

KARDIA-3: Zilebesiran as Add-on Therapy in Adults With Hypertension Who Have Established Cardiovascular Disease or Are at High Cardiovascular Risk

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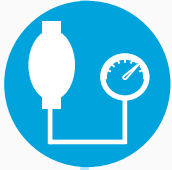
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Zilebesiran is being co-developed and will be co-commercialized by Alnylam and Roche.

The Problem: Uncontrolled Hypertension



Uncontrolled hypertension (HTN) is the greatest contributor to cardiovascular (CV) morbidity and mortality worldwide



Despite the availability of effective therapies, many patients do not achieve and maintain blood pressure (BP) goals



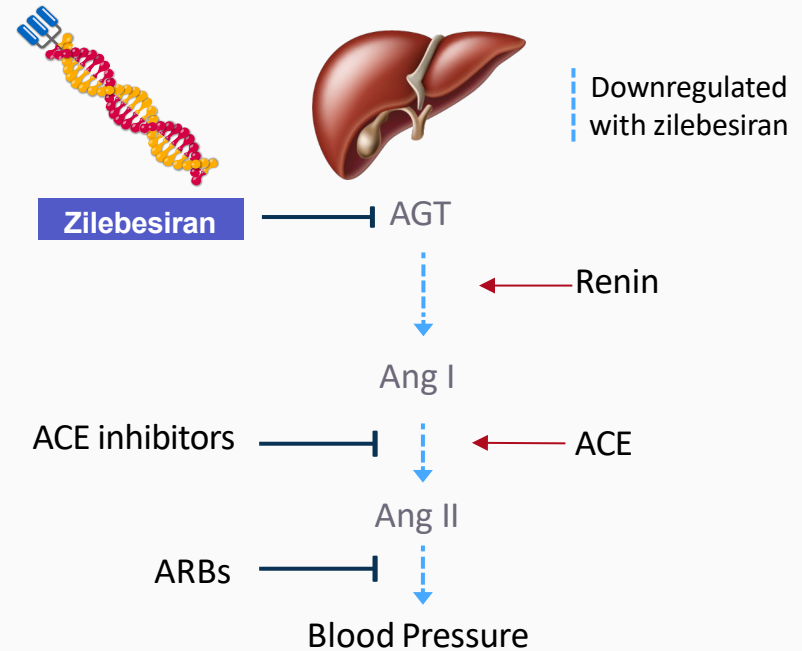
Poor adherence to daily oral therapies is an important contributor to BP goals not being met

An effective, long-acting therapy that provides continuous control of BP may help to reduce the burden of uncontrolled hypertension and CV morbidity and mortality

Zilebesiran

- Zilebesiran is an investigational RNA interference therapeutic
- Reduces hepatic production of angiotensinogen (AGT), the most upstream precursor in the RAAS pathway
- Has the potential to provide continuous control of BP with subcutaneous (SC) dosing every 6 months

Zilebesiran Suppresses the RAAS Pathway



Overview of Zilebesiran Development Program

Phase 2

KARDIA₁

Regimen: Monotherapy

Patient population (N=394):

Mild-to-moderate HTN

Efficacy:

(Placebo-adjusted office systolic BP):
up to ↓ 12 mmHg at Month 3

Safety profile: Acceptable safety

KARDIA₂

Regimen: Added to diuretic, CCB, or ARB

Patient population (N=663): HTN not
adequately controlled by standard of
care antihypertensives

Efficacy:

(Placebo-adjusted office systolic BP):
↓ 19 mmHg with diuretic at Month 3
↓ 10 mmHg with CCB at Month 3
↓ 7 mmHg with ARB at Month 3

Safety profile: Acceptable safety
including with ARB

KARDIA₃

Regimen: Combination therapy +
standard of care

Patient population (N=375):

Uncontrolled HTN (2–4
antihypertensives) with high CV risk

Aim:

