



Clinical trial results:

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

Summary

EudraCT number	2021-003776-13
Trial protocol	EE LT LV
Global end of trial date	13 September 2024

Results information

Result version number	v1
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	ALN-AGT01-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05103332
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, MA, United States, 02142
Public contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the add-on effect of zilebesiran on systolic blood pressure (SBP) in subjects with hypertension as assessed by ambulatory blood pressure monitoring (ABPM) at Month 3. Data under 'Population of Trial Subjects' (Trial Country and Age Range) are reported for the modified full analysis set (mFAS). mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	14 January 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United Kingdom: 58
Country: Number of subjects enrolled	United States: 531
Worldwide total number of subjects	658
EEA total number of subjects	30

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	444
From 65 to 84 years	214
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

663 eligible subjects were randomized to receive zilebesiran/placebo after run-in with background antihypertensive medication, with an option to receive zilebesiran in OLE. The SFU period is presented before OLE period as EudraCT does not allow the number of subjects in a subsequent period/s to exceed the number who completed the previous period.

Pre-assignment

Screening details:

Before Amendment 3 (A3) subjects completing DB could join a separate OLE study. Those completing DB before OLE study availability entered OLE in this study. Others ineligible/discontinuing DB entered SFU. With A3, OLE was closed & OLE study was canceled. Ongoing DB subjects entered SFU; those in OLE transitioned to SFU. mFAS used for DB period.

Period 1

Period 1 title	Double-Blind Period (6 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The Sponsor was also blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	DB Period: Placebo (Add-on to Indapamide)

Arm description:

Subjects were randomized to receive placebo matched to zilebesiran, as a subcutaneous (SC) injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran matching placebo, SC injection, on Day 1 of a 6-month double-blind treatment period as an add-on to indapamide.

Arm title	DB Period: Zilebesiran (Add-on to Indapamide)
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Arm description:

Subjects were randomized to receive zilebesiran, 600 milligrams (mg), as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran on Day 1 of a 6-month double-blind treatment period as add-on to indapamide.

Arm title	DB Period: Placebo (Add-on to Amlodipine)
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Arm description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran matching placebo, SC injection, on Day 1 of a 6-month double-blind treatment period as an add-on to amlodipine.

Arm title	DB Period: Zilebesiran (Add-on to Amlodipine)
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Arm description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran, SC injection, on Day 1 of a 6-month double-blind treatment period as an add-on to amlodipine.

Arm title	DB Period: Placebo (Add-on to Olmesartan)
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Arm description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran matching placebo, SC injection, on Day 1 of a 6-month double-blind treatment period as an add-on to olmesartan.

Arm title	DB Period: Zilebesiran (Add-on to Olmesartan)
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Arm description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional

oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received zilebesiran, SC injection, on Day 1 of a 6-month double-blind treatment period as an add-on to olmesartan.

Number of subjects in period 1	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)	DB Period: Placebo (Add-on to Amlodipine)
Started	64	63	120
Completed	63	59	114
Not completed	1	4	6
Physician decision	-	-	-
Lost to follow-up	-	2	1
Subject Stopped Participation in the Study	1	2	5

Number of subjects in period 1	DB Period: Zilebesiran (Add-on to Amlodipine)	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)
Started	118	146	147
Completed	115	143	139
Not completed	3	3	8
Physician decision	1	-	-
Lost to follow-up	-	-	2
Subject Stopped Participation in the Study	2	3	6

Period 2

Period 2 title	Safety Follow-up (SFU) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
Arm description:	
Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.	
Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
Started	63	59	114
Completed	57	55	106
Not completed	6	4	8
Adverse event, serious fatal	-	-	1
Physician decision	-	-	-
Reason Not Specified	-	-	1
Lost to follow-up	2	1	5
Subject Stopped Participation in the Study	4	3	1

Number of subjects in period 2	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
Started	115	143	139
Completed	104	133	126
Not completed	11	10	13
Adverse event, serious fatal	-	-	1
Physician decision	-	-	1
Reason Not Specified	1	-	2
Lost to follow-up	3	4	4
Subject Stopped Participation in the Study	7	6	5

Period 3

Period 3 title	Open-label Extension (OLE) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]

Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Arm type	Experimental
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Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received placebo during the DB period, received zilebesiran, 600 mg SC, q6M.

Arm title	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]
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Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received zilebesiran during the DB period continued receiving zilebesiran, 600 mg SC, q6M.

Arm title	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
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Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received placebo during the DB period, received zilebesiran, 600 mg SC, q6M.

Arm title	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]
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Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received zilebesiran during the DB period continued receiving zilebesiran, 600 mg SC, q6M.

Arm title	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]
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Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was

available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received placebo during the DB period, received zilebesiran, 600 mg SC, q6M.

Arm title	Post DB:Zilbesiran(DB) to Zilebesiran(OLE)/to SFU [Olmesartan]
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Arm description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Arm type	Experimental
Investigational medicinal product name	Zilebesiran
Investigational medicinal product code	ALN-AGT01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects who received zilebesiran during the DB period continued receiving zilebesiran, 600 mg SC, q6M.

Number of subjects in period 3^[1]	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
Started	26	30	48
Completed	23	29	47
Not completed	3	1	1
Physician decision	-	-	-
Reason Not Specified	3	1	-
Adverse Events	-	-	-
Lost to follow-up	-	-	1

Number of subjects in period 3^[1]	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]	Post DB:Zilbesiran(DB) to Zilebesiran(OLE)/to SFU [Olmesartan]
Started	44	66	60
Completed	42	63	56
Not completed	2	3	4
Physician decision	-	-	1
Reason Not Specified	2	2	3
Adverse Events	-	1	-

Lost to follow-up	-	-	-
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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Upon implementation of Amendment 3, all participants who had completed the DB period entered the SFU period, and those in the OLE the period did not receive any additional study drug in OLE and entered the SFU period.

Baseline characteristics

Reporting groups

Reporting group title	DB Period: Placebo (Add-on to Indapamide)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a subcutaneous (SC) injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Indapamide)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 milligrams (mg), as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Placebo (Add-on to Amlodipine)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Amlodipine)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Placebo (Add-on to Olmesartan)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Olmesartan)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)	DB Period: Placebo (Add-on to Amlodipine)
Number of subjects	64	63	120
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60.6 ± 10.2	57.9 ± 10.7	58.4 ± 9.8
Gender categorical Units: Subjects			
Female	25	30	50

