Zilebesiran: KARDIA-2 Study

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The safety and efficacy of zilebesiran are currently being investigated in clinical studies and have not been evaluated by FDA or any health authority.

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SUMMARY

- Zilebesiran is an investigational subcutaneously administered RNAi therapeutic designed to target hepatic synthesis of AGT and is currently being studied for the treatment of hypertension in adults.[1]
- KARDIA-2 was a phase 2 study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients with hypertension not adequately controlled by a standard-of-care antihypertensive medication.[2]
  - At Month 3, clinically significant reductions in 24-hour mean ambulatory SBP and office SBP were observed when zilebesiran treatment was added to a standard-of-care antihypertensive medication (indapamide, amlodipine, or olmesartan).[2] A consistent treatment effect was observed across most predefined patient subgroups among the three background medication cohorts.[3]
  - AEs of hyperkalemia, hypotension, and decreased eGFR were observed in the zilebesiran add-on treatment group at a higher rate than placebo with standard-of-care antihypertensives.[2]

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STUDY DESIGN

The KARDIA-2 study (NCT05103332) was a phase 2, randomized, double-blind, placebo-controlled, multi-center study designed to evaluate the efficacy and safety of zilebesiran as an add-on therapy in patients aged 18 to 75 years with hypertension that was not adequately controlled by a standard-of-care antihypertensive medication. Participants received a single subcutaneous injection of either zilebesiran 600 mg or placebo as an add-on treatment to the following antihypertensive agents: indapamide (diuretic) 2.5 mg daily, amlodipine (CCB) 5 mg daily, or olmesartan (ARB) 40 mg daily (20 mg daily for patients with creatinine clearance ≤60 mL/min at screening enrolled outside of the US, consistent with local labeling) for the 6 month DB period.[2]

Patients eligible for the study included those with[2]:

- An office SBP at screening ≥155 mmHg and ≤180 mmHg for patients with untreated hypertension
- An office SBP at screening ≥145 mmHg and ≤180 mmHg for patients on 1-2 antihypertensive medications
- 24-hour mean SBP >130 mmHg and ≤160 mmHg by ABPM after at least 4 weeks of run-in on protocol-specified background antihypertensive medication

The primary endpoint was the change from baseline at Month 3 in 24-hour mean SBP, assessed by ABPM.[2]

Select secondary endpoints assessed include[2]:

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

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

Patient baseline characteristics across treatment arms are shown in **Table 1**.[2]

Table 1. Baseline Demographics in KARDIA-2.[2]

Baseline Characteristic	Background Medication		
	Indapamide	Amlodipine	Olmesartan
	Placebo or zilebesiran (N=127)	Placebo or zilebesiran (N=238)	Placebo or zilebesiran (N=293)
Mean age, years (SD)	59.2 (10.5)	58.0 (10.0)	58.5 (10.5)
Male, %	56.7	56.7	57.7
Dosed in the US, %	82.7	80.3	80.2
Race, %			
White	70.1	60.9	67.9
Black or African American	23.6	33.6	26.3
24-hour mean ambulatory SBP, mmHg (SD)	143.3 (8.4)	142.9 (8.0)	143.9 (8.2)
24-hour mean ambulatory SBP ≥145 mmHg, %	46.5	39.5	46.4
Mean office SBP, mmHg (SD)	144.7 (11.8)	143.5 (11.5)	145.3 (12.9)
BMI ≥30 kg/m^2, %	66.9	62.2	56.3
eGFR <60 mL/min/1.73 m^2, %	15.7	5.5	11.3
Diabetes, %	21.3	22.3	24.2

