, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

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 post-vasectomy 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, post-ovulation 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 (if applicable; see Section 3.1)

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 child-bearing 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, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

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 every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.11.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.11.3. 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.

5.11.4. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 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 sodium intake recommended in the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.11.5. 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, are to be performed prior to dosing with protocol-specified background antihypertensive medication or study drug. Additional information on the collection of study assessments will be detailed in the Study Manuals.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs (at the discretion and oversight of the Investigator).

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 or legal guardian before the screening procedures are initiated. All patients or their legal guardians 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 once is permitted with agreement 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 Run-in Visit 1 will be updated prior to administration of protocol-specified background antihypertensive medication.

6.1.1. Retesting

If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. Retesting of ABPM at Run-in Visit 2 is permitted once, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening following agreement with the Medical Monitor. A patient will be re-consented if rescreening occurs outside of the Screening period. In this case, all screening procedures must be repeated. Patients who do not meet eligibility criteria after Run-in Visit 1 will not be rescreened.

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 Section 10.2. Office blood pressure assessments and ABPM initiation must be performed before administration of any oral antihypertensive medications and study drug (as applicable).

Patients taking oral antihypertensives prior to screening should discontinue these medications at Run-in Visit 1. The baseline ABPM and office blood pressure measured at Run-in Visit 2 must be taken within 7 days before Day 1. An HBPM unit will be provided before Run-in Visit 2 to establish the HBPM baseline, and HBPM should be collected at least 3 times during the last week prior to Day 1.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely using the methods described in Section 10.2.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.8.1 and Section 5.8.2, 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. If the ABPM recording is invalid at any point during the study, the patient will be provided 1 opportunity to repeat the recording. During the Run-in period, if the second ABPM recording is also invalid, the patient is a run-in failure.

See further details in Section 10.2 and the 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) and should be at approximately the same time of day for each assessment; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

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 as detailed in Section 10.2 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral antihypertensive medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the Study Manual.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT will be collected according to the Schedule of Assessments (Table 1). In addition, blood samples for determination of RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected only for patients randomized to receive olmesartan as protocol-specified background antihypertensive medication. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a regulated bioanalytical laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. 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 adjust dosing of zilebesiran or guide clinical management and will not be shared with sites until after study unblinding.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma 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 samples for PK analysis is in Table 2.

Plasma concentrations of zilebesiran and AS(N-1)3′ zilebesiran will be determined using a validated assay. 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, electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination will be recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured in the seated position, after the patient has rested comfortably for approximately 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, 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, or as per DMC advice.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at Day 1 only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A

stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a study drug dosing visit, it should be conducted prior to dosing. 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 evaluation (see the Study Manual for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed according to the Study Manual during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

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, QT interval, and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should 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.

When ECG and blood sample collection occur at the same visit, 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, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.4. 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, or as per DMC advice, 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. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

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. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. In patients randomized to receive olmesartan as the protocol-specified background antihypertensive medication, blood samples for RAAS 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	Chloride
Creatinine clearance	
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
Protein	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

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 days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a regulated bioanalytical laboratory.

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 child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments 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 discontinued from study drug but will continue to be followed for safety. Patients who become 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 will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.11.1 for definition of postmenopausal state).

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 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM	Parvovirus B19 DNA - quantitative
HAV antibody IgM	HHV-6 DNA viral load - quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
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 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

Abbreviations: CT=computed tomography; DNA=deoxyribonucleic acid; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All laboratory assessments will be measured in a 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; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of zilebesiran.

  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.

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.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event 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 Treatment

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.

The relationship of each AE to the protocol-specified background antihypertensive medication should also be assessed by the Investigator.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, 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 treatment during the Run-in period regardless of their relationship to the study treatment through the end of study. Study treatment is defined as protocol-specified background antihypertensive medication or study drug (zilebesiran or placebo). Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before the Run-in period will be captured as medical history (see Section 6.1), while AEs that occur after study treatment, and baseline events that worsen after study treatment, 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 treatment through the end of study. 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 related. Each AE must be described in

detail: onset time and date, description of event, severity, relationship to study treatment, 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).

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 within 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 treatment.

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 treatment, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using the Investigator's best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study treatment, 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.

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 Directive 2001/20/EC, 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 (see Section 3.1), 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 on the pregnancy reporting form. 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 90 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 participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor and Sponsor within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant 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 reporting instructions for overdose and other special situations 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.

Biological specimens 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, study participants 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 database lock and study unblinding for the analysis of the primary endpoints and secondary endpoints measured at Month 3. 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

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

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

- Indapamide cohort: 120 patients

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

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

The power is assessed by simulation based on the Mixed Model with Repeated Measurements (MMRM), with change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as response variable and treatment, time, treatment-by-time as fixed factors and corresponding baseline value as a covariate.

7.2. Statistical Methodology

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

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

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

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

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, between Run-in Visit 2 and prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

The primary endpoint is the change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM. The primary hypothesis of the add-on effect of zilebesiran compared to placebo in patients receiving each of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine or indapamide) will be tested separately at a 2-sided significance level of 0.05 using MMRM. The MMRM model will include treatment, time, treatment-by-time, and race (black or all other races) as fixed factors and baseline 24-hour mean SBP assessed by ABPM and screening eGFR as covariates.

The key secondary endpoints are:

- Change from baseline at Month 3 in office SBP
- Time-adjusted change from baseline through Month 6 in 24-hour mean SBP, assessed by ABPM
- Time-adjusted change from baseline through Month 6 in office SBP
- Proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without escape antihypertensive medication at Month 6

To control the overall type I error, the primary and key secondary endpoints will be tested in hierarchical order.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD reduction after zilebesiran treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

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

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 classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term [by dose level and overall]. AEs, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by System Organ Class and PT for each treatment arm. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug. Adverse events collected during the Run-in period will be summarized.

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 post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

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

7.2.10. Interim Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted after all patients complete the Month 3 visit or withdraw from the study prior to the Month 3 visit. No formal interim analysis is planned before the analysis at Month 3.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

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, 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/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian'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 for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented 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 study participant 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 end of study 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 participants 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 CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied 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 study 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. Formula 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.

Modification of Diet in Renal Disease Formula [Levey 2009]

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

10.2. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

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) should 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 Study Manual. Unless significant weight loss or gain occurs between visits, the patient should 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 should be used for all subsequent office blood pressure and HBPM readings. The ABPM should 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.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. 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. ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take

readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with validity assessment. An ABPM will be considered valid if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is invalid (either during the Run-in Period or after the second randomization), the patient will be provided 1 opportunity to repeat the study within 4 days. If the second ABPM recording is also invalid during screening, the patient is a run-in failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit prior to the morning dose of antihypertensive medications, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. 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) use of cannabis or THC-containing substances should be avoided for at least 2 days prior to office blood pressure measurements.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

- During the device's seated measurement protocol, the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The blood pressure device works best when you are at rest and without any distraction, so the staff will avoid interacting with you during this assessment. This assessment will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Measure standing blood pressure 1 minute after standing using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and record their response.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used will be recorded.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient should measure HBPM 3 times during the week prior to the second randomization.

After Day 1, HBPM should be measured at least once per week and may be increased at the Investigator's discretion if more frequent measurement is warranted. Patients may select the day of the week that is most convenient for their personal schedule.

CLINICAL STUDY PROTOCOL
ALN-AGT01-003
DATED 25 AUGUST 2021

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication
Short Title:	Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)
Study Drug:	Zilebesiran (ALN-AGT01)
EudraCT Number:	2021-003776-13
IND Number:	143503
Protocol Date:	Original protocol, 25 August 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD PPD

SPONSOR PROTOCOL APPROVAL

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

_____

PPD

PPD

Alnylam Pharmaceuticals, Inc.

_____

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AGT01-003 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 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Zilebesiran Used as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication

Short Title

Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication (KARDIA-2)

Study Drug

Zilebesiran (ALN-AGT01)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 80 clinical study centers worldwide.

Objectives and Endpoints

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change in 24-hour mean SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	• Change in office SBP from baseline to Month 3 • Change in 24-hour mean SBP from baseline to Month 6, assessed by ABPM • Change in office SBP from baseline to Month 6 • Change in 24-hour mean DBP from baseline to Months 3 and 6, assessed by ABPM • Change in office DBP from baseline to Months 3 and 6 • Change in daytime and nighttime mean SBP and DBP from baseline to Month 3 and Month 6, assessed by ABPM • Change in serum AGT

Objectives	Endpoints
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM response rate (by blood pressure normalization) • Proportion of patients requiring treatment with escape antihypertensive medications • Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 18)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

Study Design

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

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

Patients who meet all inclusion/exclusion criteria after the Run-in period will be randomized 1:1 to receive 600 mg zilebesiran SC or placebo SC on Day 1 of a 6-month DB treatment period as add-on therapy to their protocol-specified background antihypertensive medication.