Male	39	33	70
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Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	28	27	27
Not Hispanic or Latino	36	35	93
Unknown or Not Reported	0	1	0
Race			
Units: Subjects			
Asian	0	4	4
Black or African American	14	16	41
White	48	41	74
Native Hawaiian or Other Pacific Islander	0	1	0
Multiple	0	0	0
Other	1	1	0
Not Reported	1	0	1
24-hour Mean Systolic Blood Pressure (SBP) Assessed by Ambulatory Blood Pressure Monitoring (ABPM)			
SBP assessed by ABPM at baseline is reported here. 24-hour ABPM device was programmed to take readings every 20 minutes during day(6 am-9:59 pm) & every 30 minutes during night(10 pm-5:59 am). ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented(3 sections of 60 minutes with 0 valid readings). To summarize 24-hour ABPM, hourly adjusted mean was calculated. Hourly adjusted mean was average blood pressure(BP) for each hour of the day. 24-hour mean was average of the hourly means.			
Units: millimeter of mercury (mmHg)			
arithmetic mean	143.2	143.4	142.6
standard deviation	± 8.4	± 8.5	± 8.2

Reporting group values	DB Period: Zilebesiran (Add-on to Amlodipine)	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects	118	146	147
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	57.6	57.7	59.3
standard deviation	± 10.2	± 10.6	± 10.4
Gender categorical			
Units: Subjects			
Female	53	64	60
Male	65	82	87
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	37	47	59
Not Hispanic or Latino	81	98	88
Unknown or Not Reported	0	1	0
Race			
Units: Subjects			

Asian	8	13	3
Black or African American	39	39	38
White	71	93	106
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple	0	1	0
Other	0	0	0
Not Reported	0	0	0
24-hour Mean Systolic Blood Pressure (SBP) Assessed by Ambulatory Blood Pressure Monitoring (ABPM)			
SBP assessed by ABPM at baseline is reported here. 24-hour ABPM device was programmed to take readings every 20 minutes during day(6 am-9:59 pm) & every 30 minutes during night(10 pm-5:59 am). ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented(3 sections of 60 minutes with 0 valid readings). To summarize 24-hour ABPM, hourly adjusted mean was calculated. Hourly adjusted mean was average blood pressure(BP) for each hour of the day. 24-hour mean was average of the hourly means.			
Units: millimeter of mercury (mmHg)			
arithmetic mean	143.3	144.2	143.6
standard deviation	± 7.8	± 8.3	± 8.2

Reporting group values	Total		
Number of subjects	658		
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	282		
Male	376		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	225		
Not Hispanic or Latino	431		
Unknown or Not Reported	2		
Race			
Units: Subjects			
Asian	32		
Black or African American	187		
White	433		
Native Hawaiian or Other Pacific Islander	1		
Multiple	1		
Other	2		
Not Reported	2		
24-hour Mean Systolic Blood Pressure (SBP) Assessed by Ambulatory Blood Pressure Monitoring (ABPM)			
SBP assessed by ABPM at baseline is reported here. 24-hour ABPM device was programmed to take readings every 20 minutes during day(6 am-9:59 pm) & every 30 minutes during night(10 pm-5:59			

am). ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). To summarize 24-hour ABPM, hourly adjusted mean was calculated. Hourly adjusted mean was average blood pressure (BP) for each hour of the day. 24-hour mean was average of the hourly means.

Units: millimeter of mercury (mmHg)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	DB Period: Placebo (Add-on to Indapamide)
Reporting group description: Subjects were randomized to receive placebo matched to zilebesiran, as a subcutaneous (SC) injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB Period: Zilebesiran (Add-on to Indapamide)
Reporting group description: Subjects were randomized to receive zilebesiran, 600 milligrams (mg), as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB Period: Placebo (Add-on to Amlodipine)
Reporting group description: Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB Period: Zilebesiran (Add-on to Amlodipine)
Reporting group description: Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB Period: Placebo (Add-on to Olmesartan)
Reporting group description: Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB Period: Zilebesiran (Add-on to Olmesartan)
Reporting group description: Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.	
Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]
Reporting group description: Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period. Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]
Reporting group description: Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period. Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.	
Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
Reporting group description: Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period. Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period	

directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Reporting group title	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Reporting group title	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Reporting group title	Post DB:Zilbesiran(DB) to Zilebesiran(OLE)/to SFU [Olmesartan]
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Reporting group description:

Prior to Amendment 3, participants who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Subject analysis set title	Zilebesiran (Add-on to Olmesartan) - Actual Treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Primary: Amlodipine: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data

End point title	Amlodipine: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data ^[1]
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End point description:

24-hour (h) ABPM device was programmed to take readings every 20 minutes during day (6 am- 9:59 pm) & every 30 minutes during night (10 pm-5:59 am). ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was the average BP for each hour of the day. 24-hour mean=average of the hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy used for intercurrent event of using antihypertensive escape medication, i.e., data for SBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored. mFAS=all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed=number of subjects with data available for analysis at Month 3.

End point type	Primary
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End point timeframe:

Baseline and Month 3

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: mmHg				
least squares mean (standard error)	-0.7 (\pm 1.14)	-10.5 (\pm 1.15)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort & handle primary & key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value < 0.05 . Data for SBP, assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Amlodipine) v DB Period: Zilebesiran (Add-on to Amlodipine)
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Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001 ^[3]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	-6.6
Variability estimate	Standard error of the mean
Dispersion value	1.61

Notes:

[2] - LS Mean Difference between zilebesiran (add on to amlodipine) and placebo (add on to amlodipine), 95% CI was calculated using MMRM model.

[3] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. Unstructured covariance matrix was used.

Primary: Indapamide: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data

End point title	Indapamide: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data ^[4]
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End point description:

24-hour (h) ABPM device was programmed to take readings every 20 minutes during day (6 am- 9:59 pm) & every 30 minutes during night (10 pm-5:59 am). ABPM was considered adequate if: number of successful daytime readings were ≥33; number of successful nighttime readings were ≥11; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was the average BP for each hour of the day. 24-hour mean=average of the hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy used for intercurrent event of using antihypertensive escape medication, i.e., data for SBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored. mFAS=all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed=number of subjects with data available for analysis at Month 3.

End point type	Primary
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End point timeframe:

Baseline and Month 3

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: mmHg				
least squares mean (standard error)	-3.7 (± 1.56)	-15.7 (± 1.60)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
Statistical analysis description:	
A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort & handle primary & key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value < 0.05. Data for SBP, assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored for this endpoint.	
Comparison groups	DB Period: Placebo (Add-on to Indapamide) v DB Period: Zilebesiran (Add-on to Indapamide)
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001 ^[6]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	-7.6
Variability estimate	Standard error of the mean
Dispersion value	2.24

Notes:

[5] - LS Mean Difference between zilebesiran (add on to indapamide) and placebo (add on to indapamide), 95% CI was calculated using MMRM model.

[6] - MMRM: Fixed factors: treatment, visit, treatment-by-visit interaction, race (black/all other races); Covariates: Baseline (BA) 24-hour mean SBP using ABPM & BA estimated glomerular filtration rate (eGFR). Unstructured covariance matrix was used.