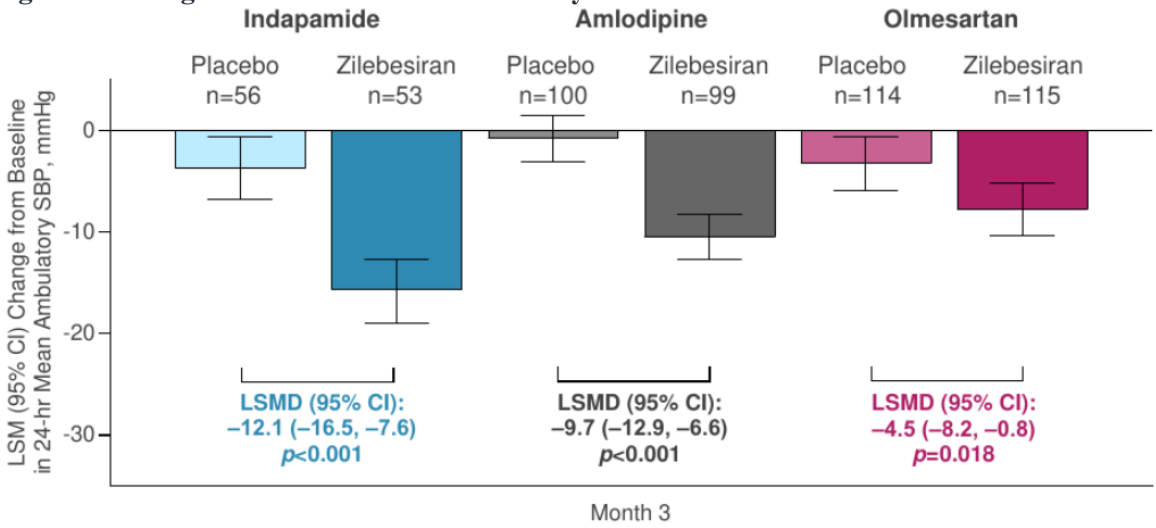
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; SD = standard deviation.

PRIMARY ENDPOINT

Change in 24-hour Mean Ambulatory SBP at Month 3

At Month 3, treatment with a single subcutaneous dose of zilebesiran 600 mg demonstrated significant reductions in 24-hour mean ambulatory SBP compared with placebo when added to indapamide, amlodipine, or olmesartan. **Figure 1** illustrates the change from baseline to Month 3 in 24-hour mean ambulatory SBP for each cohort of patients.[2]

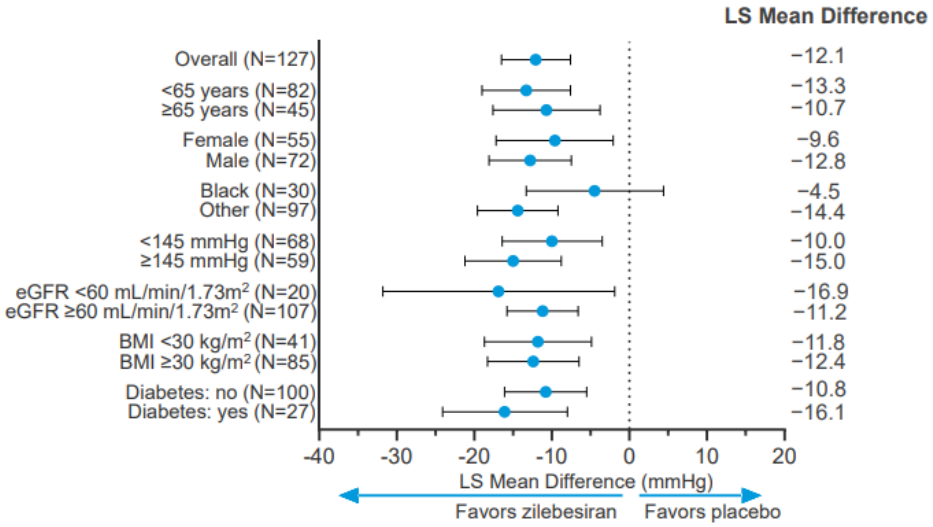
Figure 1. Change in 24-hour Mean Ambulatory SBP at Month 3.[2,a]



Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; SBP = systolic blood pressure.
[a]Ambulatory blood pressure assessed while patients were receiving or within 2 weeks of stopping any rescue medication was censored.

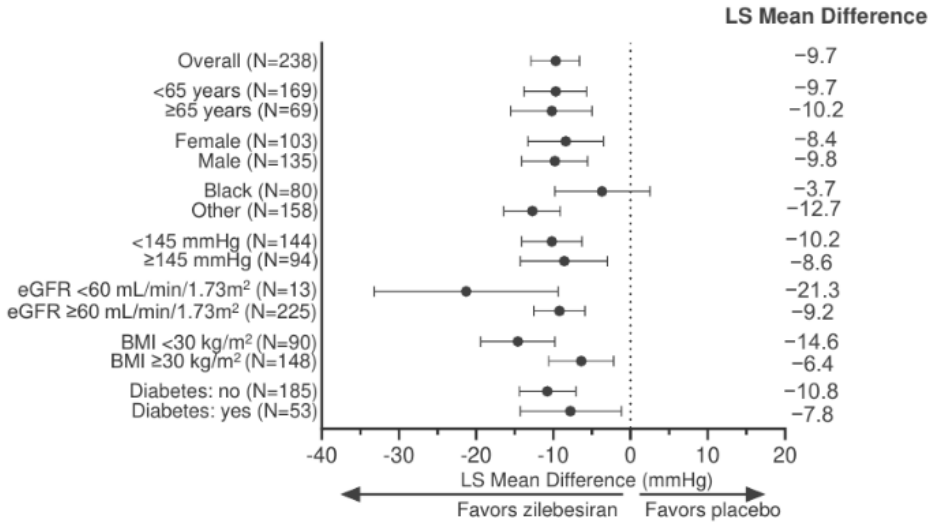
Figures 2A-2C show the change from baseline to Month 3 in 24-hour mean ambulatory SBP across predefined subgroups for each cohort.[3]

