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Pooled Safety Analysis of Zilebesiran, an Investigational Long-Acting RNA Interference Therapeutic, From Phase 2 Studies in Patients With Hypertension

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Disclosure for Akshay S. Desai, MD

Conflict	Disclosure
Research Support	Alexion, Alnylam, AstraZeneca, Avalyn, Bayer, Intellia Therapeutics, Pharmacosmos
Consultant	Abbott, Alnylam, AstraZeneca, Avidity Biosciences, Axon Therapies, Baim Institute for Clinical Research, Bayer, Biofourmis, Boston Scientific, CVS Caremark, Edwards Lifesciences, Endotronix, Medpace, Medtronic, Merck, New Amsterdam, Novartis, Parexel, Regeneron, River 2 Renal, Roche, scPharmaceuticals, Vectorious Medical Technologies, Verve Therapeutics, Volta Medical

Zilebesiran:

Zilebesiran is an investigational product in development for treatment of patients with hypertension.

Funding:

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

- Despite wide availability of effective therapies, many patients with hypertension do not achieve and maintain guideline-directed BP targets[1]

- Zilebesiran is an investigational RNAi therapeutic targeting production of AGT in the liver[2]

- Three Phase 2 trials were conducted:
  - KARDIA-1 Zilebesiran (150, 300, 600 mg Q6M, or 300 mg Q3M) monotherapy or placebo[2]
  - KARDIA-2 Zilebesiran (600 mg Q6M) or placebo added to background diuretic, CCB, or ARB[3]
  - KARDIA-3 Zilebesiran (150 [cohort B only], 300, 600 mg Q6M) or placebo, and standard of care[4,5]

- zenith, a Phase 3 CV outcomes trial, has been initiated

Objective: to provide a comprehensive safety summary across the Phase 2 program

KARDIA-3 cohort A included patients with eGFR ≥45 mL/min/1.73 m^2; cohort B included those with eGFR 30–44 mL/min/1.73 m^2 and was not powered to assess efficacy

Safety Analyses From Controlled Phase 2 Zilebesiran Trials

	KARDIA-1	KARDIA-2	KARDIA-3
Trial Setting	N=394 randomized[2] **Monotherapy in adults with mild-to-moderate hypertension**	N=663 randomized[3] **Add-on therapy in adults with hypertension uncontrolled with amlodipine, indapamide, or olmesartan**	N=375 randomized[4,5] **Adults with uncontrolled hypertension and high CV risk**
Key Results	Placebo-adjusted decrease in office systolic BP to Month 6	Placebo-adjusted decrease in office systolic BP to Month 6, greater BP-lowering in patients receiving a diuretic	Placebo-adjusted decrease in office systolic BP to Month 3[a], greater BP-lowering in patients receiving a diuretic
Primary Pooled Safety Analyses	Hypertension with low-CV risk		Hypertension with high-CV risk
	Pooled safety to Month 6		**Safety to Month 6 across Cohorts A+B**
Additional Safety Analysis	**Additional subgroup of interest:** Safety of combining zilebesiran or placebo with background RAASi (KARDIA-2/-3)		

KARDIA-3 cohort A included patients with eGFR ≥45 mL/min/1.73 m^2; cohort B included those with eGFR 30–44 mL/min/1.73 m^2 and was not powered to assess efficacy