Inform Phase 3 CV outcomes study

Phase 3

Phase 3 CV outcomes study in patients with uncontrolled HTN and high CV risk

Study Objective



To determine the efficacy, safety, and optimal dosing of zilebesiran among individuals with uncontrolled HTN and high CV risk, with or without chronic kidney disease, in order to inform the design of a CV outcomes study in this population

Key Details

Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial



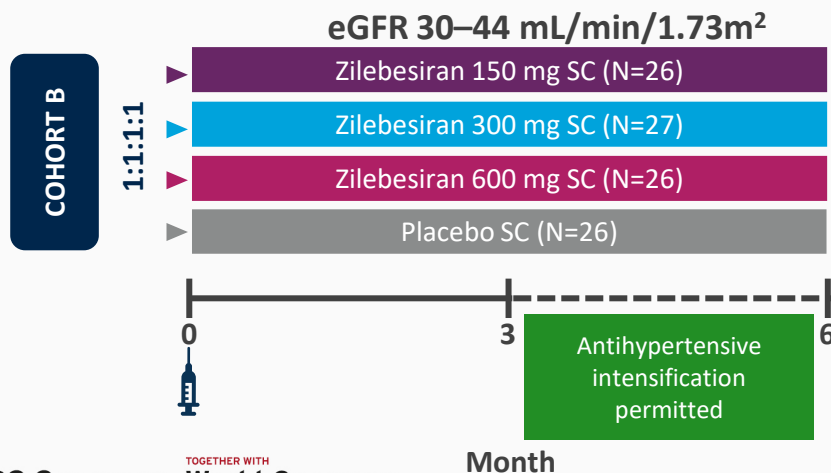
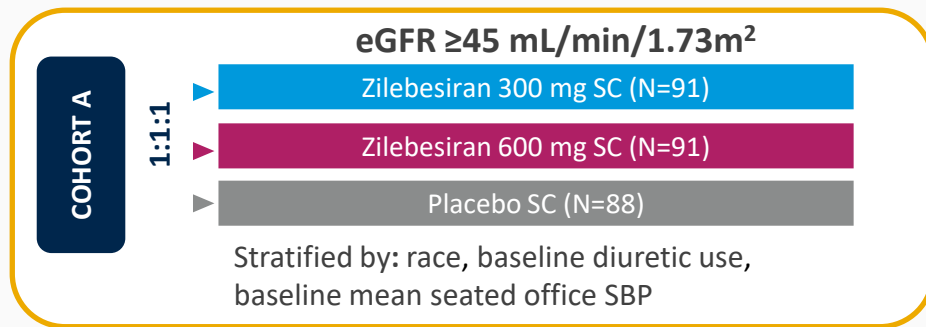
Across 5 countries:

US, Australia, Canada, UK, Switzerland

Inclusion criteria

- Established CV disease or high risk for CV disease (>15% ASCVD 10-year)
- Uncontrolled hypertension (mean office systolic BP 140–170 mmHg at screening and 24-hour mean ambulatory systolic BP 130–170 mmHg within 7 days prior to randomization)
- Already prescribed 2–4 antihypertensive drugs (including a diuretic or Ca⁺ channel blocker)

Study Design



Key Outcomes

Primary

- Change from baseline to Month 3 in mean office systolic BP

Secondary

- Change from baseline to Month 6 in mean office systolic BP
- Change from baseline to Months 3 and 6 in 24-hour mean ambulatory systolic BP
- Hourly mean changes (daytime and nighttime)

Exploratory

- Hourly mean at Month 6, assessed by ambulatory systolic BP

Mixed model for repeated measurements used for primary analysis. Changes from baseline are estimated by least squares means (95% CI).

If $P \geq 0.05$ for one dose, multiplicity testing requires $P \leq 0.025$ for remaining dose to be statistically significant.