Primary: Olmesartan: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data

End point title	Olmesartan: Change From Baseline at Month 3 in 24-hour Mean SBP Assessed by ABPM - Censored Data ^[7]
End point description:	
24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am- 9:59 pm) & every 30 minutes during night(10 pm-5:59 am). ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was the average BP for each hour of the day. 24-hour mean=average of the hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy was used for intercurrent event of using antihypertensive escape medication, i.e., data for SBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored. mFAS=all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed=number of subjects with data available for analysis at Month 3.	
End point type	Primary

End point timeframe:

Baseline and Month 3

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	115		
Units: mmHg				
least squares mean (standard error)	-3.2 (\pm 1.34)	-7.7 (\pm 1.33)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort & handle primary & key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value < 0.05. Data for SBP, assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Olmesartan) v DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.0183 ^[9]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	-0.8
Variability estimate	Standard error of the mean
Dispersion value	1.89

Notes:

[8] - LS Mean Difference between zilebesiran (add on to olmesartan) and placebo (add on to olmesartan), 95% CI was calculated using MMRM model.

[9] - MMRM: Fixed factors: treatment, visit, treatment-by-visit interaction, race (black/all other races); Covariates: Baseline (BA) 24-hour mean SBP using ABPM & BA estimated glomerular filtration rate (eGFR). Unstructured covariance matrix was used.

Secondary: Indapamide: Change From Baseline at Month 3 in Office SBP - Censored Data

End point title	Indapamide: Change From Baseline at Month 3 in Office SBP - Censored Data ^[10]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	58		
Units: mmHg				
least squares mean (standard error)	-0.8 (± 1.55)	-19.3 (± 1.52)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value <0.05 . Data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Indapamide) v DB Period: Zilebesiran (Add-on to Indapamide)
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	< 0.0001 ^[12]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	-14.2
Variability estimate	Standard error of the mean
Dispersion value	2.17

Notes:

[11] - LS Mean Difference between zilebesiran (add on to indapamide) and placebo (add on to indapamide), 95% CI was calculated using MMRM model.

[12] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Indapamide: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean SBP, Assessed by ABPM - All Collected Data

End point title	Indapamide: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean SBP, Assessed by ABPM - All Collected Data ^[13]
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End point description:

Time-adjusted change was defined as the area under the curve (AUC) of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for SBP assessed by ABPM, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: mmHg				
least squares mean (standard error)	-4.6 (± 1.30)	-15.6 (± 1.35)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for SBP assessed by ABPM, were included in the analysis for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Indapamide) v DB Period: Zilebesiran (Add-on to Indapamide)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	< 0.0001 ^[15]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	-7.3
Variability estimate	Standard error of the mean
Dispersion value	1.88

Notes:

[14] - LS Mean Difference between zilebesiran (add on to indapamide) and placebo (add on to indapamide), 95% CI was calculated using MMRM model.

[15] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Indapamide: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data

End point title	Indapamide: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data ^[16]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: mmHg				
least squares mean (standard error)	-4.5 (\pm 1.16)	-18.1 (\pm 1.18)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for office SBP were included in the analysis for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Indapamide) v DB Period: Zilebesiran (Add-on to Indapamide)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	< 0.0001 ^[18]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-13.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.9
upper limit	-10.3
Variability estimate	Standard error of the mean
Dispersion value	1.66

Notes:

[17] - LS Mean Difference between zilebesiran (add on to indapamide) and placebo (add on to indapamide), 95% CI was calculated using MMRM model.

[18] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Indapamide: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline \geq 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6

End point title	Indapamide: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline \geq 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6 ^[19]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). An ABPM was considered adequate if: 1. the number of successful daytime readings were \geq 33; 2. the number of successful nighttime readings were \geq 11; 3. no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). To summarize the 24-hour ABPM, the hourly adjusted mean was calculated. Hourly adjusted mean was the average of BP for each hour of the day. The 24-hour mean was average of the hourly means. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Month 6

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: percentage of subjects				
number (not applicable)	14.0	64.2		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous

endpoint was statistically significant at nominal
p-value < 0.05.

Comparison groups	DB Period: Placebo (Add-on to Indapamide) v DB Period: Zilebesiran (Add-on to Indapamide)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.61
upper limit	33.29

Notes:

[20] - Logistic regression model included treatment and race (black or all other races) as factors and baseline 24-hour mean SBP and baseline eGFR as covariates.

Secondary: Indapamide: Change From Baseline at Month 3 in 24-hour Mean Diastolic Blood Pressure (DBP), Assessed by ABPM - Censored Data

End point title	Indapamide: Change From Baseline at Month 3 in 24-hour Mean Diastolic Blood Pressure (DBP), Assessed by ABPM - Censored Data ^[21]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥33; number of successful nighttime readings were ≥11; no more than 3 hours are not represented (i.e., 3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was average BP for each hour of the day. 24-hour mean=average of the hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy was used for intercurrent event of using antihypertensive escape medication, i.e., data for DBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored. mFAS=randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed=number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: mmHg				
least squares mean (standard error)	-1.3 (± 0.87)	-9.1 (± 0.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Change From Baseline at Month 3 in Office DBP - Censored Data

End point title	Indapamide: Change From Baseline at Month 3 in Office DBP - Censored Data ^[22]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office DBP assessed while subjects were on and within 2 weeks after stopping any escape medication was censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	58		
Units: mmHg				
least squares mean (standard error)	-0.2 (± 1.03)	-10.5 (± 1.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data

End point title	Indapamide: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data ^[23]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for SBP and DBP, assessed using ABPM, while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-2.5 (± 1.22)	-15.4 (± 1.26)		
24-hour Mean DBP	-0.9 (± 0.76)	-8.7 (± 0.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data

End point title	Indapamide: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data ^[24]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (i.e., 3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was the average BP for each hour of the day. The 24-hour mean was average of the hourly means. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication i.e., all collected data for SBP and DBP assessed by ABPM are included in the analysis. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analyzed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-5.8 (± 1.68)	-16.1 (± 1.74)		

24-hour Mean DBP	-3.2 (\pm 1.07)	-8.0 (\pm 1.11)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data

End point title	Indapamide: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data ^[25]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP and DBP, while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	58		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-2.5 (\pm 1.35)	-17.2 (\pm 1.34)		
Office DBP	-0.7 (\pm 0.78)	-9.2 (\pm 0.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data

End point title	Indapamide: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data ^[26]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for

analysis. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP and DBP, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-7.2 (± 1.82)	-15.5 (± 1.84)		
Office DBP	-3.6 (± 1.13)	-7.8 (± 1.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All Collected Data

End point title	Indapamide: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All Collected Data ^[27]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for DBP assessed by ABPM were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: mmHg				
least squares mean (standard error)	-2.3 (± 0.77)	-8.5 (± 0.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data

End point title	Indapamide: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data ^[28]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office DBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	58		
Units: mmHg				
least squares mean (standard error)	-2.0 (± 0.67)	-9.5 (± 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data

End point title	Indapamide: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data ^[29]
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End point description:

ABPM device was programmed to take readings every 20 minutes during day (6 am- 9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). LS mean & SE were calculated using a MMRM approach. Treatment policy strategy was used for intercurrent event of using antihypertensive escape medication i.e., all collected data for daytime & nighttime SBP & DBP, assessed by ABPM, were included in analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to randomized treatment arm. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, and Month (M) 2, 3 and 6