Figure 2A. Indapamide Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[3,a]



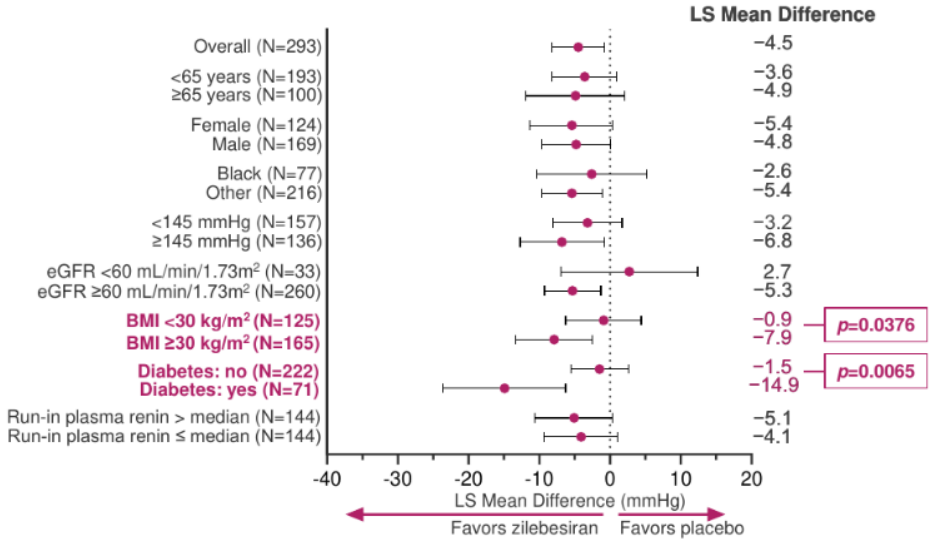
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=127.
From Saxena et al.[3]

Figure 2B. Amlodipine Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[3,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=238
From Saxena et al.[3]

Figure 2C. Olmesartan Cohort: Change in 24-hour Mean Ambulatory SBP at Month 3 Subgroup Analysis.[3,a]



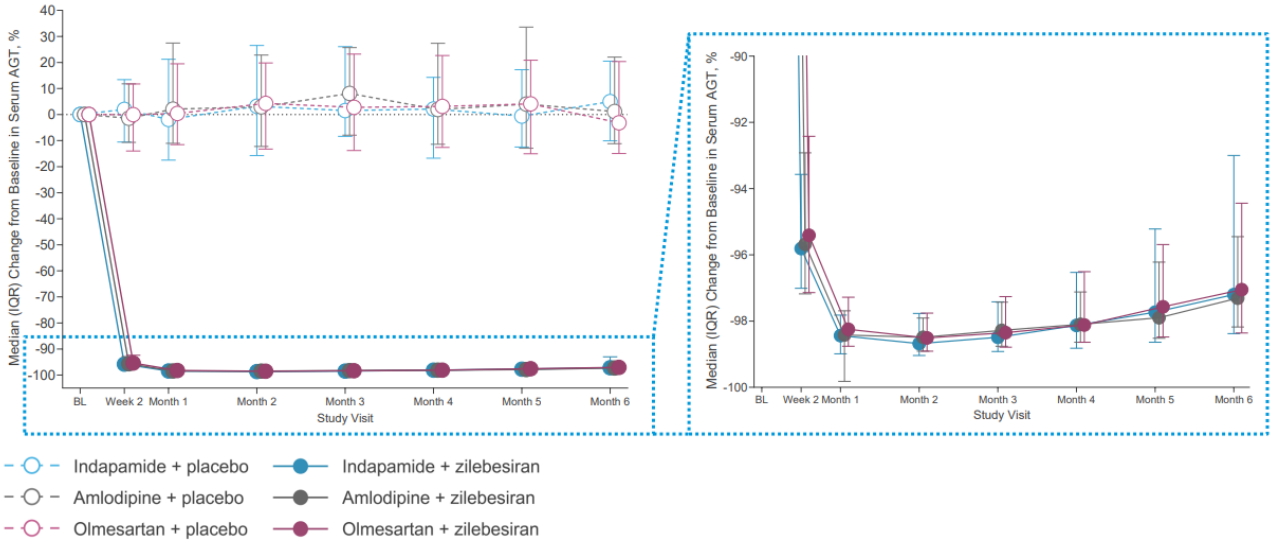
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=293
From Saxena et al.[3]