Baseline Demographics and Disease Characteristics

Cohort A

Parameter	Placebo (N=88)	Zilebesiran (N=182)	
		300 mg (N=91)	600 mg (N=91)
Mean age, years (SD)	66.3 (9.0)	67.2 (8.7)	65.6 (8.2)
Age ≥65 years, n (%)	55 (62.5)	52 (57.1)	55 (60.4)
Female sex, n (%)	33 (37.5)	45 (49.5)	43 (47.3)
Black, n (%)	20 (22.7)	19 (20.9)	23 (25.3)
Hispanic or Latino, n (%)	49 (55.7)	51 (56.0)	50 (54.9)
Previous CV event or CVD history, n (%)	19 (21.6)	27 (29.7)	15 (16.5)
Mean ASCVD score in patients without prior CV event (SD)	29.6 (12.8)	29.5 (13.1)	29.4 (11.7)
Diabetes mellitus, n (%)	47 (53.4)	42 (46.2)	50 (54.9)
eGFR ≥60 mL/min/1.73m ² , n (%)	79 (89.8)	82 (90.1)	82 (90.1)

Baseline Blood Pressure

Cohort A

Parameter	Placebo	Zilebesiran	
		300 mg	600 mg
Office BP, mmHg	n=88	n=91	n=91
Mean systolic BP (SD)	144.1 (12.4)	143.4 (13.1)	143.4 (13.4)
Mean diastolic BP (SD)	79.6 (10.3)	80.2 (11.5)	80.3 (10.8)
Mean 24-hour ambulatory BP, mmHg	n=88	n=91	n=89
Mean systolic BP (SD)	142.9 (9.0)	141.6 (8.3)	142.9 (7.7)
Mean diastolic BP (SD)	79.1 (8.6)	78.8 (8.5)	78.0 (8.9)

Baseline Antihypertensive Medications

Cohort A

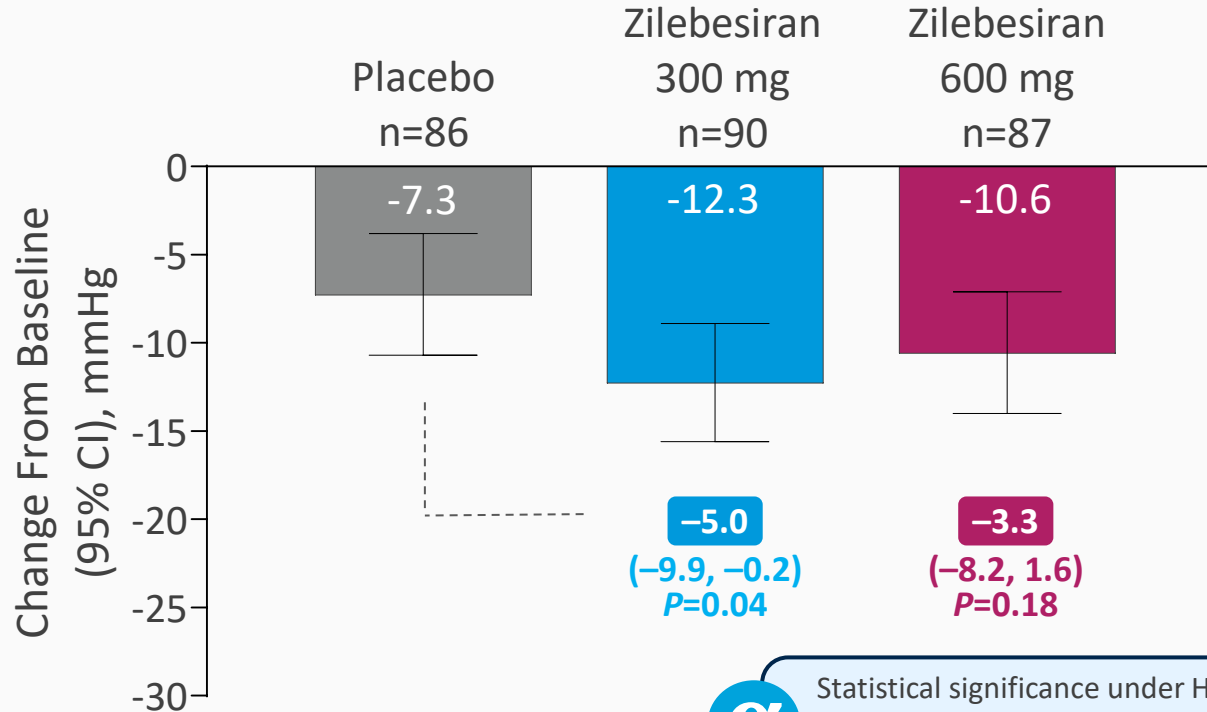
Parameter	Placebo (N=88)	Zilebesiran (N=182)	
		300 mg (N=91)	600 mg (N=91)
Baseline medications, n (%)			
ACEi or ARB	78 (88.6)	83 (91.2)	84 (92.3)
Diuretic (thiazide, thiazide-like, or loop diuretic)	55 (62.5)	62 (68.1)	61 (67.0)
CCB	58 (65.9)	52 (57.1)	46 (50.5)
Number of oral antihypertensives, n (%)			
2	47 (53.4)	40 (44.0)	57 (62.6)
3	32 (36.4)	37 (40.7)	27 (29.7)
≥4	9 (10.2)	14 (15.4)	7 (7.7)