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: mmHg				
least squares mean (standard error)				
Change in Daytime Mean SBP at M2 (n=61,54)	-1.8 (\pm 1.54)	-15.9 (\pm 1.63)		
Change in Daytime Mean SBP at M3 (n=61,54)	-5.3 (\pm 1.59)	-15.9 (\pm 1.68)		
Change in Daytime Mean SBP at M6 (n=57,53)	-6.5 (\pm 1.64)	-16.4 (\pm 1.69)		
Change in Nighttime Mean SBP at M2 (n=61,54)	-0.5 (\pm 1.44)	-13.5 (\pm 1.53)		
Change in Nighttime Mean SBP at M3 (n=61,54)	-2.9 (\pm 1.94)	-14.2 (\pm 2.05)		
Change in Nighttime Mean SBP at M6 (n=57,53)	-4.3 (\pm 2.07)	-15.2 (\pm 2.14)		
Change in Daytime Mean DBP at M2 (n=61,54)	-0.6 (\pm 0.95)	-8.6 (\pm 1.01)		
Change in Daytime Mean DBP at M3 (n=61,54)	-2.6 (\pm 0.91)	-8.7 (\pm 0.96)		
Change in Daytime Mean DBP at M6 (n=57,53)	-3.7 (\pm 1.09)	-7.7 (\pm 1.13)		
Change in Nighttime Mean DBP at M2 (n=61,54)	-0.4 (\pm 1.03)	-8.1 (\pm 1.10)		
Change in Nighttime Mean DBP at M3 (n=61,54)	-0.9 (\pm 1.12)	-8.6 (\pm 1.18)		
Change in Nighttime Mean DBP at M6 (n=57,53)	-1.8 (\pm 1.24)	-8.7 (\pm 1.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Indapamide: Percent Change From Baseline in Serum Angiotensinogen (AGT)

End point title	Indapamide: Percent Change From Baseline in Serum Angiotensinogen (AGT) ^[30]
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End point description:

Modified Pharmacodynamic (PD) Analysis Set included all subjects who received at least 1 full dose of study drug. All by-treatment analyses based on the Modified PD Analysis Set were grouped according to the treatment actually received. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, Week 2 and Months 1, 2, 3, 4, 5 and 6

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Indapamide arms.

End point values	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change at Week 2 (n=62,60)	6.37 (± 29.27)	-91.99 (± 17.89)		
Percent Change at Month 1 (n=61,61)	1.90 (± 26.11)	-92.48 (± 28.49)		
Percent Change at Month 2 (n=61,60)	4.34 (± 32.24)	-95.50 (± 15.91)		
Percent Change at Month 3 (n=61,60)	4.86 (± 28.19)	-94.80 (± 17.89)		
Percent Change at Month 4 (n=61,59)	1.81 (± 30.86)	-92.28 (± 21.64)		
Percent Change at Month 5 (n=60,58)	1.23 (± 26.19)	-93.08 (± 17.07)		
Percent Change at Month 6 (n=59,56)	4.81 (± 26.12)	-91.92 (± 16.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Change From Baseline at Month 3 in Office SBP - Censored Data

End point title	Amlodipine: Change From Baseline at Month 3 in Office SBP - Censored Data ^[31]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this

endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
End point timeframe:	
Baseline and Month 3	

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: mmHg				
least squares mean (standard error)	-1.4 (\pm 1.20)	-11.5 (\pm 1.16)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value <0.05 . Data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Amlodipine) v DB Period: Zilebesiran (Add-on to Amlodipine)
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	< 0.0001 ^[33]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-6.9
Variability estimate	Standard error of the mean
Dispersion value	1.67

Notes:

[32] - LS Mean Difference between zilebesiran (add on to amlodipine) and placebo (add on to amlodipine), 95% CI was calculated using MMRM model.

[33] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Amlodipine: Time-adjusted Change From Baseline Through Month 6 in

24-hour Mean SBP, Assessed by ABPM - All Collected Data

End point title	Amlodipine: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean SBP, Assessed by ABPM - All Collected Data ^[34]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for SBP assessed by ABPM, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analyzed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	103		
Units: mmHg				
least squares mean (standard deviation)	-1.8 (± 0.95)	-9.7 (± 0.97)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for SBP assessed by ABPM, were included in the analysis for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Amlodipine) v DB Period: Zilebesiran (Add-on to Amlodipine)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	< 0.0001 ^[36]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-5.3

Variability estimate	Standard error of the mean
Dispersion value	1.36

Notes:

[35] - LS Mean Difference between zilebesiran (add on to amlodipine) and placebo (add on to amlodipine), 95% CI was calculated using MMRM model.

[36] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Amlodipine: Change From Baseline at Month 3 in 24-hour Mean DBP, Assessed by ABPM - Censored Data

End point title	Amlodipine: Change From Baseline at Month 3 in 24-hour Mean DBP, Assessed by ABPM - Censored Data ^[37]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was average BP for each hour of the day. 24-hour mean=average of hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy was used for intercurrent event of using antihypertensive escape medication i.e., data for DBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored. mFAS=all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: mmHg				
least squares mean (standard error)	-0.8 (\pm 0.63)	-6.6 (\pm 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline ≥ 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6

End point title	Amlodipine: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline ≥ 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6 ^[38]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during the day (6 am-9:59 pm) and every 30 minutes during the night (10 pm-5:59 am). An ABPM was considered adequate if:

number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). To summarize the 24-hour ABPM, the hourly adjusted mean was calculated. Hourly adjusted mean (for summarizing 24h ABPM) was the average of BP for each hour of the day. The 24-hour mean was average of the hourly means. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Month 6

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	103		
Units: percentage of subjects				
number (not applicable)	13.7	39.8		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal $p\text{-value} < 0.05$.

Comparison groups	DB Period: Placebo (Add-on to Amlodipine) v DB Period: Zilebesiran (Add-on to Amlodipine)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.43
upper limit	10.61

Notes:

[39] - Logistic regression model included treatment and race (black or all other races) as factors and baseline 24-hour mean SBP and baseline eGFR as covariates.

Secondary: Amlodipine: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data

End point title	Amlodipine: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data ^[40]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	111		
Units: mmHg				
least squares mean (standard error)	-2.9 (± 0.82)	-11.5 (± 0.82)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for office SBP were included in the analysis for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Amlodipine) v DB Period: Zilebesiran (Add-on to Amlodipine)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	< 0.0001 ^[42]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	-6.3
Variability estimate	Standard error of the mean
Dispersion value	1.16

Notes:

[41] - LS Mean Difference between zilebesiran (add on to amlodipine) and placebo (add on to amlodipine), 95% CI was calculated using MMRM model.