SECONDARY ENDPOINTS

Change in Serum AGT

Figure 3 shows the change in AGT from baseline to Month 6 in all cohorts. Regardless of the background medication, consistent median reductions in serum AGT >95% were observed through Month 6 in patients treated with zilebesiran.[2]

Figure 3. Change from Baseline to Month 6 in Serum AGT.[2]

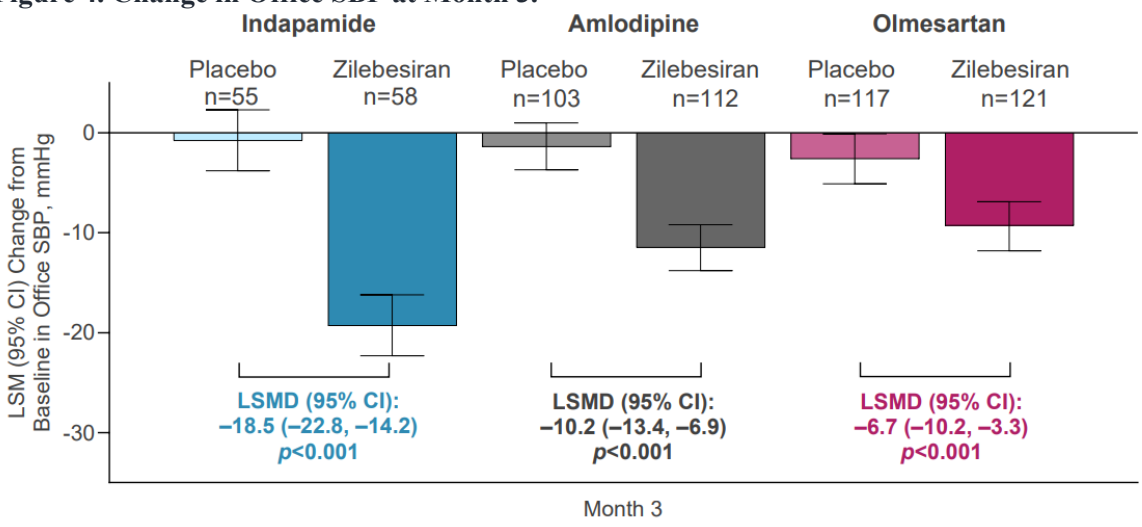


Abbreviations: AGT = angiotensinogen; BL = baseline; IQR = interquartile range.
From Bakris et al[2]

Change in Office SBP at Month 3

At Month 3, treatment with a single subcutaneous dose of zilebesiran 600 mg demonstrated significant reductions in office SBP compared with placebo when added to indapamide, amlodipine, or olmesartan. **Figure 4** shows the change from baseline to Month 3 in office SBP.[2]

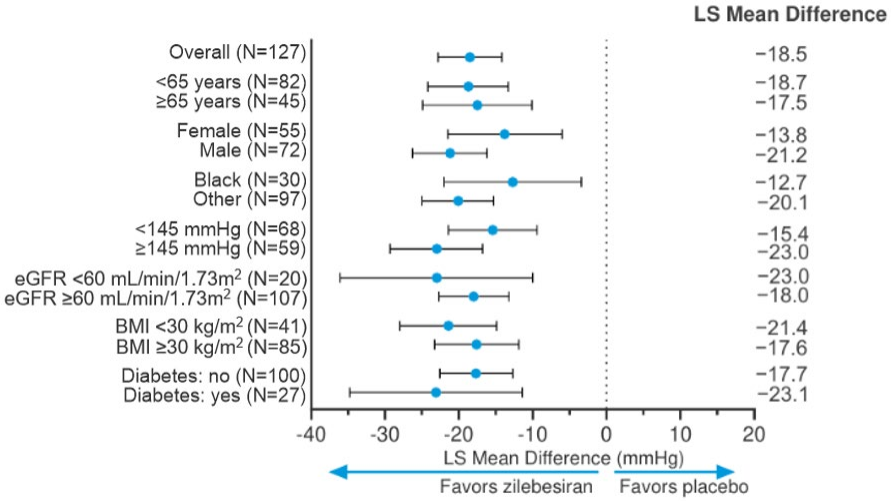
Figure 4. Change in Office SBP at Month 3.[2,a]



Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; SBP = systolic blood pressure.
[a]Office blood pressure assessed while patients were receiving, or within 2 weeks of stopping any rescue medication is censored.
From Bakris et al.[2]

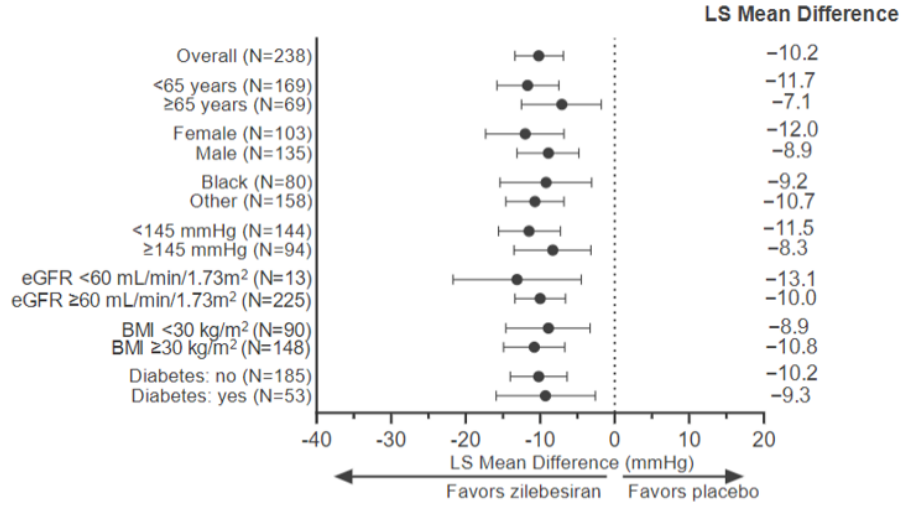
Figures 5A-5C show the change from baseline to Month 3 in office SBP across predefined subgroups for each cohort.[3]

Figure 5A. Indapamide Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[3,a]



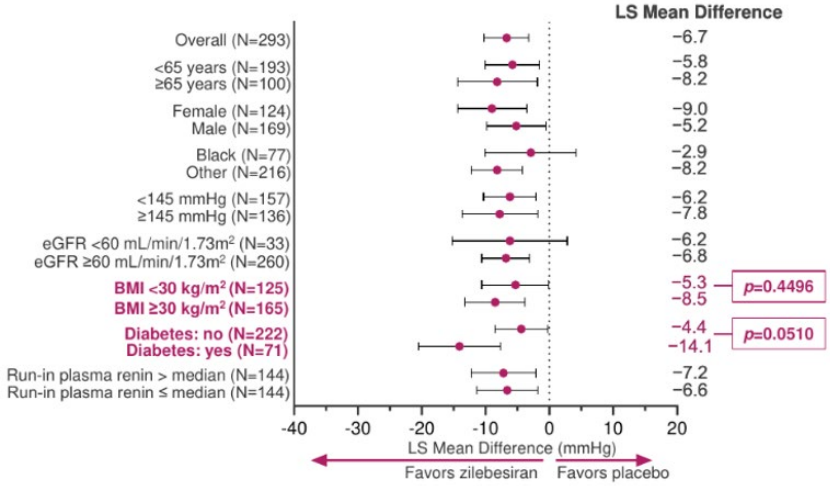
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=127.
From Saxena et al.[3]

Figure 5B. Amlodipine Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[3,a]



Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=238
From Saxena et al.[3]

Figure 5C. Olmesartan Cohort: Change in Office SBP at Month 3 Subgroup Analysis.[3,a]