RESULTS:

Cohort A

Placebo-Adjusted Change From Baseline to Month 3 in Office Systolic BP

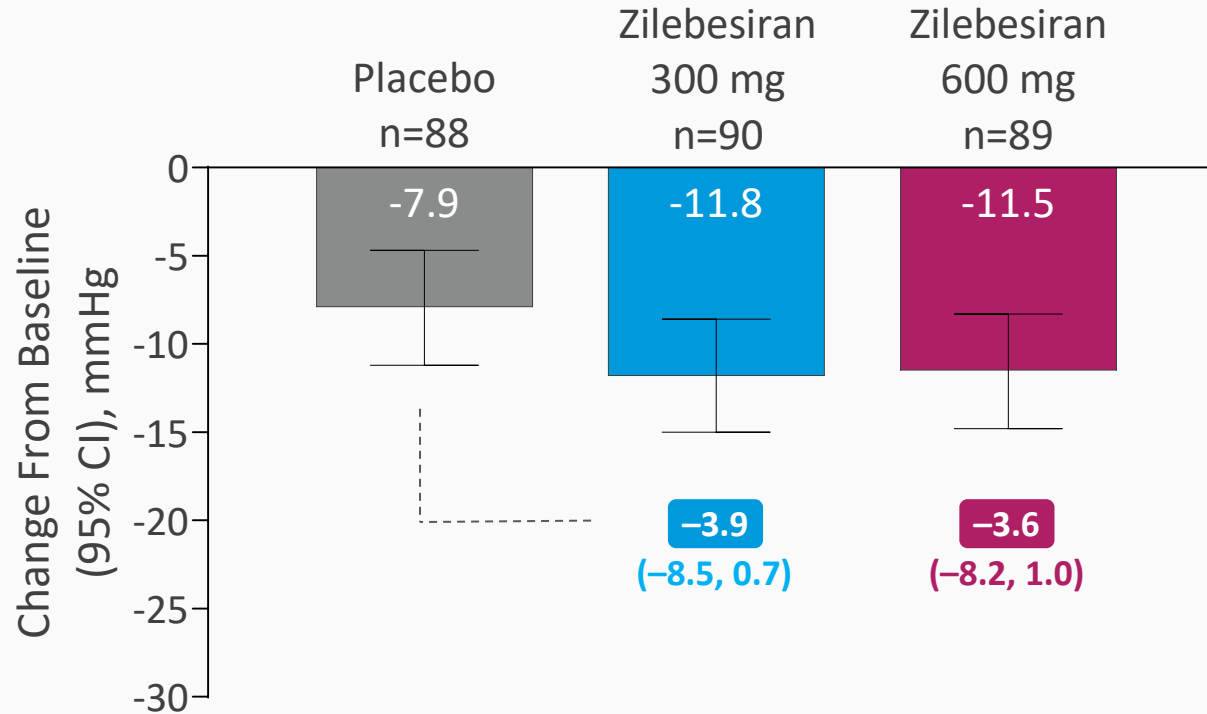
Primary Outcome



Statistical significance under Hochberg multiplicity control: If P value of one dose exceeds 0.05 (2-sided), threshold for remaining dose is $P \leq 0.025$

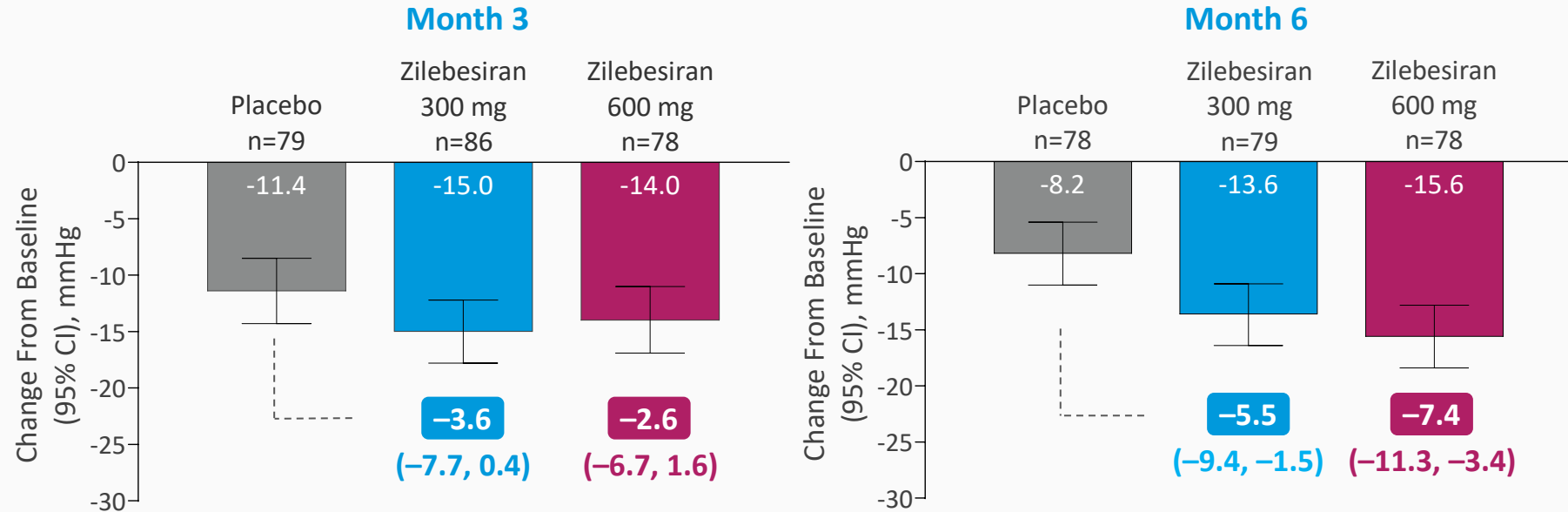
Placebo-Adjusted Change From Baseline to Month 6 in Office Systolic BP