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

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

Number of Planned Patients

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

Diagnosis and Main Eligibility Criteria

This study will include adults (18 to 75 years, inclusive) with untreated hypertension or on stable therapy with up to 2 antihypertensive medications of the following classes: an angiotensin converting enzyme inhibitor, angiotensin II-receptor blocker, renin inhibitor, calcium channel blocker, thiazide diuretic, and/or thiazide-like diuretic. Patients should have a 24-hour mean systolic blood pressure (SBP) >130 mmHg and ≤160 mmHg by ambulatory blood pressure monitoring (ABPM) after at least 4 weeks of run-in on protocol-specified background antihypertensive medication. Patients with secondary hypertension or orthostatic hypotension will be excluded.

Study Drug, Dose, and Mode of Administration

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

Patients randomized to receive zilebesiran will be administered 600 mg SC once during the 6-month DB treatment period; all patients will receive 600 mg SC once every 6 months during the OLE period.

Reference Treatment, Dose, and Mode of Administration

Placebo (phosphate-buffered saline for SC administration) will be administered at the same dosing interval and volume as the study drug during the 6-month DB period.

Protocol-specified Background Antihypertensive Medication, Dose, and Mode of Administration

Patients will be randomized to 1 of the following protocol-specified background antihypertensive medications to be administered orally once daily during the Run-in and 6-month DB periods:

- Olmesartan: 40 mg (or 20 mg for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks.
- Amlodipine: 5 mg
- Indapamide: 2.5 mg

Duration of Treatment and Study Participation

The duration of treatment with zilebesiran is up to 18 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 20 months, including up to 2 months of the Screening and Run-in periods, and up to 18 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months.

Statistical Methods

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period. Randomization on Day 1 will be stratified by race (black or all other races), baseline blood pressure (24-hour mean SBP < or ≥145 mmHg), and screening estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73m^2).

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

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

The populations (analysis sets) are defined as follows:

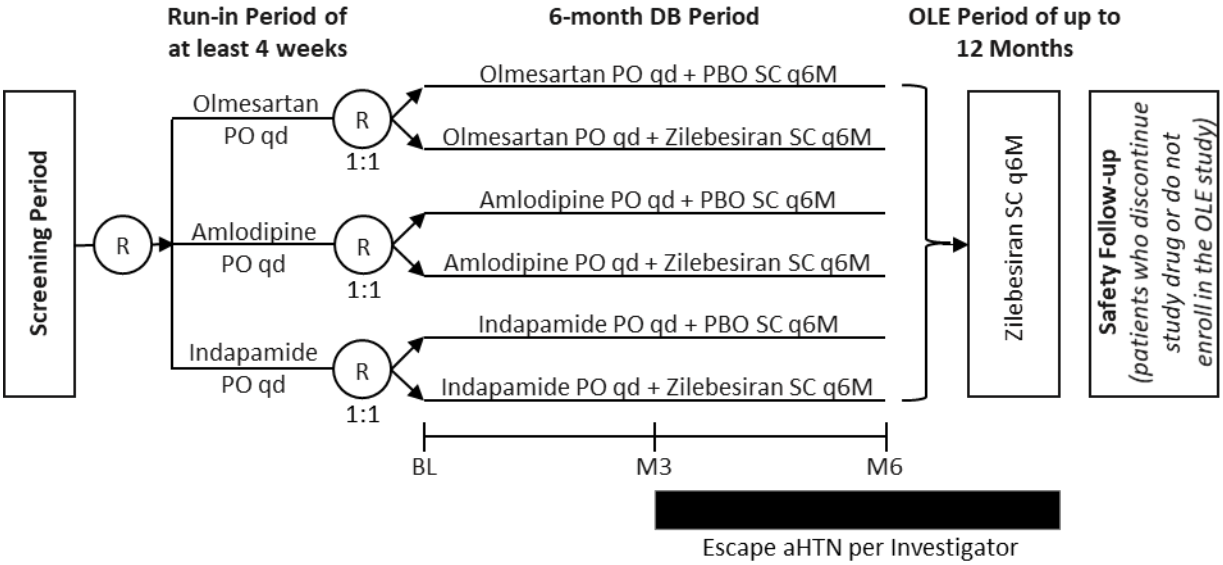
- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **Pharmacokinetic (PK) Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug and who have an evaluable baseline and at least 1 evaluable post-baseline PD measurement will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. The primary endpoint is the change in 24-hour mean SBP from baseline to Month 3, assessed by ABPM. The primary hypothesis of the add-on effect of zilebesiran compared to placebo in patients receiving each of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine or indapamide) will be tested separately. To control the overall type I error, the following secondary endpoints will be tested in hierarchical order, only if the primary endpoint is statistically significant:

- Change in office SBP from baseline to Month 3
- Change in 24-hour mean SBP from baseline to Month 6, assessed by ABPM
- Change in office SBP from baseline to Month 6

Safety data will be summarized descriptively.

Figure 1: Study Design



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

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site			Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)		Screening Period	Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
Informed consent	Section 8.1.1	X																
Assign patient identification no.	Section 3.4	X																
Medical history	Section 6.1	X																
Demographics	Section 6.1	X																
Inclusion/exclusion criteria	Sections 4.1 and 4.2	X	X	X														
Serum pregnancy test/FSH screening	Table 6 and Sections 6.5.5.3 and 6.5.6.7; FSH to confirm post-menopausal state if applicable	X																
Full physical exam	Section 6.5.3	X			X							X					X	
Height, body weight, and BMI	Section 6.5.2; Height measured at Day 1 only				X				X			X			X	X	X	
Single 12-Lead ECG	Section 6.5.4	X			X							X				X	X	
Serum chemistry[c]	Table 6; Section 6.5.5	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Hematology, urinalysis, coagulation[c]	Table 6; Section 6.5.5	X		X	X				X			X			X	X	X	X

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
LFTs[c]	Table 6; See Table 7 for additional LFTs indicates for patients with abnormalities listed in Section 5.2.4	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Spot urine for albumin and creatinine[c]	Section 6.5.5	X		X	X				X			X				X	X	
Fasting plasma glucose, insulin, lipid panel, and HbA1c[c]	Section 6.5.5.1	X		X	X				X			X				X	X	
Vital signs and office blood pressure[d]	Sections 6.2 and 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour ABPM[e]	Section 6.2.1			X				X	X			X			X	X	X	X
HBPM[f]	Section 6.2.3			X	At least 3x/week													
Discontinue prior oral antihypertensive medications (if taking)	Section 3.1		X															
Urine pregnancy test[b]	Table 6 and Sections 6.5.5.3 and 6.5.6.7		X		X							X				X	X	

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
RAAS biomarkers: renin concentration, aldosterone, Ang I/II	Section 6.3; Only in patients randomized to receive olmesartan		X		X				X									
Optional exploratory biomarkers (urine, plasma, serum)	Section 6.6		X		X		X		X			X			X	X	X	
Randomization to protocol-specified background antihypertensive medication	Section 3.4; Randomization may occur on Run-in Visit 1 or 1 business day prior		X															
Protocol-specified background antihypertensive medication administration	Section 5.3		Daily															
Protocol-specified background antihypertensive medication pill count	Section 5.10			X	X		X	X	X	X	X	X						
24-hour urine for sodium and creatinine	Sections 6.5.5 and 6.6			X					X									
Plasma for PK	Section 6.4 and Table 2				X							X						

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
Immunogenicity (ADA)	Section 6.5.5.2				X				X			X			X	X	X	X
Serum AGT	Section 6.3				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference and waist-to-hip ratio	Section 6.5.2				X							X				X	X	
Exploratory DNA sample (optional)	Section 6.6				X													
Neurologic evaluation[g] and symptom-directed physical exam	Section 6.5.3															X		X
Randomization to zilebesiran or placebo	Section 3.4; Randomization may occur on Day 1 or 1 business day prior				X													
Study drug administration (zilebesiran or placebo)	Section 5.2.2				X							X				X		
AEs	Section 6.5.6.2; Record SAEs after signing of ICF; record non-serious AEs after first dose of		Continuous															

Table 1: Schedule of Assessments

Shading indicates visits that must be performed at the site		Screening Period	Run-in Period[a]		Double-blind Period[a]								OLE Period (Optional)[a]					Safety Follow-up
Study Visit (Month)			Run-In Visit 1	Run-In Visit 2		W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M12	M18/EOT/ET	Q6M post last dose of study drug
Study Day (±Visit Window)	**See Section/Table for details; Notes**	D-60 to -1			D1	D15±2	D29±2	D57±7	D85±7	D113±7	D141±7	D169±7	D197±7	D225±7	D253±7	D337±7	D505±14	±14
	protocol-specified background antihypertensive medication																	
Concomitant medications	Section 5.9	Continuous																

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

Notes:

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

12 months, whichever comes earlier. During this Follow-up period, HBPM monitoring may continue at the discretion of the Investigator. The ADA sample should only be collected at the first Follow-up visit during the Follow-up period.

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

Footnotes:

[a] **All assessments, except for postdose PK sample collection (Table 2), are to be performed prior to administration of protocol-specified background antihypertensive medications (including Run-In Visit 1) and study drug (as applicable).**

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

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

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

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

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

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

Table 2: PK Time Points

Study Day	Sampling Time (hh:mm)	Plasma PK Sample
Day 1	Predose (any time before dosing)	X
	04:00 (±30 min)	X
Day 169±7	Predose (any time before dosing)	X
	04:00 (±30 min)	X

Abbreviations: hh:mm=hour:minute; min=minutes; PK=pharmacokinetics.
Notes:

- The hour (±range) indicates 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.