[a]Statistical significance was not reached after multiplicity control

KARDIA

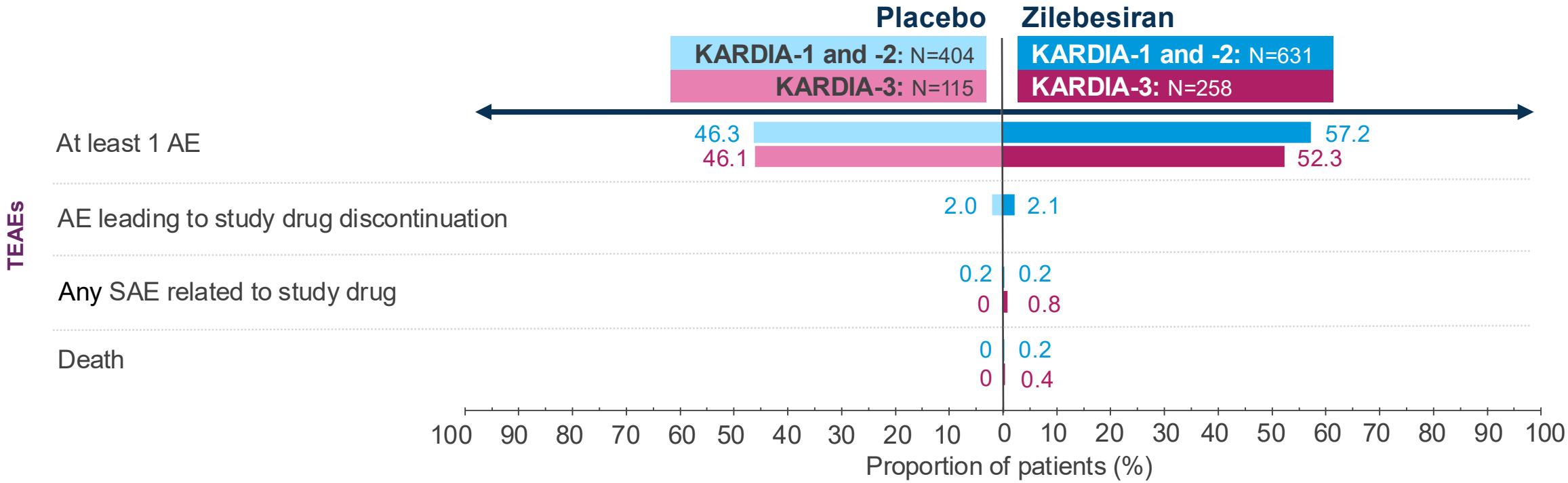
Baseline Demographics and Characteristics

Parameter	KARDIA-1 and -2		KARDIA-3 (Cohorts A & B)	
	Placebo N=404	Zilebesiran N=631	Placebo N=115	Zilebesiran N=258
Age, years, mean (SD)	58.2 (10.5)	57.6 (10.4)	67.3 (8.9)	67.5 (8.9)
Age ≥65 years, n (%)	130 (32.2)	187 (29.6)	76 (66.1)	165 (64.0)
Female, n (%)	176 (43.6)	273 (43.3)	42 (36.5)	124 (48.1)
Black, n (%)	111 (27.5)	169 (26.8)	24 (20.9)	63 (24.4)
Hispanic or Latino, n (%)	111 (27.5)	188 (29.8)	63 (54.8)	129 (50.0)
Diabetes mellitus, n (%)	82 (20.3)	133 (21.1)	67 (58.3)	134 (51.9)
Baseline eGFR, mL/min/1.73 m^2, median (IQR)	79.1 (22.2)	80.1 (20.6)	80.9 (40.9)	71.3 (44.6)
Baseline eGFR <60 mL/min/1.73 m^2, n (%)	43 (10.6)	61 (9.7)	35 (30.4)	93 (36.0)
Serum potassium, mmol/L, median (IQR)	4.25 (0.50)	4.30 (0.50)	4.30 (0.60)	4.30 (0.60)
Office systolic BP, mmHg, mean (SD)	144.7 (12.6)[a]	142.8 (11.6)[b]	144.6 (12.3)	144.5 (13.8)
24-hour mean ambulatory systolic BP, mmHg, mean (SD)	143.0 (8.2)	142.7 (8.3)	143.7 (9.6)	142.1 (8.4)[c]

Safety analysis set
[a]Patients with available data n=401. [b]Patients with available data n=630. [c]Patients with available data n=256