Secondary Outcome

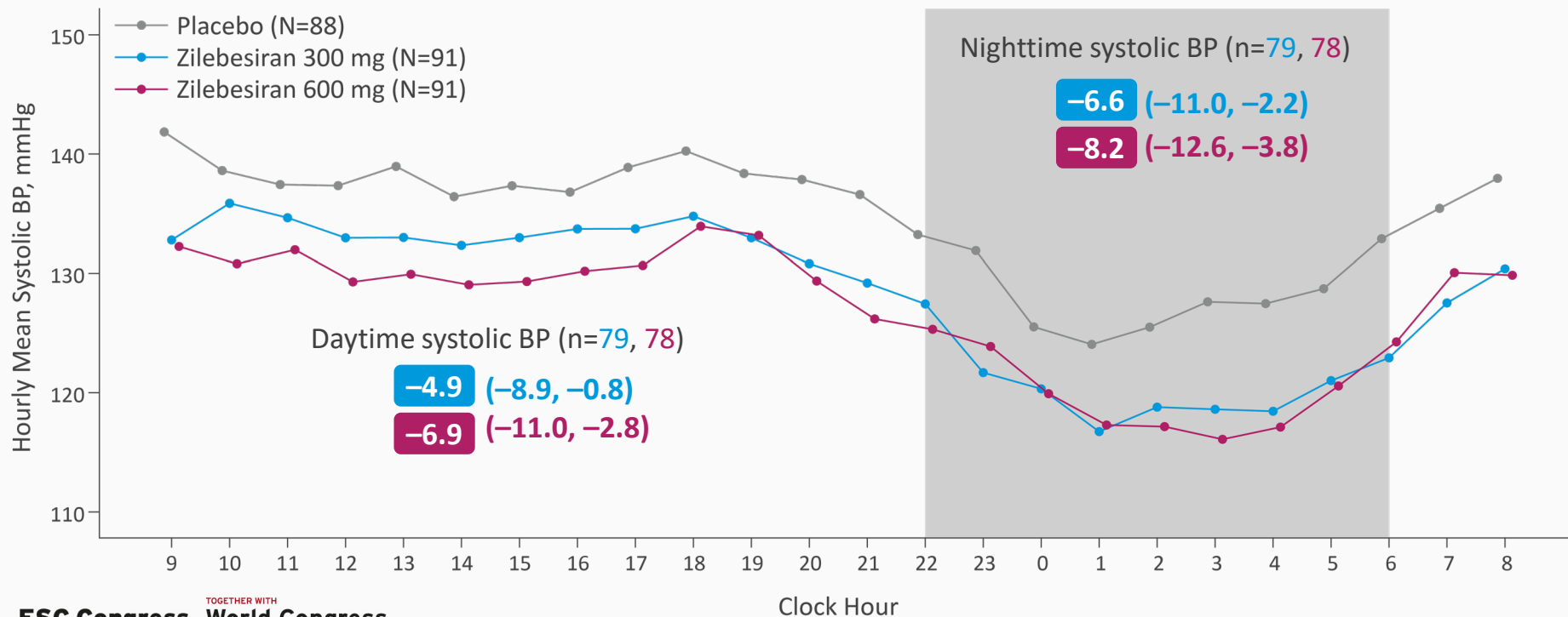


Placebo-Adjusted Change From Baseline in 24-Hour Mean Ambulatory Systolic BP

Secondary Outcomes



Hourly Mean (Exploratory) and Placebo-Adjusted Change From Baseline (Secondary) in Mean Daytime/Nighttime Ambulatory SBP at Month 6