[42] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Amlodipine: Change From Baseline at Month 3 in Office DBP - Censored Data

End point title	Amlodipine: Change From Baseline at Month 3 in Office DBP - Censored Data ^[43]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office DBP assessed while subjects were on and within 2 weeks after stopping any escape medication was censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: mmHg				
least squares mean (standard error)	-1.2 (± 0.84)	-6.2 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data

End point title	Amlodipine: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data ^[44]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP and DBP, while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	112		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-1.4 (± 0.95)	-11.3 (± 0.96)		
Office DBP	-0.6 (± 0.60)	-6.1 (± 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data

End point title	Amlodipine: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data ^[45]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for SBP and DBP, assessed using ABPM, while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-0.9 (± 0.99)	-9.9 (± 1.00)		
24-hour Mean DBP	-0.7 (± 0.56)	-6.4 (± 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data

End point title	Amlodipine: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data ^[46]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was the average BP for each hour of the day. The 24-hour mean was average of the hourly means. LS mean & SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication i.e., all collected data for SBP and DBP assessed by ABPM are included in the analysis. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	103		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-3.0 (\pm 1.26)	-9.0 (\pm 1.26)		
24-hour Mean DBP	-1.6 (\pm 0.68)	-5.7 (\pm 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data

End point title	Amlodipine: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data ^[47]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP and DBP, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	111		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-5.8 (± 1.12)	-12.6 (± 1.13)		
Office DBP	-3.5 (± 0.74)	-6.7 (± 0.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All Collected Data

End point title	Amlodipine: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All Collected Data ^[48]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for DBP assessed by ABPM were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	103		
Units: mmHg				
least squares mean (standard error)	-1.1 (± 0.53)	-6.2 (± 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data

End point title	Amlodipine: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data ^[49]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office DBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	111		
Units: mmHg				
least squares mean (standard error)	-1.4 (± 0.52)	-6.2 (± 0.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data

End point title	Amlodipine: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data ^[50]
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End point description:

ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) & every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). LS mean & SE were calculated using a MMRM approach. Treatment policy strategy was used for intercurrent event of using antihypertensive escape medication, i.e., all collected data for daytime & nighttime SBP & DBP, assessed by ABPM, were included in analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to randomized treatment arm. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, and Month 2, 3 and 6

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: mmHg				
least squares mean (standard error)				
Change in Daytime Mean SBP at M2 (n=112,108)	-2.2 (\pm 1.24)	-9.3 (\pm 1.26)		
Change in Daytime Mean SBP at M3 (n=110,101)	-1.3 (\pm 1.14)	-11.0 (\pm 1.18)		
Change in Daytime Mean SBP at M6 (n=102,103)	-3.3 (\pm 1.31)	-9.1 (\pm 1.31)		
Change in Nighttime Mean SBP at M2 (n=112,108)	0.1 (\pm 1.31)	-7.3 (\pm 1.34)		
Change in Nighttime Mean SBP at M3 (n=110,101)	0.1 (\pm 1.34)	-8.9 (\pm 1.39)		
Change in Nighttime Mean SBP at M6 (n=102,103)	-2.6 (\pm 1.48)	-8.8 (\pm 1.48)		
Change in Daytime Mean DBP at M2 (n=112,108)	-0.8 (\pm 0.70)	-6.4 (\pm 0.72)		
Change in Daytime Mean DBP at M3 (n=110,101)	-0.8 (\pm 0.66)	-7.2 (\pm 0.69)		
Change in Daytime Mean DBP at M6 (n=102,103)	-1.5 (\pm 0.74)	-5.8 (\pm 0.74)		
Change in Nighttime Mean DBP at M2 (n=112,108)	-0.4 (\pm 0.76)	-5.2 (\pm 0.77)		
Change in Nighttime Mean DBP at M3 (n=110,101)	-0.4 (\pm 0.76)	-5.6 (\pm 0.79)		
Change in Nighttime Mean DBP at M6 (n=102,103)	-1.4 (\pm 0.84)	-5.8 (\pm 0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amlodipine: Percent Change From Baseline in Serum AGT

End point title	Amlodipine: Percent Change From Baseline in Serum AGT ^[51]
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End point description:

Modified PD Analysis Set included all subjects who received at least 1 full dose of study drug. All by-treatment analyses based on the Modified PD Analysis Set were grouped according to the treatment actually received. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, Week 2 and Months 1, 2, 3, 4, 5 and 6

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Amlodipine arms.

End point values	DB Period: Placebo (Add-on to Amlodipine)	DB Period: Zilebesiran (Add-on to Amlodipine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change at Week 2 (n=116,113)	2.67 (± 22.81)	-92.80 (± 15.99)		
Percent Change at Month 1 (n=117,112)	9.62 (± 35.83)	-95.35 (± 21.36)		
Percent Change at Month 2 (n=115,111)	11.23 (± 35.17)	-97.45 (± 8.59)		
Percent Change at Month 3 (n=113,109)	12.78 (± 34.90)	-96.37 (± 11.24)		
Percent Change at Month 4 (n=112,112)	12.42 (± 41.83)	-96.52 (± 8.41)		
Percent Change at Month 5 (n=111,107)	10.81 (± 37.94)	-93.87 (± 19.20)		
Percent Change at Month 6 (n=112,109)	9.51 (± 48.05)	-94.52 (± 9.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean SBP, Assessed by ABPM - All Collected Data

End point title	Olmesartan: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean SBP, Assessed by ABPM - All Collected Data ^[52]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for SBP assessed by ABPM, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
End point timeframe:	
Baseline through Month 6	
Notes:	
[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.	

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	116		
Units: mmHg				
least squares mean (standard error)	-5.8 (± 0.99)	-7.6 (± 1.01)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
Statistical analysis description:	
A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for SBP assessed by ABPM, were included in the analysis for this endpoint.	
Comparison groups	DB Period: Placebo (Add-on to Olmesartan) v DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority ^[53]
P-value	= 0.2103 ^[54]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1.42

Notes:

[53] - LS Mean Difference between zilebesiran (add on to olmesartan) and placebo (add on to olmesartan), 95% CI was calculated using MMRM model.

[54] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline 24-hour mean SBP assessed by ABPM and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Olmesartan: Change From Baseline at Month 3 in Office SBP - Censored Data

End point title	Olmesartan: Change From Baseline at Month 3 in Office SBP -
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	121		
Units: mmHg				
least squares mean (standard error)	-2.6 (± 1.25)	-9.3 (± 1.23)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in order the endpoints are reported. Hierarchical testing sequence continued only when previous endpoint was statistically significant at nominal p-value <0.05 . Data for office SBP assessed while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Olmesartan) v DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority ^[56]
P-value	= 0.0002 ^[57]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	-3.3
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[56] - LS Mean Difference between zilebesiran (add on to olmesartan) and placebo (add on to olmesartan), 95% CI was calculated using MMRM model.

[57] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Olmesartan: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data

End point title	Olmesartan: Time-adjusted Change From Baseline Through Month 6 in Office SBP - All Collected Data ^[58]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	134		
Units: mmHg				
least squares mean (standard error)	-6.3 (± 0.81)	-10.8 (± 0.81)		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at nominal p-value < 0.05. All collected data for office SBP were included in the analysis for this endpoint.