KARDIA

Summary of Treatment-Emergent Adverse Events

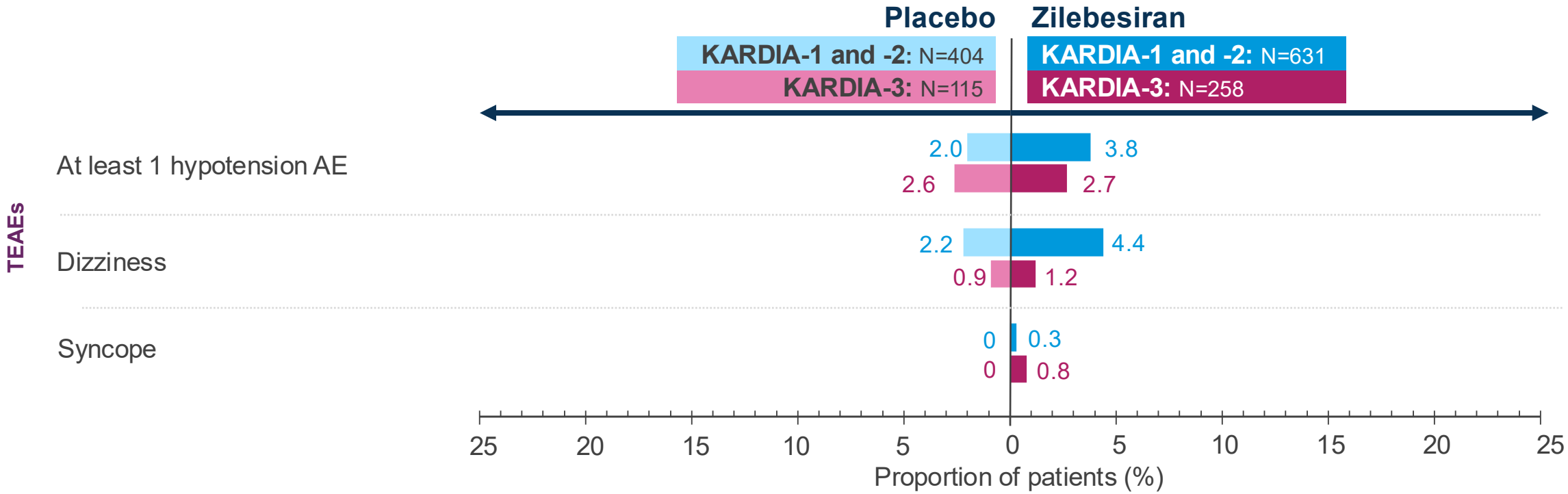


- Most AEs were mild or moderate in severity, transient, and resolved without intervention
- There were two deaths during the double-blind period; neither considered treatment-related by the investigator
  - Cardio-pulmonary arrest on Day 5 after zilebesiran (KARDIA-1)
  - Cardiac arrest on Day 85 after zilebesiran (KARDIA-3)

- AE, adverse event

AEs classified as leading to study drug discontinuation were only reportable for patients in KARDIA-1 and KARDIA-2, where an open label extension was planned.

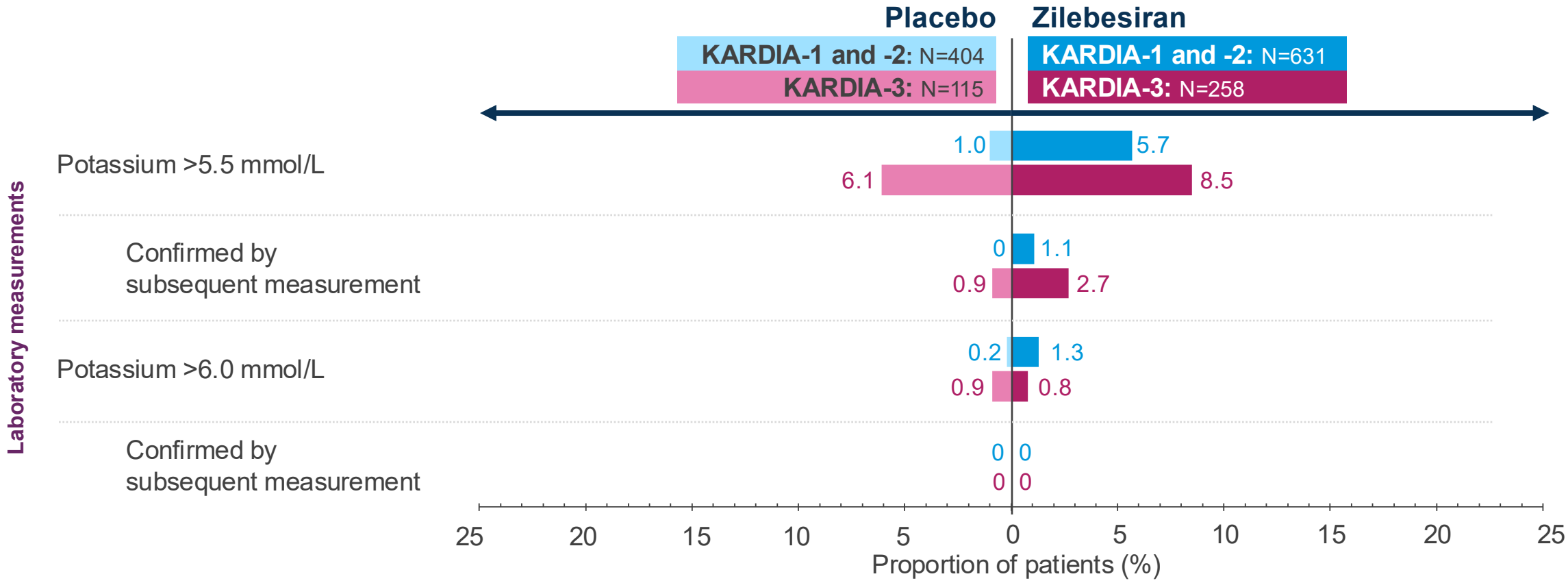
Hypotension and Related AEs



- Majority of events were mild or moderate in severity, transient, and resolved without intervention
- For zilebesiran-treated patients who received interventions, these mainly consisted of increased fluid or sodium intake or adjustment of background antihypertensive medications