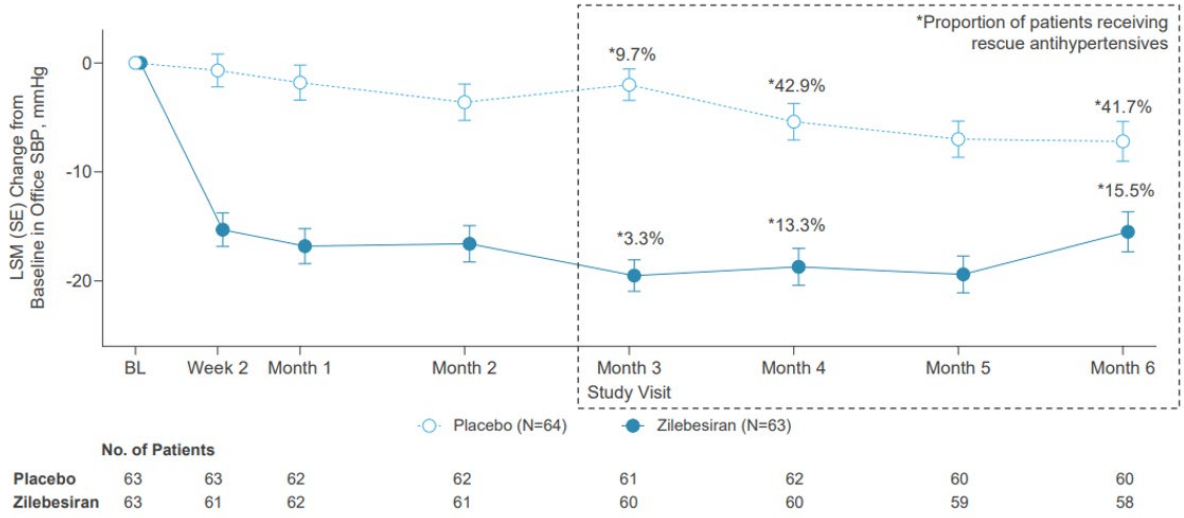


Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; LS = least squares; SBP = systolic blood pressure.
[a]Modified full analysis set: N=293
From Saxena et al.[3]

Change in Office SBP Through Month 6

At Month 6, treatment with a single subcutaneous dose of zilebesiran 600 mg demonstrated significant reductions in office SBP compared with placebo when added to indapamide, amlodipine, or olmesartan. **Figures 6A-6C** show the change in office SBP from baseline through Month 6 over time for each cohort and identifies the proportion of patients who received rescue hypertensives from Month 3-6.[2]

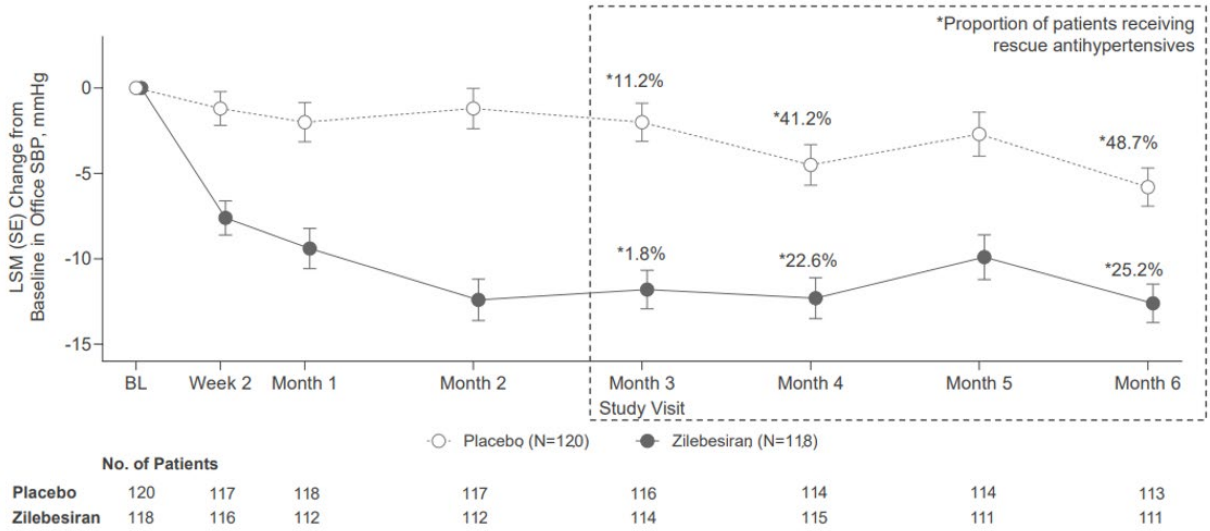
Figure 6A. Indapamide Cohort: Change in Office SBP Through Month 6.[2]