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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
AngI/II	Angiotensin I/II
ARB	Angiotensin II-receptor blocker
AST	Aspartate aminotransferase
CCB	Calcium channel blocker
CPC	Clinical product complaint
DB	Double-blind
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein
HOMA	Homeostatic model assessment
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
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measurements
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
OLE	Open-label extension
PD	Pharmacodynamics
PK	Pharmacokinetic
PT	Preferred term
RAAS	Renin-angiotensin-aldosterone system
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
siRNA	Small interfering RNA
SGLT2	Sodium-glucose co-transporter 2
ULN	Upper limit of normal

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing zilebesiran (ALN-AGT01), a subcutaneously (SC) administered investigational agent comprised of 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-AGT01-003 (KARDIA-2) is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy, safety, and pharmacodynamics (PD) of zilebesiran administered SC as an add-on therapy in patients with hypertension despite treatment with a standard of care antihypertensive medication. Patients will be randomized to run-in on 1 of 3 protocol-specified antihypertensive medications open-label for at least 4 weeks (olmesartan, amlodipine, or indapamide). At the end of the Run-in period, patients with uncontrolled blood pressure will be randomized 1:1 to receive zilebesiran or placebo as add-on therapy to the protocol-specified background antihypertensive medication for 6 months during the double-blind (DB) period. After completion of the 6-month DB period, patients may be eligible to participate in a separate zilebesiran open-label extension (OLE) study. If an individual patient reaches Month 6 prior to availability of the OLE study, they may discontinue their protocol-specified background antihypertensive medication and receive open-label zilebesiran (600 mg once every 6 months) for up to 12 additional months until the OLE study is open and then transition.

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean systolic blood pressure (SBP), assessed by ambulatory blood pressure monitoring (ABPM), from baseline to Month 3, relative to placebo. Secondary and exploratory objectives of the study include evaluating the add-on efficacy of zilebesiran on other measures of blood pressure response (including longer treatment durations, eg, 6 months) and evaluating the PD effect of zilebesiran, including reduction in circulating AGT concentration.

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 and Krousel-Wood 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 and Balatbat 2019; McClellan 2019; Services 2020]

The Sponsor is developing zilebesiran, a novel synthetic RNA interference (RNAi) therapeutic, for SC administration for the treatment of hypertension. 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-aldosterone system (RAAS) 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 (AngII).

Zilebesiran is being studied in the ongoing 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 in obese patients (Part D), and as a single dose of 800 mg co-administered for 2 weeks with 300 mg irbesartan (Part E). Preliminary data are available from Parts A, B, and E. Dose-dependent and durable reductions in circulating AGT were observed after single SC doses of zilebesiran, accompanied by clinically significant reductions in SBP and diastolic blood pressure (DBP). Sustained reductions in serum AGT were observed for up to 6 months following a single dose of zilebesiran.

Most adverse events (AEs) have been mild or moderate in severity, and there have been no severe or serious adverse events (SAEs) related to study drug. There have been no clinically significant elevations in serum creatinine or serum potassium. No patient has required intervention for low blood pressure. No clinically significant alanine aminotransferase (ALT) elevations have been observed in patients who received zilebesiran doses as high as 800 mg. Injection site reactions (ISRs) were reported in a minority of patients and were all mild and transient events that resolved without intervention.

Because most patients with hypertension eventually progress to require treatment with more than 1 antihypertensive class,[Williams 2018] it is anticipated that zilebesiran may be used together with other standard of care antihypertensive medication. This Phase 2 study will further quantify the antihypertensive effects of zilebesiran as add-on therapy in patients with hypertension not adequately controlled by a standard of care antihypertensive medication. The consistent and durable PD effect of zilebesiran is expected to achieve the unique benefit of continuous 24-hour blood pressure lowering with infrequent SC dosing.

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

1.3. Benefit-Risk Assessment

Clinical data available from Study 001 indicate that zilebesiran may offer the benefit of sustained blood pressure reduction to patients with hypertension with infrequent administration (ie, once every 3 months or once every 6 months). The mean SBP reduction observed after single zilebesiran doses of 100 mg or higher exceeds 10 mmHg, which is comparable to the effect of conventional antihypertensives.[Abraham 2015; Materson 1993] The blood pressure of patients will be closely monitored, and after Month 3, escape antihypertensive medications will be added as needed to control blood pressure.

Given the mechanism of action and mode of administration of zilebesiran, potential theoretical risks include liver transaminase elevations and ISRs. Like any antihypertensive therapy, there is also a theoretical risk of hypotension with zilebesiran. 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, and escape antihypertensive medications are permitted to manage uncontrolled blood pressure following 3 months of add-on treatment with zilebesiran. Detailed guidance is provided to Investigators for potential liver transaminase elevations (Section 5.2.4), hypotension (Section 5.8.1), hypertension (Section 5.8.2), renal dysfunction (Section 5.8.3), and hyperkalemia (Section 5.8.4). An independent Data Monitoring Committee (DMC) will monitor and ensure the safety of study participants (see Section 3.6).

Based on available data from 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. This experience supports that the theoretical risks of treatment are low and can be managed through the proposed monitoring and safety mitigations. In addition to study drug, each patient will receive a protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide). These agents are approved standard medications that will be dosed in accordance with local labeling.

While zilebesiran is designed to inhibit the RAAS, its site of action (AGT) in the RAAS is unique, and its tissue specificity for the liver is hypothesized to improve its renal safety profile relative to conventional RAAS blockade,[Mullick 2017; Uijl 2019] both in the context of monotherapy and when used together with a conventional RAAS blocker such as olmesartan. In the latter setting, zilebesiran is hypothesized to add antihypertensive benefit when added to a conventional RAAS blocker without the increased incidence of RAAS inhibitor-associated renal adverse effects that have been observed in prior trials of conventional dual RAAS blockade.[Makani 2013] Patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 or urine albumin:creatinine $\geq$300mg/g will be exclusively assigned to the olmesartan cohort to ensure that patients with proteinuric chronic kidney disease or diabetes continue the RAAS inhibition standardly recommended for their renal indication throughout the study.

This study's monitoring plan is designed to meet the standards set by prior studies of conventional RAAS 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

highest risk to have events (eGFR <30 mL/min/1.73m^2, baseline serum potassium >5 mEq/L, or poorly controlled diabetes) 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).

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

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

Objectives	Endpoints
Primary	
• To evaluate the add-on effect of zilebesiran on SBP as assessed by ABPM at Month 3	• Change in 24-hour mean SBP from baseline to Month 3, assessed by ABPM
Secondary	
Through Month 6 • To evaluate the add-on effect of zilebesiran on blood pressure assessed by ABPM • To evaluate the add-on effect of zilebesiran on office blood pressure • To characterize the PD effects of zilebesiran	• Change in office SBP from baseline to Month 3 • Change in 24-hour mean SBP from baseline to Month 6, assessed by ABPM • Change in office SBP from baseline to Month 6 • Change in 24-hour mean DBP from baseline to Months 3 and 6, assessed by ABPM • Change in office DBP from baseline to Months 3 and 6 • Change in daytime and nighttime mean SBP and DBP from baseline to Month 3 and Month 6, assessed by ABPM • Change in serum AGT
Exploratory	
• To evaluate the add-on effect of zilebesiran, over time, on other measures of blood pressure reduction (through Month 6)	• Office blood pressure and ABPM response rate (by blood pressure reduction) • Office blood pressure and ABPM response rate (by blood pressure normalization) • Proportion of patients requiring treatment with escape antihypertensive medications

Objectives	Endpoints
	• Change in pulse pressure from baseline to Month 3 and Month 6, assessed by ABPM and office blood pressure • Change in SBP and DBP from baseline assessed by HBPM
• To characterize the plasma PK of zilebesiran	• Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran
• To assess the effect of zilebesiran on exploratory biomarkers of the RAAS (only for patients randomized to olmesartan as their protocol-specified background antihypertensive medication)	• Change from baseline in plasma renin concentration, aldosterone, AngI, and AngII
• To evaluate the immunogenicity of zilebesiran	• Incidence and titers of ADA
• To assess the effect of zilebesiran on body weight, BMI, and morphometric measurements	• Change from baseline in body weight, BMI, waist circumference, and waist-to-hip ratio
• To assess the effect of zilebesiran on metabolic syndrome parameters	• Change from baseline in HbA1c, fasting plasma glucose, insulin, HOMA index, and serum lipid profile
• To characterize the PD effects of zilebesiran (after Month 6)	• Change in serum AGT
• To assess the long-term treatment effect of zilebesiran (through Month 18)	• Change from baseline in SBP and DBP assessed by ABPM, office blood pressure, and HBPM
Safety	
• To evaluate the safety of zilebesiran in patients with hypertension	• Frequency of AEs

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

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

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

Run-in Period

Patients who complete the Screening period and meet all inclusion/exclusion criteria for enrollment will be randomized as described in Section 3.4 to receive open-label therapy with olmesartan (40 mg orally once daily [or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling for olmesartan]), amlodipine (5 mg orally once daily), or indapamide (2.5 mg orally once daily) as their protocol-specified background antihypertensive medication during a Run-in period of at least 4 weeks. Prior antihypertensive medications (if taking) will be discontinued upon the start of this Run-in period (Run-in Visit 1) for at least 4 weeks before Run-in Visit 2 to washout their effects.