KARDIA

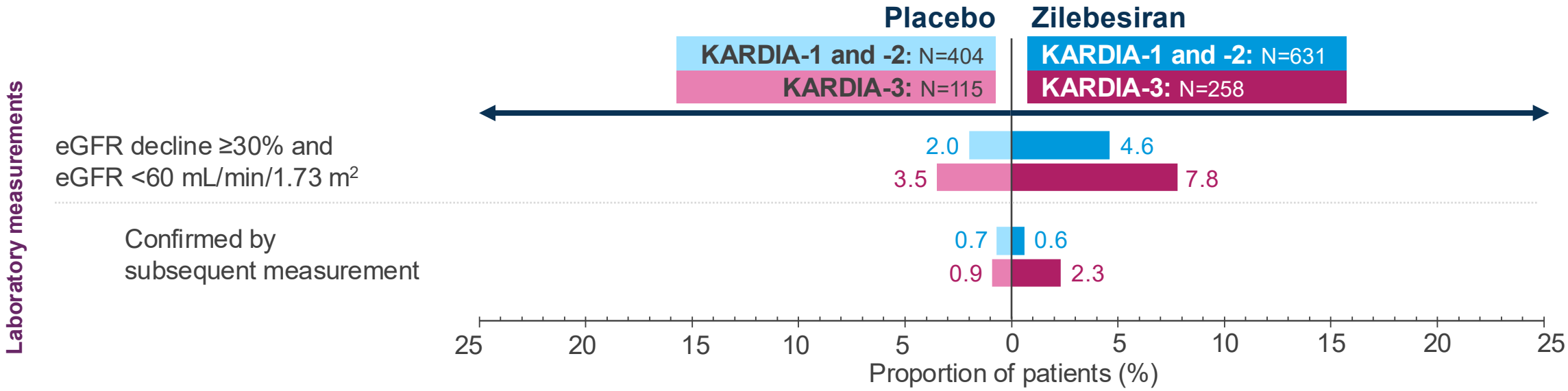
Hyperkalemia Laboratory Assessments



- All events were mild or moderate in severity and nonserious; the majority resolved without intervention
  - Seven patients (placebo n=2, zilebesiran n=5) received potassium binders; 5 of whom had baseline eGFR <60 mL/min/1.73 m^2

Confirmed by subsequent measurement means assessment remained in defined range on the next available measurement

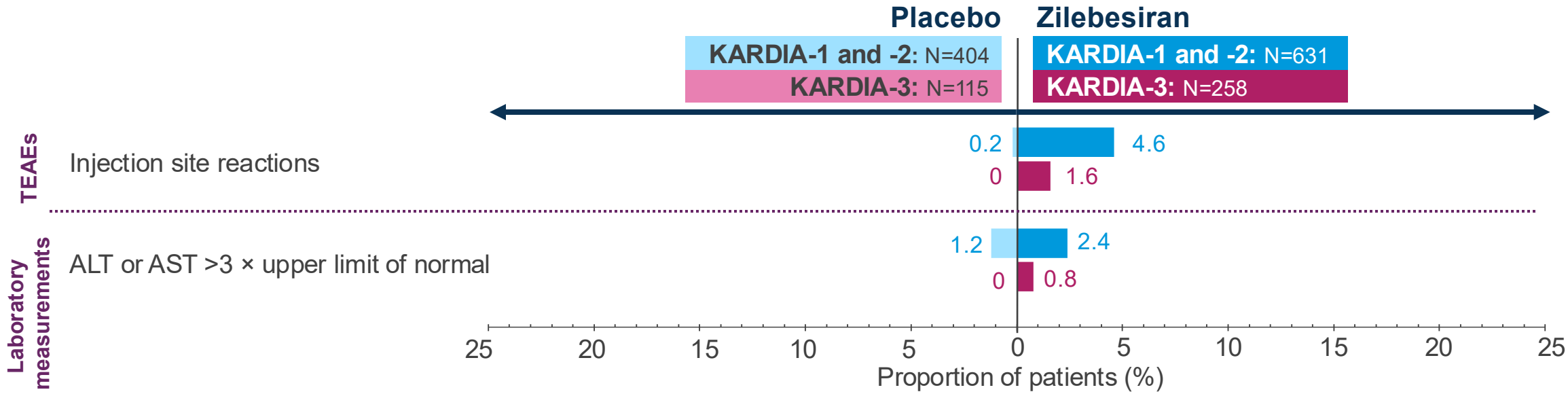
eGFR Changes and Renal AEs



- Majority of renal AEs were mild or moderate in severity, nonserious, and resolved without intervention