	Time-Adjusted 24-hour Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	-11.0 (-14.7, -7.3), p<0.001	-13.6 (-16.9, -10.3), p<0.001

Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; SBP = systolic blood pressure; SE = standard error.
From Bakris et al.[2]

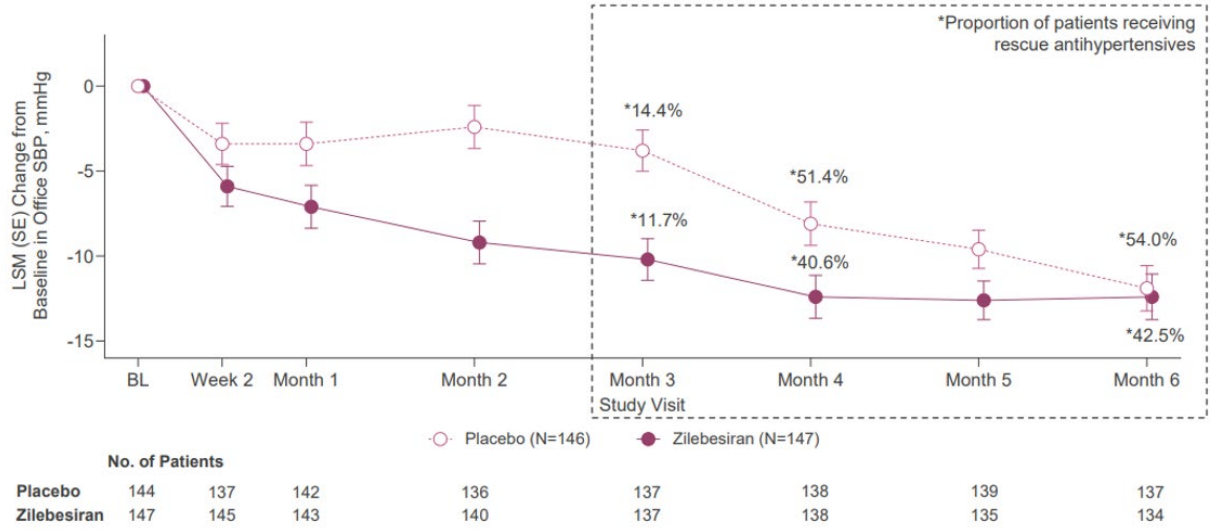
Figure 6B. Amlodipine Cohort: Change in Office SBP Through Month 6.[2]



	Time-Adjusted 24-hour Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	-7.9 (-10.6, -5.3), p<0.001	-8.6 (-10.9, -6.3), p<0.001

Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; SBP = systolic blood pressure; SE = standard error.
From Bakris et al.[2]

Figure 6C. Olmesartan Cohort: Change in Office SBP Through Month 6.[2]



	Time-Adjusted 24-hour Mean Ambulatory SBP	Time-Adjusted Office SBP
LSMD vs placebo, mmHg (95% CI)	-1.8 (-4.6, 1.0), p=0.210	-4.5 (-6.8, -2.3), p<0.001

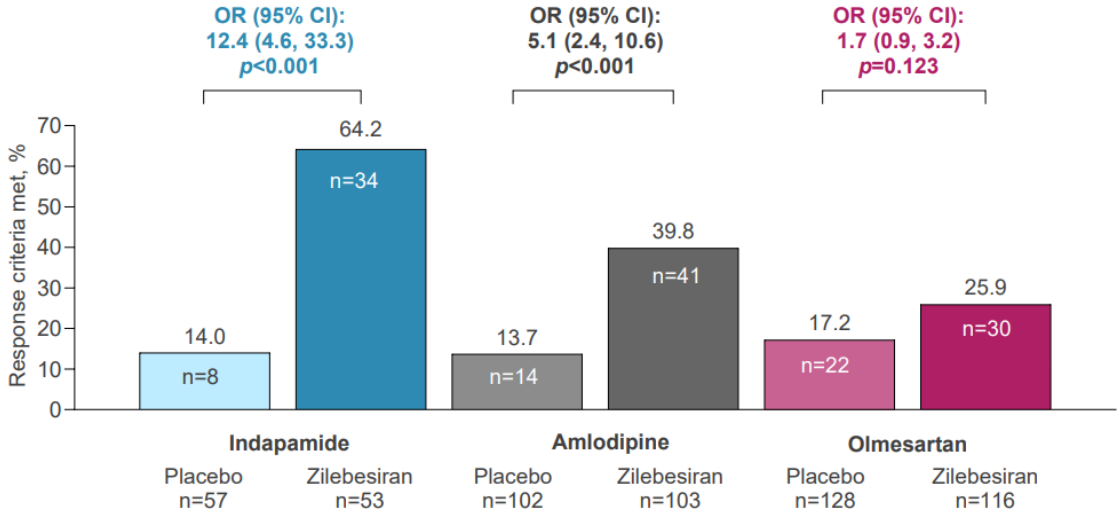
Abbreviations: CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; SBP = systolic blood pressure; SE = standard error.
From Bakris et al.[2]