Comparison groups	DB Period: Placebo (Add-on to Olmesartan) v DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority ^[59]
P-value	< 0.0001 ^[60]
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	-2.3
Variability estimate	Standard error of the mean
Dispersion value	1.14

Notes:

[59] - LS Mean Difference between zilebesiran (add on to olmesartan) and placebo (add on to olmesartan), 95% CI was calculated using MMRM model.

[60] - MMRM model included treatment, visit, treatment-by-visit interaction, race (black or all other races) as fixed factors, with baseline office SBP and baseline eGFR as covariates. Unstructured covariance matrix was used.

Secondary: Olmesartan: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline \geq 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6

End point title	Olmesartan: Percentage of Subjects With 24-hour Mean SBP <130 mmHg and/or Reduction From Baseline \geq 20 mmHg Assessed by ABPM Without Escape Antihypertensive Medications at Month 6 ^[61]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during the day (6 am to 9:59 pm) and every 30 minutes during the night (10 pm to 5:59 am). An ABPM was considered adequate if: 1. the number of successful daytime readings were \geq 33; 2. the number of successful nighttime readings were \geq 11; 3. no more than 3 hours are not represented (i.e., 3 sections of 60 minutes where 0 valid readings were obtained). To summarize the 24-hour ABPM, the hourly adjusted mean was calculated. Hourly adjusted mean was the average of BP for each hour of the day. The 24-hour mean was average of the hourly means. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Month 6

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	116		
Units: percentage of subjects				
number (not applicable)	17.2	25.9		

Statistical analyses

Statistical analysis title	Placebo vs Zilebesiran
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error at $\alpha=0.05$ within each cohort and handle primary and key secondary endpoints analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when the previous

endpoint was statistically significant at nominal p-value < 0.05.

Comparison groups	DB Period: Placebo (Add-on to Olmesartan) v DB Period: Zilebesiran (Add-on to Olmesartan)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123 ^[62]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	3.23

Notes:

[62] - Logistic regression model included treatment and race (black or all other races) as factors and baseline 24-hour mean SBP and baseline eGFR as covariates.

Secondary: Olmesartan: Change From Baseline at Month 3 in 24-hour Mean DBP, Assessed by ABPM - Censored Data

End point title	Olmesartan: Change From Baseline at Month 3 in 24-hour Mean DBP, Assessed by ABPM - Censored Data ^[63]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during the day (6 am-9:59 pm) & every 30 minutes during the night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥33; number of successful nighttime readings were ≥11; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). 24-hour mean=average of the hourly means. LS mean & SE were calculated using a MMRM approach. Hypothetical strategy was used for intercurrent event of using antihypertensive escape medication, i.e., data for DBP assessed using ABPM, while subjects were on & within 2 weeks after stopping any escape medication were censored for this endpoint. mFAS=all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed=number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	115		
Units: mmHg				
least squares mean (standard error)	-1.4 (± 0.78)	-3.4 (± 0.78)		

Statistical analyses

Secondary: Olmesartan: Change From Baseline at Month 3 in Office DBP - Censored Data

End point title	Olmesartan: Change From Baseline at Month 3 in Office DBP - Censored Data ^[64]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office DBP assessed while subjects were on and within 2 weeks after stopping any escape medication was censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline and Month 3

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	121		
Units: mmHg				
least squares mean (standard error)	-2.0 (± 0.86)	-5.3 (± 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data

End point title	Olmesartan: Time-adjusted Change From Baseline Through Month 3 in 24-hour Mean SBP and DBP, Assessed by ABPM - Censored Data ^[65]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for SBP and DBP, assessed using ABPM, while subjects were on and within 2 weeks after stopping any escape medication were censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	115		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-2.2 (± 1.12)	-5.3 (± 1.13)		
24-hour Mean DBP	-1.1 (± 0.63)	-2.3 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data

End point title	Olmesartan: Time-adjusted Change From Baseline in Office SBP and DBP Through Month 3 - Censored Data ^[66]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Hypothetical strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., data for office SBP and DBP, while subjects were on and within 2 weeks after stopping any escape medication was censored for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 3.

End point type	Secondary
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End point timeframe:

Baseline through Month 3

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	121		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-2.4 (± 0.99)	-7.9 (± 0.97)		
Office DBP	-1.2 (± 0.65)	-3.8 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data

End point title	Olmesartan: Change From Baseline at Month 6 in 24-hour Mean SBP and DBP, Assessed by ABPM - All Collected Data ^[67]
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End point description:

24-hour ABPM device was programmed to take readings every 20 minutes during day (6 am-9:59 pm) and every 30 minutes during night (10 pm-5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). Hourly adjusted mean (for summarizing 24h ABPM) was average BP for each hour of the day. The 24-hour mean was average of the hourly means. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication i.e., all collected data for SBP & DBP assessed by ABPM are included in the analysis. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	116		
Units: mmHg				
least squares mean (standard error)				
24-hour Mean SBP	-9.2 (\pm 1.24)	-8.3 (\pm 1.29)		
24-hour Mean DBP	-5.2 (\pm 0.73)	-4.3 (\pm 0.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All Collected Data

End point title	Olmesartan: Time-adjusted Change From Baseline Through Month 6 in 24-hour Mean DBP, Assessed by ABPM - All
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for DBP assessed by ABPM were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	116		
Units: mmHg				
least squares mean (standard error)	-3.1 (± 0.58)	-3.5 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data

End point title	Olmesartan: Change From Baseline at Month 6 in Office SBP and DBP - All Collected Data ^[69]
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End point description:

The mean office BP in the sitting position was used for the analysis. Office BP in the sitting position was collected with a set of 4 replicates. The average of the last 3 replicates was calculated and used for analysis. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office SBP and DBP, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline and Month 6

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	134		
Units: mmHg				
least squares mean (standard error)				
Office SBP	-11.9 (± 1.33)	-12.4 (± 1.34)		
Office DBP	-7.0 (± 0.76)	-7.1 (± 0.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data

End point title	Olmesartan: Change From Baseline in Daytime and Nighttime SBP and DBP by ABPM at Each Visit - All Collected Data ^[70]
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End point description:

ABPM device was programmed to take readings every 20 minutes during day (6 am to 9:59 pm) and every 30 minutes during night (10 pm to 5:59 am). An ABPM was considered adequate if: number of successful daytime readings were ≥ 33 ; number of successful nighttime readings were ≥ 11 ; and no more than 3 hours are not represented (3 sections of 60 minutes with 0 valid readings). LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for daytime and nighttime SBP and DBP, assessed by ABPM, were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, and Month 2, 3 and 6