Confirmed by subsequent measurement means assessment remained in defined range on the next available measurement

Other Adverse Events and Measurements



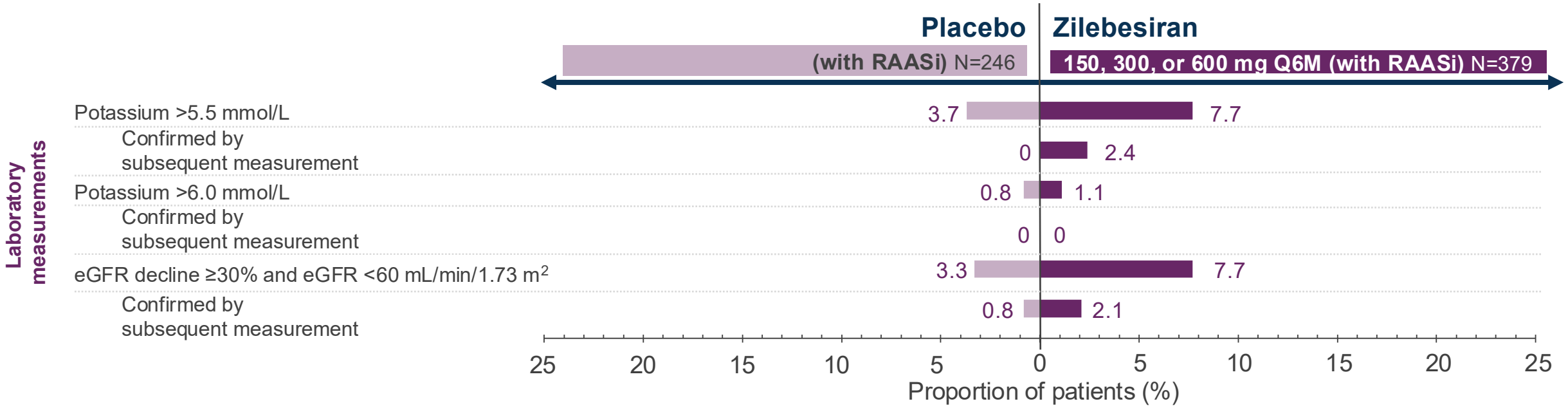
- Most ISRs were transient, mild or moderate in severity, and nonserious with no associated systemic AEs; two patients had an ISR that led to study drug discontinuation
- No patients met biochemical Hy's law criteria
  - Most hepatic AEs were mild or moderate and resolved while receiving study drug; none were serious or accompanied by bilirubin increase

Combination of Zilebesiran with RAASi: Summary of Safety

KARDIA-2 — Subgroup of interest: background olmesartan + zilebesiran

KARDIA-3 — Subgroup of interest: baseline ACEi or ARB + zilebesiran

Pooled analyses of all KARDIA patients receiving a background RAASi



- Rates of hyperkalemia and eGFR decline were similar to those in the overall Phase 2 population

Patients in the placebo and zilebesiran groups received olmesartan in KARDIA-2 and standard of care RAASi in KARDIA-3.
Confirmed by subsequent measurement means assessment remained in defined range on the next available measurement

Scan to View

KARDIA Phase 2 Program Safety Conclusions

- In this pooled analysis of safety data from double-blind treatment periods across the Phase 2 program:
  - Zilebesiran was associated with low rates of hypotension, hyperkalemia, and eGFR decline
  - Higher rates of AEs were seen in patients assigned to zilebesiran than placebo
  - However, SAEs were rare, and laboratory abnormalities were typically transient and resolved without intervention
  - In patients receiving zilebesiran concurrently with a RAASi, rates of hyperkalemia and eGFR decline were similar to those in the overall Phase 2 population
- These data support continued investigation of zilebesiran 300 mg Q6M in the Phase 3 ZENITH trial, which is exploring CV outcomes in patients with uncontrolled hypertension and established CVD or high CV risk