SBP Response at Month 6 Without Rescue Medication

At Month 6, treatment with zilebesiran resulted in a larger proportion of patients achieving a SBP response without rescue medication. The response criterion was defined as a 24-hour mean ambulatory SBP

<130 mmHg and/or reduction ≥20 mmHg without additional antihypertensives. **Figure 7** shows the proportion of patients achieving SBP response at Month 6 without rescue medication in each cohort.[2]

Figure 7. Proportion of Patients Achieving SBP Response at Month 6 Without Rescue Medication.[2]



Abbreviations: CI = confidence interval; OR = odds ratio.
From Bakris et al.[2]

SAFETY RESULTS

During the 6-month treatment period, there were no deaths or AEs leading to study discontinuation. Laboratory abnormalities of interest were mild, occurred in the first 3 months, and resolved upon repeat measurement within 1-2 weeks without intervention (**Table 2**).[2] No apparent safety trends were observed by subgroup.[3]

Table 2. Zilebesiran Safety Summary Over 6 Months.[2]

Patients with an AE, n (%)	Background Medication					
	Indapamide		Amlodipine		Olmesartan	
	Placebo (N=64)	Zilebesiran (N=63)	Placebo (N=120)	Zilebesiran (N=118)	Placebo (N=145)	Zilebesiran (N=148)
At least 1 AE	25 (39.1)	31 (49.2)	56 (46.7)	64 (54.2)	69 (47.6)	87 (58.8)
At least 1 serious AE	2 (3.1)	0	1 (0.8)	3 (2.5)	4 (2.8)	4 (2.7)
Hypotension/orthostatic hypotension AE	0	0	4 (3.3)	7 (5.9)	3 (2.1)	7 (4.7)
Potassium >5.5 nmol/L	0	2 (3.2)	1 (0.8)	8 (6.8)	3 (2.1)	10 (6.8)
Confirmed by repeat measure	0	1 (1.6)	0	2 (1.7)	0	2 (1.4)
≥30% decrease from baseline in eGFR (mL/min/1.73m^2)	1 (1.6)	8 (12.7)	5 (4.2)	10 (8.5)	4 (2.8)	10 (6.8)
Confirmed by repeat measure	0	3 (4.8)	2 (1.7)	1 (0.8)	1 (0.7)	4 (2.7)
>2x increase from baseline in creatinine (µmol/L)	0	0	0	0	0	3 (2.0)
Confirmed by repeat measure	0	0	0	0	0	1 (0.7)

Abbreviations: AE = adverse event; eGFR = estimated glomerular filtration rate.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AGT = angiotensinogen; ARB = angiotensin receptor blocker; BL = baseline; BMI = body mass index; CCB = calcium channel blocker; CI = confidence interval; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; IQR = interquartile range; LS = least squares; LSM = least squares mean; LSMD = least squares mean difference; OLE = open-label extension; OR = odds ratio; RNAi = RNA interference; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; US = United States.

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REFERENCES

1. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389(3):228-238. doi:10.1056/NEJMoa2208391
2. Bakris GL, Desai AS, Aswad A, et al. Zilebesiran in combination with a standard-of-care antihypertensive in patients with inadequately controlled hypertension: Primary results from the phase 2 KARDIA-2 study. Presented at: American College of Cardiology (ACC) Annual Scientific Session; April 6-8, 2024; Atlanta, GA, USA.
3. Saxena M, Aswad A, Badariene J, et al. Subgroup results from KARDIA-2: Impact of demographic and baseline disease characteristics on zilebesiran response in patients with hypertension uncontrolled by a standard oral antihypertensive. Presented at: European Society of Cardiology (ESC) Congress; August 30 - September 2, 2024; London, UK.