Patients who do not tolerate run-in treatment or who do not meet eligibility for randomization at Day 1 will be withdrawn from the study and returned to their prior medication regimen in coordination with their usual health providers.

DB Period

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

Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the patient's protocol-specified background antihypertensive medication per Investigator judgement for elevated blood pressure as described in Table 4.

OLE Period

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

During the OLE period of this study, Investigators will use escape antihypertensive medications as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring.

Safety Follow-up Period

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

Patients who discontinue study drug prior to the Month 6 visit will also be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration)

through Month 6. If a patient discontinues study drug after the Month 6 visit, end of treatment (EOT)/early termination (ET) assessments should be performed.

An independent DMC will oversee the safety and overall conduct of this study, and an independent Clinical Event Adjudication Committee will review suspected renal events to adjudicate whether they meet criteria for acute kidney injury.

The planned enrollment for this study is approximately 800 patients to be randomized into the Run-in period and approximately 630 patients (300 patients in the olmesartan arm, 210 patients in the amlodipine arm, and 120 patients in the indapamide arm) to be randomized in the DB period.

The duration of treatment with zilebesiran is up to 18 months. The estimated total time on study for patients who rollover to the separate OLE study is up to approximately 20 months, including up to 2 months of the Screening and Run-in periods, and up to 18 months of treatment. For all patients who discontinue study drug or do not roll over to the separate OLE study, the Safety Follow-up period is up to 12 months.

3.2. Scientific Rationale for Study Design

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

The primary objective of the study is to evaluate the efficacy of zilebesiran as an add-on therapy for the treatment of hypertension by evaluating the change in 24-hour mean SBP, assessed by ABPM, from baseline to Month 3, relative to placebo.

Patients with hypertension often require treatment with multiple antihypertensive drugs to reach target blood pressure,[Williams 2018] and it is anticipated that zilebesiran may be administered to individuals on a background of other antihypertensive medications. Therefore, this study evaluates the effects of zilebesiran relative to placebo in patients whose blood pressure is not adequately controlled despite treatment with 1 of the 3 major drug classes recommended for initial treatment of hypertension by all clinical guidelines: RAAS inhibitors (ie, angiotensin converting enzyme [ACE] inhibitors, angiotensin II-receptor blockers [Avni], or a direct renin inhibitor), diuretics, and calcium channel blockers (CCBs).[Whelton 2018; Williams 2018] Studying coadministration with olmesartan will assess if the synergistic antihypertensive effects recently observed in rodents treated with both an ARB and an AGT-targeting GalNAc-siRNA will translate into clinically significant blood pressure reduction in hypertensive patients given zilebesiran as an add-on to conventional RAAS inhibition.[Uijl 2019] In addition, it will examine the safety and tolerability of liver-specific AGT targeting during treatment with a conventional RAAS blocker (olmesartan). The newer-generation ARB olmesartan was selected because of its high potency relative to early-generation RAAS inhibitors,[Ojima 2011; White 2011] enabling a robust test for added efficacy when combined with zilebesiran. The maximum dose of olmesartan permitted per local labeling will be used to further increase the rigor of this efficacy evaluation. The thiazide-like diuretic indapamide was selected in accordance with recent guidelines that highlight the greater potency and durability of thiazide-like diuretics over other diuretics.[Burnier 2019] The long-acting dihydropyridine CCB amlodipine was selected given its

extensive use in clinical practice and randomized controlled trials.[Dahlof 2005; Jamerson 2008; Julius 2004]

During the study, blood pressure will be monitored with both automated office blood pressure measurements and outpatient 24-hour ABPM (EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016). 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 3 times per week) measurements will be collected through a third method, oscillometric home blood pressure monitoring (HBPM), to assess long-term blood pressure variability and 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] Principles for Clinical Evaluation of New Antihypertensive Drugs, 2000 and EMA/CHMP/29947/2013/Rev. 4; Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, 2016), 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 at Month 3 and will continue throughout the remainder of the study (see Table 4). The term “escape antihypertensive medication” is used to refer to any oral antihypertensive medication initiated to control blood pressure after Day 1. Separate from these treat-to-target modifications, 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.

If a patient requires treatment with an oral escape antihypertensive medication before Month 6, a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already the protocol-specified background antihypertensive medication) should be added because there is extensive experience combining these classes with antihypertensive drugs that impact the RAAS.

After the 6-month DB period, protocol-specified background antihypertensive medication (olmesartan, amlodipine, or indapamide) will be discontinued, and patients may be eligible to participate in a separate zilebesiran OLE study. If an individual patient reaches Month 6 prior to availability of the separate OLE study, they may receive open-label zilebesiran at 600 mg SC once every 6 months for up to 12 additional months until the separate OLE study is open and then transition. Because many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be monitored monthly from Month 6 to Month 9.

During the OLE period, Investigators will use escape antihypertensive medications of permitted classes as described in Table 4 to control blood pressure, guided by continued blood pressure monitoring and following current care guidelines.[Whelton 2018; Williams 2018] Olmesartan, amlodipine, and indapamide will be discontinued as protocol-specified background antihypertensive medication during the OLE period; however, patients may continue to receive amlodipine or indapamide as escape antihypertensive medication at the Investigator’s discretion. The use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure should be avoided throughout the study.

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 RAAS inhibitors[McMurray 2016; Parving 2012].

3.3. Justification for Dose

The dose of zilebesiran in this study (600 mg once every 6 months) was selected on the basis of data from the Phase 1 Study 001, in which single zilebesiran doses up to 800 mg were found to have an acceptable safety profile, and dose-dependent, clinically significant placebo-corrected reductions in mean SBP >10 mmHg by 24-hour ABPM were observed at doses as low as 100 mg. An acceptable safety profile was also observed for a single zilebesiran dose of 800 mg under low-salt/high-salt conditions or co-administered for 2 weeks with 300 mg irbesartan once daily. The selected dose of 600 mg is predicted to result in a median serum AGT reduction of 94.9% at trough (Month 6), translating to a median SBP reduction of 11.6 mmHg as monotherapy.

The protocol-specified background antihypertensive medications are standard agents recommended in international and regional hypertension guidelines, and the selected regimens are standard doses used for their approved indication of hypertension.[Whelton 2018; Williams 2018] Indapamide will be dosed at 2.5 mg orally once daily, and amlodipine will be dosed at 5 mg orally once daily. The dose regimens for indapamide and amlodipine used in this study were selected on the basis of their common use in clinical care (when used both individually and combined with other classes of antihypertensives) and their expected efficacy, safety, and tolerability. Olmesartan will be dosed at the maximum dose allowed per local labeling: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US; Olmetec Product Information, September 2020).[von Bergmann 2001]

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 should contact the Interactive Response Technology (IRT) to obtain a patient identification number.

The Investigator or designee will contact the IRT to randomize the patient at Run-in Visit 1 and again at Day 1 after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at each visit.

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

All other patients will be randomized 10:7:4 to run-in open-label on 1 of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide), with targeted sample sizes across cohorts as described in Section 7.1. If 1 cohort completes enrollment first, this cohort will be deactivated for future randomization. The remaining 2 cohorts will be

randomized using the original ratio. After the second cohort completes enrollment, all subsequent patients will be assigned to the last cohort.

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

3.5. Blinding

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

Zilebesiran and placebo will be packaged identically. Because zilebesiran may be slightly visually distinguishable from placebo, the vials will be masked in such a way as to hide the identity of the study drug contained within. For administration, syringes will be masked by a site pharmacist or delegate prior to withdrawing the study drug from vial. See the Pharmacy Manual for additional details. The study drug will be administered under the supervision of the Investigator (see Section 5.2.2).

3.5.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary, in IRT. 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 (eTMF).

Refer to the IRT instructions for details on unblinding.

3.6. Data Monitoring Committee

An independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

3.7. Clinical Event Adjudication Committees

An independent Clinical Event Adjudication Committee of 2 or more nephrologists will review the suspected renal events blinded to treatment assignment to adjudicate whether they meet

diagnostic criteria for acute kidney injury and, if so, their potential staging and contributing factors. Details are provided in the Renal Event Adjudication Committee charter.

3.8. Definition of End of Study for an Individual Patient

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

- has completed at least the Month 6 visit and enrolled in the separate OLE study, or
- has completed the Safety Follow-up visits as described in Section 3.1 for patients who discontinue study drug or do not enroll in the separate OLE study.