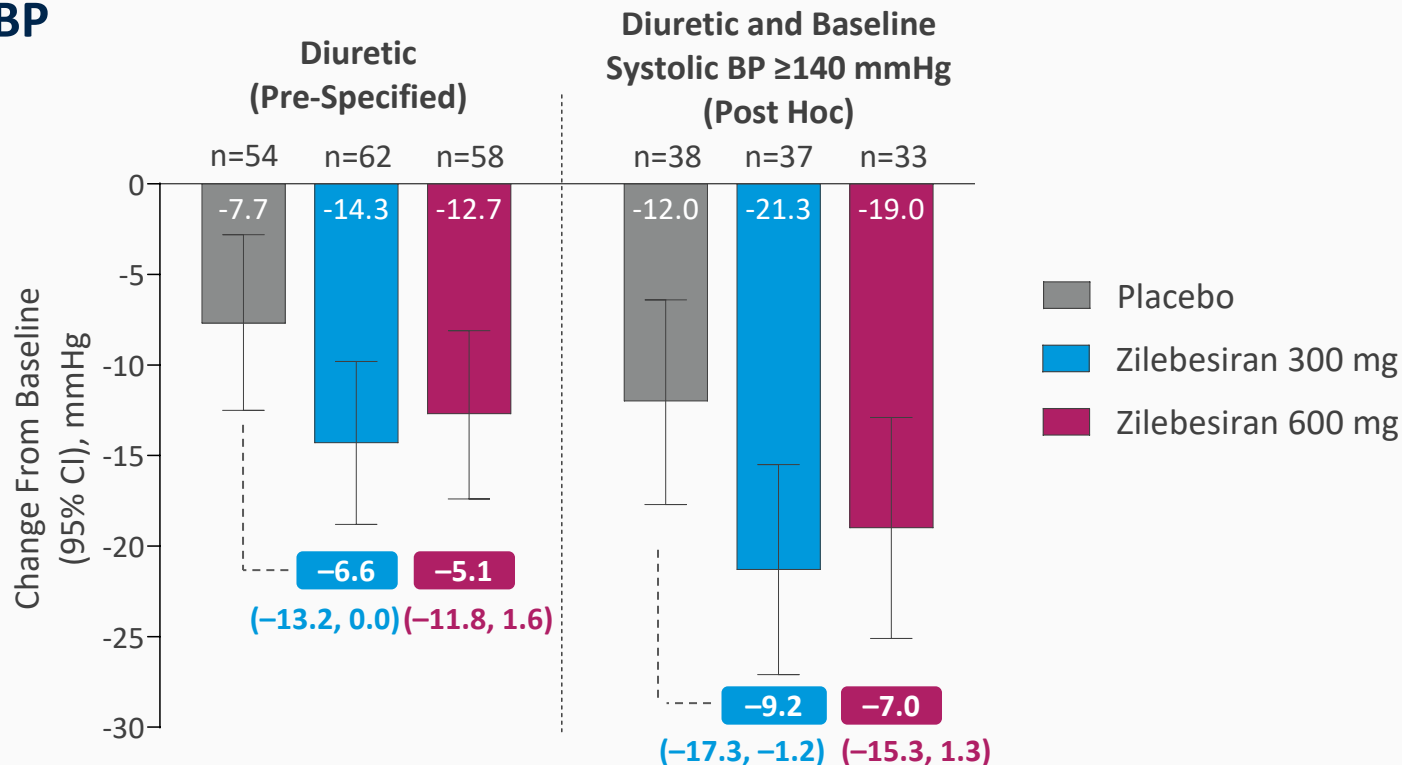


Safety Profile Through Month 6

n (%)	Placebo (N=88)	Zilebesiran	
		300 mg (N=91)	600 mg (N=91)
At least 1 AE	38 (43.2)	47 (51.6)	46 (50.5)
At least 1 serious AE	4 (4.5)	1 (1.1)	6 (6.6)
Suspected unexpected serious adverse reaction	0	0	1 (1.1)
Death	0	0	0
Hypotension/orthostatic hypotension AE	3 (3.4)	3 (3.3)	4 (4.4)
Potassium >5.5 mmol/L	4 (4.5)	4 (4.4)	8 (8.8)
Confirmed by subsequent measurement	1 (1.1)	3 (3.3)	1 (1.1)
Potassium >6.0 mmol/L	0	0	0
eGFR ≥30% decrease from baseline and <60 (mL/min/1.73m ²)	1 (1.1)	5 (5.5)	8 (8.8)
Confirmed by subsequent measurement	1 (1.1)	2 (2.2)	2 (2.2)