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	147		
Units: mmHg				
least squares mean (standard error)				
Change in Daytime Mean SBP at M2 (n=132,128)	-1.0 (± 1.39)	-3.3 (± 1.41)		
Change in Daytime Mean SBP at M3 (n=133,129)	-3.7 (± 1.29)	-8.5 (± 1.31)		
Change in Daytime Mean SBP at M6 (n=128,116)	-8.8 (± 1.29)	-8.3 (± 1.34)		
Change in Nighttime Mean SBP at M2 (n=132,128)	-2.4 (± 1.53)	-2.7 (± 1.56)		

Change in Nighttime Mean SBP at M3 (n=133,129)	-5.3 (± 1.35)	-7.4 (± 1.37)		
Change in Nighttime Mean SBP at M6 (n=128,116)	-9.7 (± 1.35)	-8.4 (± 1.41)		
Change in Daytime Mean DBP at M2 (n=132,128)	-0.5 (± 0.76)	-1.2 (± 0.77)		
Change in Daytime Mean DBP at M3 (n=133,129)	-1.7 (± 0.76)	-3.9 (± 0.78)		
Change in Daytime Mean DBP at M6 (n=128,116)	-5.0 (± 0.76)	-4.3 (± 0.79)		
Change in Nighttime Mean DBP at M2 (n=132,128)	-1.3 (± 0.86)	-1.4 (± 0.87)		
Change in Nighttime Mean DBP at M3 (n=133,129)	-2.6 (± 0.86)	-3.2 (± 0.87)		
Change in Nighttime Mean DBP at M6 (n=128,116)	-5.5 (± 0.85)	-4.2 (± 0.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Olmesartan: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data

End point title	Olmesartan: Time-adjusted Change From Baseline Through Month 6 in Office DBP - All Collected Data ^[71]
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End point description:

Time-adjusted change was defined as the AUC of BP change from baseline divided by the duration of the time period. LS mean and SE were calculated using a MMRM approach. Treatment policy strategy was used for the intercurrent event of using antihypertensive escape medication, i.e., all collected data for office DBP were included in the analysis for this endpoint. The mFAS included all randomized subjects who received any amount of study drug. Analysis was grouped according to the randomized treatment arm. Subjects analysed is the number of subjects with data available for analysis at Month 6.

End point type	Secondary
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End point timeframe:

Baseline through Month 6

Notes:

[71] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	134		
Units: mmHg				
least squares mean (standard error)	-3.5 (± 0.53)	-5.8 (± 0.52)		

Statistical analyses

Secondary: Olmesartan: Percent Change From Baseline in Serum AGT

End point title	Olmesartan: Percent Change From Baseline in Serum AGT ^[72]
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End point description:

Modified PD Analysis Set included all subjects who received at least 1 full dose of study drug. All by-treatment analyses based on the Modified PD Analysis Set were grouped according to the treatment actually received. 'n' indicates the unique number of subjects out of all the assessed subjects who were evaluable for the specified category. Different subjects may have contributed data for each category.

End point type	Secondary
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End point timeframe:

Baseline, Week 2 and Months 1, 2, 3, 4, 5 and 6

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The analysis of this endpoint was intended for participants in the Olmesartan arms.

End point values	DB Period: Placebo (Add-on to Olmesartan)	Zilebesiran (Add-on to Olmesartan) - Actual Treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	144	148		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change at Week 2 (n=139,139)	8.08 (± 86.70)	-87.83 (± 35.99)		
Percent Change at Month 1 (n=143,140)	4.64 (± 28.05)	-92.61 (± 25.21)		
Percent Change at Month 2 (n=136,137)	4.87 (± 29.58)	-92.58 (± 29.50)		
Percent Change at Month 3 (n=137,136)	6.45 (± 28.36)	-92.98 (± 23.98)		
Percent Change at Month 4 (n=138,135)	4.62 (± 27.62)	-91.66 (± 25.44)		
Percent Change at Month 5 (n=139,131)	5.82 (± 31.65)	-91.14 (± 24.14)		
Percent Change at Month 6 (n=138,133)	1.93 (± 26.66)	-88.22 (± 41.42)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Period: Day 1 to Month 6; OLE Arms: First zilebesiran dose to 6 months after last dose (Placebo/Zilebesiran: Month 6 to Month 30; Zilebesiran/Zilebesiran: Day 1 to Month 30); Mortality-SFU: Up to 36 months (1 month=28 days). DB Period: mSAS.

Adverse event reporting additional description:

Per planned analysis, only TEAEs were reported for DB and overall zilebesiran exposure. All Zilebesiran Treated Set reports TEAEs for all subjects receiving zilebesiran, including subjects on zilebesiran during DB & continuing it after Month 6 & those on placebo in DB later switching to zilebesiran after Month 6.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	DB Period: Placebo (Add-on to Indapamide)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a subcutaneous (SC) injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Indapamide)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 milligrams (mg), as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to indapamide. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Placebo (Add-on to Amlodipine)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Amlodipine)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to amlodipine. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Placebo (Add-on to Olmesartan)
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Reporting group description:

Subjects were randomized to receive placebo matched to zilebesiran, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB Period: Zilebesiran (Add-on to Olmesartan)
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Reporting group description:

Subjects were randomized to receive zilebesiran, 600 mg, as a SC injection, on Day 1 of the 6-month DB treatment period as an add-on therapy to olmesartan. Starting at Month 3, additional conventional oral antihypertensives ("escape antihypertensive medications") may be added to the subject's protocol-specified background antihypertensive medication per Investigator judgement.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M.

Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Reporting group title	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with indapamide was discontinued at the start of OLE period.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Reporting group title	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with amlodipine was discontinued at the start of OLE period.

Reporting group title	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and received treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Reporting group title	DB (Zilebesiran) to OLE (Zilebesiran) [Olmesartan Cohort]
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Reporting group description:

Prior to Amendment 3, subjects who completed the DB period before a separate OLE study was available, entered the OLE period of this study and continued treatment with zilebesiran 600 mg SC q6M. Protocol-specified background antihypertensive treatment with olmesartan was discontinued at the start of OLE period.

Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and

transitioned to the SFU period.

Reporting group title	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (placebo) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Reporting group title	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
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Reporting group description:

Prior to Amendment 3, subjects who were ineligible for the OLE study or who discontinued treatment (zilebesiran) during DB period entered SFU period.

Upon implementation of Amendment 3, subjects who completed the DB period entered the SFU period directly, and those already in OLE period did not receive any additional study drug in OLE and transitioned to the SFU period.