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
2. Male or female

Patient and Disease Characteristics

3. Has hypertension as follows:
   a. Untreated hypertension (not taking antihypertensive medication), or
   b. Treated hypertension on stable therapy with up to 2 antihypertensive medications that include the following classes: an ACE inhibitor, ARB, renin inhibitor, CCB, thiazide diuretic, and/or thiazide-like diuretic. Stable therapy is defined as having no change in antihypertensive medication or dose within 30 days prior to screening, and the doses have to be at least half of the maximally approved daily doses per local labeling.
4. Office SBP at Run-in Visit 1 as follows:
   a. ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
   b. ≥145 mmHg and ≤180 mmHg for patients on antihypertensive medications
5. 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM at Run-in Visit 2 after at least 4 weeks of run-in.
6. ≥80% adherence to the protocol-specified background antihypertensive medication during the Run-in period as assessed by pill count performed at Run-in Visit 2.

Informed Consent

7. 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 moderate-to-severe obstructive sleep apnea with or without receiving nasal continuous positive airway pressure therapy, renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation, or other cause of secondary hypertension)
2. Orthostatic hypotension, 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) at screening or during the Run-in period

Laboratory Assessments

3. Has any of the following laboratory parameter assessments at screening or Run-in Visit 2:
    a. ALT or aspartate aminotransferase (AST) >2× upper limit of normal (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. Potassium <lower limit of normal range or >5 mEq/L
    e. Sodium <lower limit of normal range
    f. eGFR <30 mL/min/1.73m^2 (calculation will be based on the Modification of Diet in Renal Disease formula; refer to Section 10.1)

Prior/Concomitant Therapy

4. Received an investigational agent within the last 30 days or 5 half-lives of the investigational agent, whichever is longer, prior to Run-in Visit 1 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.
5. Currently taking, taken within 30 days prior to first randomization, or anticipated to receive during the course of the study, 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 should be excluded.[Whelton 2018]
6. Currently taking, taken within 30 days prior to first randomization, or anticipated to receive during the course of the study, sodium-glucose co-transporter 2 (SGLT2) inhibitors
7. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted. In addition, consecutive (daily) use of over-the-counter NSAIDs should be avoided for at

least 7 days prior to ABPM, office blood pressure, or laboratory assessments. Paracetamol/acetaminophen for analgesia will be allowed.

8. Anticipates using organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol) during the course of the study
9. Currently taking, taken within 6 months prior to first randomization, or anticipated to receive an RNAi therapeutic (approved or investigational)

Medical Conditions

10. Current or prior history of intolerance to an ARB, ACE inhibitor (other than cough), direct renin inhibitor, CCB (including but not limited to significant peripheral edema), or thiazide/thiazide-like diuretic
11. History of multiple drug allergies or history of allergic reaction to any component of or excipient in the study drug
12. Type 1 diabetes mellitus, poorly controlled Type 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.0%), newly diagnosed Type 2 diabetes mellitus (within 6 months prior to first randomization), or laboratory evidence of diabetes during screening (fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], random plasma glucose ≥200 mg/dL [11.1 mmol/L], or HbA1c ≥6.5%) without known diagnosis of diabetes
13. Has known active human immunodeficiency virus infection; or known current or chronic hepatitis C virus (HCV) or hepatitis B virus infection.
14. History of clinically significant cardiovascular event (eg, stroke, transient ischemic attack, myocardial infarction, unstable angina, coronary artery bypass grafting or other cardiothoracic surgeries, percutaneous coronary intervention, hospitalization due to heart failure) within 6 months prior to first randomization
15. Known history of angioedema
16. Clinically significant valvular heart disease
17. New York Heart Association II to IV heart failure
18. Uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia/supraventricular tachycardia, or atrial fibrillation with rapid ventricular response in the 3 months prior to first randomization
19. Has undergone liver transplantation or is anticipated to be on an active liver transplantation waiting list during the study treatment period
20. History of renal transplantation
21. 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
22. Clinically significant illness, in the opinion of the Investigator, within 7 days prior to either randomization
23. History of intolerance to SC injection(s) that could potentially hinder study drug administration or evaluation of local tolerability

24. Has planned major surgery or general anesthesia during the study

Contraception, Pregnancy, and Breastfeeding

25. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.11.1
26. Female patient is pregnant, planning a pregnancy, or breast-feeding

Alcohol, Nicotine, or Cannabis Use and Substance Abuse

27. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]).
28. History of alcohol or substance abuse (licit or illicit drugs) within the last 12 months before screening, in the opinion of the Investigator
29. 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
30. Unwilling or unable to abstain from use of cannabis or delta-9-tetrahydrocannibinol-containing substances (included by smoking, vaping, dabbing, or ingesting/edibles)

Other Restrictions

31. Third shift, night shift, or 24-hour shift workers
32. Arm circumference exceeds the maximum cuff size of any of the blood pressure instruments provided by the Sponsor
33. Unable or unwilling to perform HBPM as specified

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or 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 discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or 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

Reasons for discontinuation of study drug include any of the following:

- Significant protocol deviation; which includes required treatment with prohibited medication (as defined in Section 5.9.1) per Investigator discretion
- AE

- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and 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.

If a patient has an AE, including SAEs, and/or laboratory abnormalities that in the judgment of the investigator, taking into account the patient's overall status, requires interruption or discontinuation from treatment with study drug, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month DB period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 6 assessments) will be encouraged to remain on the study and complete assessments (excluding pharmacokinetic [PK] assessments) through Month 6. They will also be asked to complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete EOT/ET assessments and complete Safety Follow-up visits once every 6 months after the last dose of study drug per the safety follow-up schedule (see Table 1) until PD recovery or 12 months (whichever is earlier); see Section 3.1.

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study before Month 6 should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 6-month DB period, every effort should be made to conduct the Month 6 visit assessments at an earlier time (see Table 1).

A patient considering stopping participation in the study during the OLE period should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete the assessments scheduled for the EOT/ET visit and complete Safety Follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient consents.

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. Data collected from the patient can continue to be used.

Note, in countries where the collection and processing of the patient's personal data is based on consent, if a patient withdraws consent to collect and process the patient's personal data (see Section 4.3.2.2), as applicable, personal data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data or Objection to Process Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the Investigator at any time in writing or in any other form that may be locally required. Also, where allowed by local law, the patient may object to the collection, storage, and use of the patient's personal data, informing the Investigator at any time in writing or in any other form that may be locally required. In both cases, the Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal/objection) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

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 even if study drug is discontinued.

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 center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

No additional patients may be enrolled to mitigate the impact of patients who discontinue the study drug or stop participation in the study after the second randomization at Day 1.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug and protocol-specified background antihypertensive medication supplied by the Sponsor 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 and protocol-specified background antihypertensive medication that have been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of zilebesiran SC and placebo SC 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 (phosphate-buffered saline for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to zilebesiran.

5.2.2. Dose and Administration

During the 6-month DB period, patients will be administered 600 mg zilebesiran or placebo, at the same volume, as SC injections once every 6 months. During the OLE period, all patients will receive 600 mg zilebesiran SC once every 6 months.

Study drug injections 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. If a local reaction around the injection site occurs, photographs may be obtained. 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 study drug withdrawal from the vial. A full description of the blinding procedure is included in the Pharmacy Manual.

If a patient does not receive a dose of study drug within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered up to 85 days before the next scheduled dose. Thereafter, the dose will be considered missed and not administered.

If a patient misses a dose of study drug, the Investigator should discuss with the Medical Monitor whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

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

5.2.3. Dose Modifications

Dose modifications of study drug are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator, and the Medical Monitor should be contacted.

5.2.4. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. Dosing decisions may be made based on the most recently available liver function test (LFT) results from a central laboratory (Table 6).
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 3.
3. For any ALT or AST elevation >3×ULN:
   a. If local laboratory results are obtained, confirm with a 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 6 and Table 7.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 3.

Table 3: Monitoring and Dosing 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	• May continue dosing • Evaluate the initial elevation in LFT per the following assessments: – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • Monitor at least every 2 weeks (LFT and coagulation per Table 6) • If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing
>5× to 8×ULN	• Hold study drug dosing until recovery to ≤1.5×ULN or baseline; may resume dosing after discussion with the Medical Monitor • Evaluate the initial elevation in LFT per the following assessments – Table 7 (all assessments to be performed once) – Hematology, serum chemistry, LFT, and coagulation per Table 6 • 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 biweekly • If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing
>8×ULN	Permanently discontinue study drug dosing after confirmation of the transaminase value at the central laboratory.

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

5.2.5. Neurological Criteria for Withholding, Monitoring, and Stopping Study Drug Dosing

Clinically significant events that may be consistent with potential decreased proprioception (including but not limited to unusual clumsiness, gait abnormalities, and unexplained balance/coordination issues that are either absent at or worsening from the baseline) should be reported as an AE. If the treatment-emergent AE is persistent and considered related to study drug, specialty consultation with a neurologist should be considered. However, if such a treatment-emergent AE is serious or severe (regardless of the Investigator's assessment of relatedness), the patient must be referred for neurologist consultation, and study drug dosing must be held until that consultation is complete. Resumption of dosing must be approved by the Medical Monitor.

5.3. Protocol-specified Background Antihypertensive Medications

All patients will be randomized to receive 1 of the 3 following standard of care oral antihypertensive medications during a Run-in period of at least 4 weeks and will continue this

protocol-specified background antihypertensive medication through Month 6. Protocol-specified background antihypertensive medications will be supplied by the Sponsor.

- Olmesartan: 40 mg orally once daily (or 20 mg orally once daily for patients with creatinine clearance ≤60 mL/min enrolled at sites outside of the US, consistent with local labeling). At the Investigator's discretion, patients who are randomized to receive 40 mg olmesartan once daily may initiate treatment at 20 mg once daily and then uptitrate to the full dose of 40 mg once daily after 1 to 2 weeks (in this case, the patient must take the full olmesartan dose of 40 mg once daily for at least 4 weeks prior to reassessment at Run-in Visit 2).
- Amlodipine: 5 mg orally once daily
- Indapamide: 2.5 mg orally once daily

Protocol-specified antihypertensive medications may be downtitrated or temporarily discontinued per Investigator judgement for low blood pressure (see Section 5.8.1). At the Investigator's discretion, oral antihypertensive agents, including protocol-specified background antihypertensive medication, may be prophylactically held during intercurrent illness or volume depletion.

5.4. Preparation, Handling, and Storage

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

Study drug will be stored upright at approximately 2 to 30°C until dose preparation. Protocol-specified background antihypertensive medication will be stored according to the storage instructions on the label. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the affected study drug or protocol-specified background antihypertensive medication 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 protocol-specified background antihypertensive medication and additional storage will be provided in the Pharmacy Manual.

5.5. Packaging and Labeling

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

5.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug and protocol-specified background antihypertensive medication supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug and protocol-specified background antihypertensive medication 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 and protocol-specified background antihypertensive medication. Used, partially used, and unused study drug and protocol-specified background antihypertensive medication will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

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

5.7. Clinical Product Complaints

5.7.1. Definition

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 nonmedical in nature; however, it is possible that investigational product 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.

5.7.2. Reporting

For product complaints, the Sponsor or its designee should be notified within 24 hours using the process outlined in the Pharmacy Manual. CPCs that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.6. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.8. Monitoring for Potential Clinical Events

5.8.1. 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 at least 3 times per week 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 (supine 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). Oral antihypertensives should be downtitrated/interrupted in reverse order to how they were added (ie, interrupt escape antihypertensive medications before protocol-specified background antihypertensive medications).
- 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 orthostatic intolerance syndromes 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.

5.8.2. 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 4.

Table 4: 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. • Until double-blind data are generated that demonstrate acceptable safety and added antihypertensive efficacy of zilebesiran when combined with olmesartan, the use of conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors) as escape antihypertensive agents for high blood pressure will be avoided throughout the study. • If added, escape antihypertensives must be used per their labeled instructions and in accordance with current clinical guidelines.[Whelton 2018; Williams 2018]
Day 1 to Month 3	<u>Intervene if clinically significant blood pressure elevation:</u> • Because of the gradual onset of effects of zilebesiran, interventions for asymptomatic hypertension should be avoided in the first 6 weeks after the patient's first administration of 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 (whichever agent is not already the protocol-specified background antihypertensive medication) as an escape antihypertensive medication.
Months 3 to 6	<u>Treat to target blood pressure using a CCB and/or thiazide/thiazide-like diuretic (whichever agent is not already a protocol-specified background antihypertensive medication):</u> • At Month 3, a CCB and/or a thiazide/thiazide-like diuretic should be added as an escape antihypertensive medication if the daytime mean SBP is ≥135 mmHg by ABPM. If the Investigator feels there is a compelling clinical reason to wait, the rationale for exception should be documented in the eCRF. • After Month 3, other escape antihypertensive medications may also be added per Investigator judgement for persistent elevations in SBP above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Williams 2018]

Study Period	Intervention
Month 6 to End of Study (OLE period)	Treat to target blood pressure using Investigator's choice of oral antihypertensive(s). • At Month 6, protocol-specified background antihypertensive medications (olmesartan, amlodipine, or indapamide) will be discontinued. • Patients who continue into the OLE period will initiate open-label treatment with 600 mg zilebesiran once every 6 months. As many patients will receive zilebesiran for the first time at Month 6, office blood pressure and serum chemistries will be carefully monitored monthly from Month 6 to Month 9, and Investigators will be prepared to downtitrate or interrupt escape antihypertensive medications if low blood pressure develops (see Section 5.8.1). • If the Month 6 ABPM is in target (daytime mean SBP <135 mmHg), escape antihypertensive medications (if taken) may be downtitrated or interrupted per Investigator judgement to determine if the patient's blood pressure remains within target on zilebesiran treatment alone. • During the OLE period, oral antihypertensive medications may be added per Investigator judgement for persistent elevations in blood pressure above target (target defined as office SBP <140 mmHg, HBPM SBP <135 mmHg, or daytime mean SBP by ABPM <135 mmHg).[Whelton 2018; Williams 2018]

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; OLE=open-label extension; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

5.8.3. 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 RAAS 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 or to ≤30 mL/min/1.73m^2, 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 or to ≤25 mL/min/1.73m^2, the Investigator should obtain confirmatory repeats tests, look

for potentially reversible causes of renal dysfunction, and contact the Sponsor to discuss the potential interruption of study drug and/or oral antihypertensives. Serum creatinine should be monitored at least weekly until improving.

5.8.4. 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 5 apply for potassium elevations detected by laboratory monitoring.[McMurray 2016; Parving 2012]

Table 5: 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 (at least weekly if in the first 6 weeks of treatment or at least once monthly afterwards)	• Confirm potassium concentration in a non-hemolyzed sample • Consider interruption of open-label olmesartan (in patients randomized to receive it as their protocol-specified background antihypertensive medication) according to Investigator medical judgement • Consider interruption or delay of study drug administration, according to Investigator medical judgment • Apply all measures outlined for serum K^+ ≥5.2 and <5.5 mmol/L • Repeat K^+ measurement after 2 to 3 days • If K^+ <5.5 mmol/L, consider resumption of study drug (if interrupted) with repeat potassium within 5 days • If K^+ persistently elevated ≥5.5 mmol/L, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available	• Immediately interrupt study drug • Confirm potassium concentration in a non-hemolyzed sample • Urgently evaluate patient and treat hyperkalemia as clinically indicated. After urgent treatment, consider treatment with patiromer (or with sodium zirconium cyclosilicate), if available • Apply all measures outlined for serum K^+ ≥5.5 and <6.0 mmol/L • No resumption of study drug without individualized case discussion with and permission from Alnylam Medical Monitor

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).

The availability of patiromer and sodium zirconium cyclosilicate (ZS-9) will be assessed at participating study sites. These potassium-binding drugs are indicated for the treatment of hyperkalemia and have been shown to safely reduce serum potassium levels and to maintain long-term normokalemia in chronic kidney disease patients receiving background conventional RAAS inhibitor therapy.[Georgianos and Agarwal 2018; Weir 2015]

5.9. 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 other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug for at least 4 days after each dose of study drug.

Occasional use of 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 7 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 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.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator, except as described in Section 5.9.1. 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.

5.9.1. Prohibited Concomitant Medication

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

- Conventional RAAS inhibitors (ARBs, ACE inhibitors, or direct renin inhibitors), except for olmesartan as protocol-specified background antihypertensive medication during the 6-month DB period
- SGLT2 inhibitors (eg, empagliflozin, canagliflozin, and dapagliflozin)
- Prescription NSAIDs
- Organic nitrate preparations (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, pentaerythritol)
- An RNAi 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).
- 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.

5.10. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff. Compliance with protocol-specified background antihypertensive medication will be assessed through pill count by study staff.

5.11. Other Requirements

5.11.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before the first dose of protocol-specified background antihypertensive medication, throughout study participation, and through safety follow-up (if applicable; see Section 3.1).

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 post-vasectomy 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, post-ovulation

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 (if applicable; see Section 3.1)

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 child-bearing 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 tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient ICFs.

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 every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.3).

5.11.2. Alcohol Restrictions

Patients should limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] =1 measure of spirits [approximately 1 fluid ounce] =½ pint of beer [approximately 284 mL]) for the duration of the study. Compliance with alcohol restrictions should be assessed on a regular basis by the Investigator throughout the course of the study.

5.11.3. 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.

5.11.4. Cannabis Restriction

Use of cannabis or delta-9-tetrahydrocannibinol-containing substances (included by smoking, vaping, dabbing, or ingesting/edibles) should be avoided throughout the course of the study given their effects on blood pressure.

5.11.5. Dietary Recommendations

All patients will receive educational materials on diet with recommendations to limit sodium consumption to approximately 2.0 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 sodium intake recommended in the 2018 European

Society of Cardiology/European Society of Hypertension Guidelines for both hypertensive patients and for the general population.[Williams 2018]

On days on which samples for fasting lipid panel and glycemic assessments are collected, patients are required to fast for ≥10 hours before sample collection (Section 6.5.5.1).

5.11.6. Exercise

Patients should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

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, are to be performed prior to dosing with protocol-specified background antihypertensive medication or study drug. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples and measurement of vital signs (at the discretion and oversight of the Investigator).

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 or legal guardian before the screening procedures are initiated. All patients or their legal guardians 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 once is permitted with agreement 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 Run-in Visit 1 will be updated prior to administration of protocol-specified background antihypertensive medication.

6.1.1. Retesting

If in the Investigator's judgement, the screening or Run-in laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale must be documented. Laboratory values can be retested once during screening and once during the Run-in period provided that the patient can be evaluated for eligibility and randomized within the allowed Screening and Run-in periods. Retesting of ABPM at Run-in Visit 2 is permitted once as described in Section 6.2.1, with eligibility assessed by the second ABPM result.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return once for rescreening following agreement with the Medical Monitor. A patient will be re-consented if rescreening occurs outside of the Screening period. In this case, all screening procedures must be repeated. Patients who do not meet eligibility criteria after Run-in Visit 1 will not be rescreened.

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 Section 10.2. Office blood pressure assessments and ABPM initiation must be performed before administration of any oral antihypertensive medications and study drug (as applicable).

Patients taking oral antihypertensives prior to screening should discontinue these medications at Run-in Visit 1. The baseline ABPM and office blood pressure measured at Run-in Visit 2 must be taken within 7 days before Day 1. An HBPM unit will be provided before Run-in Visit 2 to establish the HBPM baseline. HBPM must be collected daily for at least 1 week during the Run-in period to establish baseline, starting at 1 week prior to Run-in Visit 2 and continuing to Day 1. After Day 1, the frequency of HBPM should be at least 3 recordings per week.

ABPM placement may be performed at home by appropriately trained individuals, as detailed in the Study Manual. If a patient is unable to report to the site for an office blood pressure assessment, a substitute “remote visit blood pressure measurement” may be obtained remotely using the methods described in Section 10.2.

Recommendations for approach and monitoring of low blood pressure/hypotension and hypertensive escape are provided in Section 5.8.1 and Section 5.8.2, respectively.

6.2.1. ABPM

The ABPM must be started prior to the morning dose of oral antihypertensive medication. Consecutive (daily) use of over-the-counter NSAIDs should be avoided for at least 7 days prior to ABPM measurements.

Adequacy will be assessed for all ABPMs. If the ABPM recording is inadequate, the patient will be provided 1 opportunity to repeat the study. During the Run-in period, if the second ABPM recording is also inadequate, the patient is a run-in failure.

See further details in Section 10.2 and the 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) and should be at approximately the same time of day for each assessment; therefore, visits should be scheduled at approximately the same time of day, whenever possible. Office blood pressure must include orthostatic measurements (seated and standing).

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 should be avoided for at least 7 days prior to blood pressure measurements.

The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the Study Manual.

6.2.3. HBPM

The HBPM should be measured in the morning upon waking, prior to breakfast/caffeine or taking morning oral antihypertensive medications. HBPM is not required at times when ABPM is being assessed. The patient should be seated comfortably with the back supported and the feet flat on the floor as detailed in Section 10.2 and the Study Manual.

6.3. Pharmacodynamic Assessments

Blood samples for determination of AGT will be collected according to the Schedule of Assessments (Table 1). In addition, blood samples for determination of RAAS biomarkers (plasma renin concentration, AngI, AngII, and aldosterone) will be collected only for patients randomized to receive olmesartan as protocol-specified background antihypertensive medication. Blood samples for PD assessments must be collected before study drug administration (on days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days). Blood AGT levels will be analyzed at a regulated bioanalytical laboratory by enzyme-linked immunosorbent assay for measurement of PD effect. 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 adjust dosing of zilebesiran or guide clinical management and will not be shared with sites until after study unblinding.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of plasma 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 samples for PK analysis is in Table 2.

Plasma concentrations of zilebesiran and AS(N-1)3′ zilebesiran will be determined using a validated assay. 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,

electrocardiogram (ECG) findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination will be recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include 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). When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible. Vital signs should be measured in the seated position, after the patient has rested comfortably for approximately 10 minutes. Body temperature in degrees Celsius will be obtained via oral, tympanic, 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, or as per DMC advice.

6.5.2. Weight, Height, and Morphometrics

Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF. Height will be measured at Day 1 only. Height will be measured in centimeters. Body weight should be measured in kilograms to the first decimal point in patients wearing light clothing and without shoes.

Waist circumference and waist-to-hip-ratio will also be collected as specified in the Schedule of Assessments (Table 1) and will be recorded on the eCRF. For waist circumference and waist-to-hip ratio, patients should wear minimal clothing to ensure that the measuring tape is correctly positioned. Patients should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Hip circumference measurement should be taken around the widest portion of the buttocks. Patients are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. A stretch-resistant tape that provides a constant 100 g of tension is recommended. Measurements should be obtained with the tape positioned parallel to the floor and performed using the same procedure throughout the study.

The reading is taken to the nearest centimeter and entered in the source document. Each measurement should be repeated twice; if the measurements are within 1 cm of each other, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); if a physical examination is scheduled for a study drug dosing visit, it should be conducted prior to dosing. 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 evaluation (see the Study Manual for further details on the assessments to be performed as part of the neurological evaluation).

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit. Neurological evaluation should be performed according to the Study Manual during all symptom-directed physical examinations regardless of whether neurological symptoms have been experienced by the patient.

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, QT interval, and Fridericia-corrected QT interval will be obtained using a local machine, as specified in the Schedule of Assessments (Table 1). Patients should 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.

When ECG and blood sample collection occur at the same visit, 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, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.4. 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, or as per DMC advice, 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. Clinical laboratory assessments are listed in Table 6 and will be assessed as specified in the Schedule of Assessments (Table 1).

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. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. Consecutive (daily) use of over-the-counter NSAIDs should be avoided for at least 7 days prior to laboratory assessments. In patients randomized to receive olmesartan as the protocol-specified background antihypertensive medication, blood samples for RAAS 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. A 24-hour urine collection for sodium and creatinine will be performed at time points listed in the Schedule of Assessments (Table 1). These 24-hour collections should be obtained within 2 days before the ABPM associated with the same visit.

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	Chloride
Creatinine clearance	
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	Leukocyte esterase
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	
Fasting Lipid Panel and Glycemic Assessments (see Section 6.5.5.1)	
Lipid panel, including HDL-C, non-HDL-C, LDL-C, apolipoprotein A1, triglycerides, total cholesterol	Insulin
Fasting plasma glucose	HbA1c
Immunogenicity (see Section 6.5.5.2)	
ADA	
Pregnancy Testing/FSH Screening (see Section 6.5.5.3)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ADA=anti-drug antibodies; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=hemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; RBCs=red blood cells.

6.5.5.1. Fasting Lipid Panel and Glycemic Assessments

Blood samples for fasting plasma glucose, insulin, lipid panel (including total cholesterol, high-density lipoprotein [HDL-C], non-HDL-C, low-density lipoprotein, apolipoprotein A1, and triglycerides), and HbA1c will be collected at the time points listed in the Schedule of Assessments (Table 1). Patients are required to fast for ≥10 hours before sample collection for fasting glucose, insulin, lipid panel, and HbA1c. Samples should be collected at approximately the same time of day (±2 hours).

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 days when study drug is to be dosed) or at a time point corresponding to the time of study drug dosing (on other days) as specified in the Schedule of Assessments (Table 1). A blood sample to evaluate ADA will be collected at the ET visit, if applicable. Blood samples for ADA will be analyzed at a regulated bioanalytical laboratory.

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 child-bearing potential. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter per the Schedule of Assessments 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 discontinued from study drug but will continue to be followed for safety. Patients who become 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 will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal (see Section 5.11.1 for definition of postmenopausal state).

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 5.2.4. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 7 will be performed 1 time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 6, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for dose modification or withholding the study drug, is described in Section 5.2.4.

Table 7: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBsAb, HBc antibody IgM	Parvovirus B19 DNA - quantitative
HAV antibody IgM	HHV-6 DNA viral load - quantitative
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
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 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

Abbreviations: CT=computed tomography; DNA=deoxyribonucleic acid; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen
Note:

- All assessments will be measured in 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; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of zilebesiran.

  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.

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.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Adverse event 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 Treatment

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.

The relationship of each AE to the protocol-specified background antihypertensive medication should also be assessed by the Investigator.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, 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 treatment during the Run-in period regardless of their relationship to the study treatment through the end of study. Study treatment is defined as protocol-specified background antihypertensive medication or study drug (zilebesiran or placebo). Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before the Run-in period will be captured as medical history (see Section 6.1), while AEs that occur after study treatment, and baseline events that worsen after study treatment, 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 treatment through the end of study. 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 related. Each AE must be described in

detail: onset time and date, description of event, severity, relationship to study treatment, 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).

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 within 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 treatment.

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 treatment, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using the Investigator's best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study treatment, 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.

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 Directive 2001/20/EC, 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 (see Section 3.1), 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 on the pregnancy reporting form. 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 90 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 participant or taken by the participant that is >2× the assigned dose during a single administration and/or ≥2 doses within ½ the intended dosing interval.

The Sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor and Sponsor within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant 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 reporting instructions for overdose and other special situations 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.

Biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1). In addition to the dedicated collections for optional exploratory biomarkers (urine, plasma, serum), aliquots from each 24-hour urine collection will be archived for optional potential exploratory investigations. 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, study participants 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 database lock and study unblinding for the analysis of the primary endpoints and secondary endpoints measured at Month 3. 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

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

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

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

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

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

7.2. Statistical Methodology

All analyses will be performed within each of the 3 protocol-specified background antihypertensive medication cohorts. 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.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS)**: All randomized patients who received any amount of study drug. All by-treatment analyses based on the FAS will be according to the randomized treatment arm.
- **Safety Analysis Set**: All patients who received any amount of study drug, grouped according to the treatment actually received.
- **PK Analysis Set**: All patients who received at least 1 full dose of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.
- **PD Analysis Set**: All patients who received at least 1 full dose of study drug and who have an evaluable baseline and at least 1 evaluable post-baseline PD measurement will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized.

In general, baseline will be defined as the average of all assessments, including unscheduled assessments, between Run-in Visit 2 and prior to the first dose of study drug. Details of the definition will be specified in the SAP.

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint is the change in 24-hour mean SBP from baseline to Month 3, assessed by ABPM. The primary hypothesis of the add-on effect of zilebesiran compared to placebo in patients receiving each of 3 protocol-specified background antihypertensive medications (olmesartan, amlodipine or indapamide) will be tested separately at a 2-sided significance level of 0.05 using MMRM. The MMRM model will include change from baseline in 24-hour mean SBP assessed by ABPM at Month 3 as the response variable; treatment, time, treatment-by-time, and race (black or all other races) as fixed factors; and corresponding baseline value and screening eGFR as covariates.

7.2.5.2. Secondary Endpoints

To control the overall type I error, the following secondary endpoints will be tested in hierarchical order, only if the primary endpoint is statistically significant:

- Change in office SBP from baseline to Month 3
- Change in 24-hour mean SBP from baseline to Month 6, assessed by ABPM
- Change in office SBP from baseline to Month 6

The remaining secondary endpoints below will not be tested in the hierarchical order:

- Change in 24-hour mean DBP from baseline to Months 3 and 6, assessed by ABPM
- Change in office DBP from baseline to Months 3 and 6
- Change in daytime and nighttime mean SBP and DBP from baseline to Month 3 and Month 6, assessed by ABPM
- Change in serum AGT

Blood pressure-related secondary endpoints will be analyzed by the MMRM model similar to the primary endpoint. In addition, for change in office SBP and DBP, time-adjusted average from

Month 1 to Month 3 and from Month 1 to Month 6 will be analyzed. Change in serum AGT will be summarized descriptively.

Details of the analysis method for primary, secondary, and exploratory endpoints will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will include the evaluation of changes in levels of serum AGT and other exploratory biomarkers of the RAAS pathway. Descriptive statistics for observed levels and the relative change from baseline for all measured biomarkers will be presented for each of the postdose time points.

Statistical comparison of the biomarker levels (absolute and/or change from baseline) across treatment groups may be explored. Details of the analysis will be specified in the SAP.

Population PK/PD analysis may be conducted to evaluate the dose-response relationships for PD reduction after zilebesiran treatment. Additionally, the relationship between lowering of serum AGT and blood pressure may be explored within a modeling framework. If conducted, these analyses will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.7. Pharmacokinetic Analysis

Plasma concentrations of zilebesiran and its metabolite AS(N-1)3′ zilebesiran will be summarized using descriptive statistics.

Population PK analysis may be conducted on the PK data from this study. If conducted, the analysis methods will be described in a pharmacometrics analysis plan and results will be presented in a separate report.

7.2.8. Safety Analyses

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

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 classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term [by dose level and overall]. AEs, SAEs, related AEs, AEs leading to discontinuation of study drug, and AEs leading to death will be summarized by System Organ Class and PT for each treatment arm. By patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug. Adverse events collected during the Run-in period will be summarized.

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 post-baseline grade (or category) will be presented for

laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

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

7.2.10. Interim Analysis

The analysis of the primary endpoint and secondary endpoints measured at Month 3 will be conducted after all patients complete the Month 3 visit or withdraw from the study prior to the Month 3 visit. No formal interim analysis is planned before the analysis at Month 3.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

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, 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/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian'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 for approval before patients are enrolled under the amended protocol, and patients or their legal guardians must be re-consented 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 study participant 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 end of study 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 participants 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 CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied 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 study 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. Formula 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.

Modification of Diet in Renal Disease Formula [Levey 2009]

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

10.2. Measurement of Blood Pressure

All blood pressure measurements (office, ABPM, and HBPM) must be taken using the standardized equipment provided by the Sponsor, according to the methods described in the relevant user manuals.

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) should 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 Study Manual. Unless significant weight loss or gain occurs between visits, the patient should 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 should be used for all subsequent office blood pressure and HBPM readings. The ABPM should 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.

ABPM

The appropriately sized cuff should be placed on the correct arm following the instructions in the Study Manual. Consecutive (daily) use of over-the-counter NSAIDs should be avoided for at least 7 days prior to ABPM measurements. ABPM should be started prior to the morning dose of antihypertensive medication. All ABPM collections must be in the outpatient/ambulatory state. ABPM recordings that are associated with dosing visits must be obtained in advance of the visit (within 7 days before the corresponding dosing visit) and the results reviewed prior to dosing.

During the 24-hour monitoring period, patients must avoid strenuous exercise but should otherwise maintain their usual level of physical activity. The ABPM is programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). While awake, the patient should hold their arm still by their side while

the device is inflating for a reading. Patients must record the timing of going to sleep, waking up, and any oral medications taken during the ABPM, and these responses must be entered into the eCRF.

After the monitoring period is complete, upload the ABPM data to receive a report with adequacy assessment. An ABPM will be considered adequate if (1) the number of successful daytime readings is ≥33, (2) the number of successful nighttime readings is ≥11, and (3) no more than 3 hours are not represented (ie, 3 sections of 60 minutes where 0 valid readings were obtained). If the ABPM recording is inadequate (either during the Run-in Period or after the second randomization), the patient will be provided 1 opportunity to repeat the study within 2 days. If the second ABPM recording is also inadequate during screening, the patient is a run-in failure.

Office Blood Pressure

Office blood pressure must be measured using the automated blood pressure device provided by the Sponsor and the arm selected during screening.

Office blood pressure should be measured early in the visit, before phlebotomy or other potentially stressful assessments. To minimize confounding by circadian changes, study visits should be scheduled for a consistent timeframe of the day. 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 should be avoided for at least 7 days prior to office blood pressure measurements.

Before measuring blood pressure, confirm that there has been no exercise or use of caffeine or nicotine- or tobacco-containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, nicotine patches, or e-cigarettes) within the last 30 minutes. If necessary, delay blood pressure assessment to meet these requirements. Because a full bladder can impact blood pressure measurements, ask the patient to use the bathroom before the assessment.

All office blood pressure assessments will include both seated and standing measurements.

Seated Office Blood Pressure Measurement: For seated measurements, the patient should be in a comfortable resting position in a chair with their back supported and their feet flat on the floor.

- Place the appropriately sized cuff on the correct arm with no clothing between the patient's arm and the cuff and with the midpoint of the bladder length positioned over the brachial artery (located by palpation). The arm should be supported on an armrest or table with mid-cuff at heart level and the palm facing the ceiling.
- Follow the Study Manual to initiate the automated blood pressure device's seated measurement protocol. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.
- During the device's seated measurement protocol, the patient should remain at rest without distraction (avoid mobile phones). The following script may be used: "The

blood pressure device works best when you are at rest and without any distraction, so the staff will avoid interacting with you during this assessment. This assessment will include a 5-minute period of rest, followed by about 5 minutes of the device inflating to measure your blood pressure".

Standing Office Blood Pressure Measurement: A standing measurement should be obtained immediately after collection of the seated measurements.

- Being careful to maintain the cuff's position, ask the patient to stand with the cuffed arm bent slightly and the hand of the cuffed arm supported at heart level.
- Measure standing blood pressure 1 minute after standing using the automated blood pressure device's single measurement protocol.
- After the standing measurement, ask the patient if they experienced dizziness or light-headedness when standing and record their response.

If a patient is unable to report to the site for an office blood pressure assessment, a substitute "remote visit blood pressure measurement" may be obtained remotely by a visiting nurse or other appropriately trained personnel. If a home visit is not possible, a "remote visit blood pressure measurement" should instead be obtained using the patient's HBPM instrument under direct supervision (phone call or teleconferencing) by appropriately trained study staff, following the instructions detailed in the Study Manual. Results and the remote method used will be recorded.

HBPM

Patients should measure HBPM in the morning, prior to breakfast/caffeine or taking morning oral medications. HBPM is not required at times when ABPM is being assessed. The HBPM measurement should be obtained in a room without distractions, seated comfortably with the back supported and feet flat on the floor. The patient will initiate the automated blood pressure program on their HBPM device. This program includes a 5-minute period of rest, followed by 4 sequential blood pressure measurements at 1-minute intervals. The seated blood pressure for the visit will be defined by the average of the last 3 individual measurements.

To establish baseline, each patient must measure HBPM daily at least 1 week prior to the second randomization. If adequate baseline HBPM data are not collected during the Run-in Period, the patient is a run-in failure.

After Day 1, HBPM should be measured at least 3 times per week. Patients may select the 3 days of the week that are most convenient for their personal schedule.