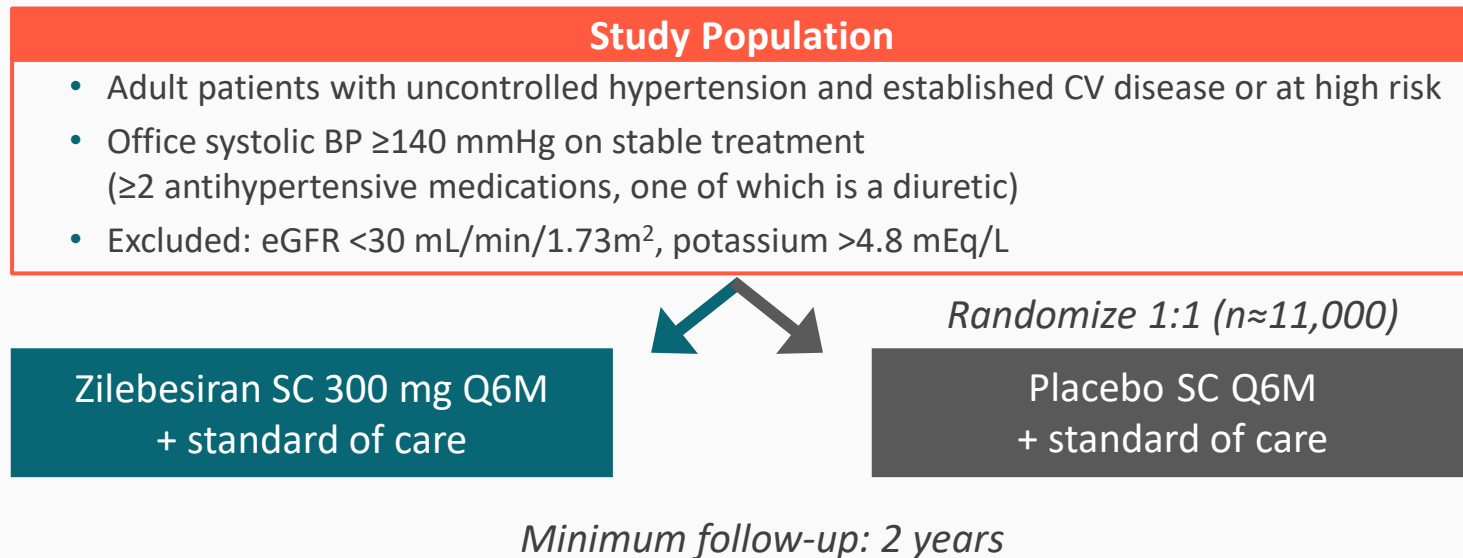
- Most AEs were mild or moderate and rates of hyperkalemia, kidney dysfunction, and hypotension were low
- Most instances of hyperkalemia or kidney dysfunction were not confirmed by subsequent measurement

Subgroup Analysis – Placebo-Adjusted Change From Baseline to Month 3 in Office Systolic BP



- Post hoc subgroup changes were sustained to Month 6: 300 mg (-8.3 ($-16.4, -0.2$) mmHg) and 600 mg (-6.2 ($-14.4, 2.0$) mmHg)

Phase 3 CV Outcomes Trial Design



Primary Outcome: CV death, nonfatal MI, nonfatal stroke, or HF event



KARDIA Conclusions

- Among individuals with CV disease or at high CV risk who have uncontrolled HTN on multiple antihypertensives, single doses of zilebesiran 300 mg or 600 mg led to respective 5.0 mmHg and 3.3 mmHg reductions in office systolic BP at 3 months compared with placebo; statistical significance was not reached.
- Subgroup analyses suggest that those on a diuretic may experience greater BP lowering with zilebesiran.
- Zilebesiran demonstrated an acceptable safety profile with low rates of hyperkalemia, kidney dysfunction, and hypotension, consistent with findings from previous studies.
- The ZENITH trial will evaluate the impact of this novel, long-acting therapy on CV outcomes in patients with HTN and established CV disease or high CV risk.

**Thank you to the investigators and especially the participants who made the
KARDIA-3 trial possible**