Serious adverse events	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)	DB Period: Placebo (Add-on to Amlodipine)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	1 / 120 (0.83%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 64 (1.56%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB Period: Zilebesiran (Add-on to Amlodipine)	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 118 (2.54%)	4 / 145 (2.76%)	4 / 148 (2.70%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Erectile dysfunction			
subjects affected / exposed	0 / 118 (0.00%)	1 / 145 (0.69%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 118 (0.00%)	2 / 145 (1.38%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			

subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 118 (0.00%)	1 / 145 (0.69%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 118 (0.85%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incarcerated umbilical hernia subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis subjects affected / exposed	1 / 118 (0.85%)	0 / 145 (0.00%)	2 / 148 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Acute kidney injury subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed	0 / 118 (0.00%)	1 / 145 (0.69%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			

subjects affected / exposed	1 / 118 (0.85%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 145 (0.69%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 145 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	1 / 63 (1.59%)	1 / 48 (2.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 26 (3.85%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 26 (3.85%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 63 (1.59%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 63 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]	DB (Zilebesiran) to OLE (Zilebesiran) [Olmesartan Cohort]
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 118 (2.54%)	3 / 66 (4.55%)	7 / 148 (4.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 118 (0.00%)	1 / 66 (1.52%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 118 (0.00%)	1 / 66 (1.52%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 118 (0.00%)	1 / 66 (1.52%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 118 (0.85%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 118 (0.85%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	1 / 118 (0.85%)	0 / 66 (0.00%)	2 / 148 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 66 (1.52%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 66 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			

subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incarcerated umbilical hernia subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 6
Proctitis subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Acute kidney injury subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			

subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DB Period: Placebo (Add-on to Indapamide)	DB Period: Zilebesiran (Add-on to Indapamide)	DB Period: Placebo (Add-on to Amlodipine)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 64 (17.19%)	14 / 63 (22.22%)	21 / 120 (17.50%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 64 (12.50%)	4 / 63 (6.35%)	16 / 120 (13.33%)
occurrences (all)	9	4	16
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 64 (1.56%)	4 / 63 (6.35%)	4 / 120 (3.33%)
occurrences (all)	1	4	4
Dizziness			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	0 / 120 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 64 (0.00%)	4 / 63 (6.35%)	0 / 120 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 120 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	1 / 64 (1.56%)	2 / 63 (3.17%)	2 / 120 (1.67%)
occurrences (all)	1	2	2

Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	2 / 63 (3.17%) 3	1 / 120 (0.83%) 1
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Non-serious adverse events	DB Period: Zilebesiran (Add-on to Amlodipine)	DB Period: Placebo (Add-on to Olmesartan)	DB Period: Zilebesiran (Add-on to Olmesartan)
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 118 (22.03%)	29 / 145 (20.00%)	41 / 148 (27.70%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 6	17 / 145 (11.72%) 17	14 / 148 (9.46%) 16
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 118 (4.24%) 7	5 / 145 (3.45%) 6	4 / 148 (2.70%) 4
Dizziness subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 6	3 / 145 (2.07%) 5	11 / 148 (7.43%) 18
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	2 / 118 (1.69%) 2	1 / 145 (0.69%) 1	4 / 148 (2.70%) 4
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	0 / 118 (0.00%) 0	0 / 145 (0.00%) 0	0 / 148 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 6	3 / 145 (2.07%) 3	5 / 148 (3.38%) 5
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	4 / 118 (3.39%) 4	3 / 145 (2.07%) 3	8 / 148 (5.41%) 15

Non-serious adverse events	DB (Placebo) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Zilebesiran) to OLE (Zilebesiran) [Indapamide Cohort]	DB (Placebo) to OLE (Zilebesiran) [Amlodipine Cohort]
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Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 26 (3.85%)	19 / 63 (30.16%)	6 / 48 (12.50%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	7 / 63 (11.11%) 7	3 / 48 (6.25%) 3
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0	6 / 63 (9.52%) 6 3 / 63 (4.76%) 3	0 / 48 (0.00%) 0 0 / 48 (0.00%) 0
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	5 / 63 (7.94%) 8	0 / 48 (0.00%) 0
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0 1 / 26 (3.85%) 1	1 / 63 (1.59%) 1 3 / 63 (4.76%) 4	1 / 48 (2.08%) 1 3 / 48 (6.25%) 3
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 63 (4.76%) 5	1 / 48 (2.08%) 1

Non-serious adverse events	DB (Zilebesiran) to OLE (Zilebesiran) [Amlodipine Cohort]	DB (Placebo) to OLE (Zilebesiran) [Olmesartan Cohort]	DB (Zilebesiran) to OLE (Zilebesiran) [Olmesartan Cohort]
Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 118 (30.51%)	23 / 66 (34.85%)	51 / 148 (34.46%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	8 / 118 (6.78%) 8	6 / 66 (9.09%) 6	14 / 148 (9.46%) 19
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	6 / 118 (5.08%) 8	5 / 66 (7.58%) 6	7 / 148 (4.73%) 7
Dizziness subjects affected / exposed occurrences (all)	8 / 118 (6.78%) 9	3 / 66 (4.55%) 3	12 / 148 (8.11%) 20
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	3 / 118 (2.54%) 3	3 / 66 (4.55%) 4	7 / 148 (4.73%) 8
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	4 / 66 (6.06%) 4	5 / 148 (3.38%) 5
COVID-19 subjects affected / exposed occurrences (all)	9 / 118 (7.63%) 9	2 / 66 (3.03%) 2	8 / 148 (5.41%) 8
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	5 / 118 (4.24%) 7	4 / 66 (6.06%) 4	10 / 148 (6.76%) 18

Non-serious adverse events	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Indapamide]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Indapamide]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Amlodipine]
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 63 (0.00%) 0	0 / 63 (0.00%) 0	0 / 114 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 63 (0.00%) 0	0 / 63 (0.00%) 0	0 / 114 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 63 (0.00%) 0	0 / 63 (0.00%) 0	0 / 114 (0.00%) 0

General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 63 (0.00%)	0 / 114 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Amlodipine]	DB (Placebo) to SFU or OLE (Zilebesiran) to SFU [Olmesartan]	DB (Zilebesiran) to SFU/OLE (Zilebesiran) to SFU [Olmesartan]
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 118 (0.00%)	0 / 143 (0.00%)	0 / 148 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2022	The following changes were made as per Amendment 01: 1. Removed the requirement to consider subjects who do not establish baseline home blood pressure monitoring (HBPM) as run-in failures, and revised the frequency of HBPM measurements after randomization. 2. Removed 24-hour ambulatory blood pressure monitoring (ABPMs) at Month 18 and during the safety follow-up period. 3. Removed limitations on the allowable classes and doses of prior antihypertensive medication. 4. Increased number of clinical study centers worldwide to approximately 120. 5. Removed the exclusion criterion for being unable or unwilling to perform HBPM. 5. Defined key secondary and other secondary endpoints and modified exploratory endpoints.
22 September 2022	The following changes were made as per Amendment 02: 1. Extended the duration of the study. 2. Increased the number of subjects randomized into the Run-in period. 3. Increased the number of clinical study sites. 4. Added exclusion criterion for subjects placed in an institution on the basis of an official or court order. 5. Revised the duration of rest required before vital sign collection. 5. Added forehead scan as a method of temperature collection.
20 July 2023	The following changes were made as per Amendment 03: 1. Closed the OLE period and provided instructions for subjects to complete the study. 2. Added details on the home healthcare process. 3. Removed the reference to database lock for the Month 3 analysis. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported