KARDIA-3 Study Design: Zilebesiran as Add-On Therapy in Patients with High Cardiovascular Risk and Hypertension Inadequately Controlled by Standard of Care Antihypertensives

For US HCPs Only

Scan to View Congress Material Presented

Andrea Havasi[1], Neha Pagidipati[2], George L Bakris[3], Michael Weber[4], Monica Bengus[5], Shruti Daga[6], Zhihua Xiang[1], Tiffany Zee[1], Ishir Bhan[1], Christopher B Granger[2]

[1]Alnylam Pharmaceuticals, Cambridge, MA, USA; [2]Duke Clinical Research Institute, Durham, NC, USA; [3]The University of Chicago Medicine, Chicago, IL, USA; [4]SUNY Downstate College of Medicine, SUNY Downstate Health Sciences University, New York, NY, USA; [5]F. Hoffman-La Roche, Basel, Switzerland; [6]Roche Products Ltd, Welwyn Garden City, UK

Conclusions

- **KARDIA-3 will provide efficacy and safety data on zilebesiran in patients with or at high risk of developing cardiovascular (CV) disease, including those with the common comorbidity of advanced chronic kidney disease (CKD).**
- **This is the first Phase 2 trial of an RNA interference therapeutic targeting angiotensinogen (AGT) in patients with inadequately controlled hypertension who are at high CV risk, which addresses a population with high unmet need.**
- **This global trial is ongoing; the first patient was enrolled in KARDIA-3 in April 2024.**

Introduction

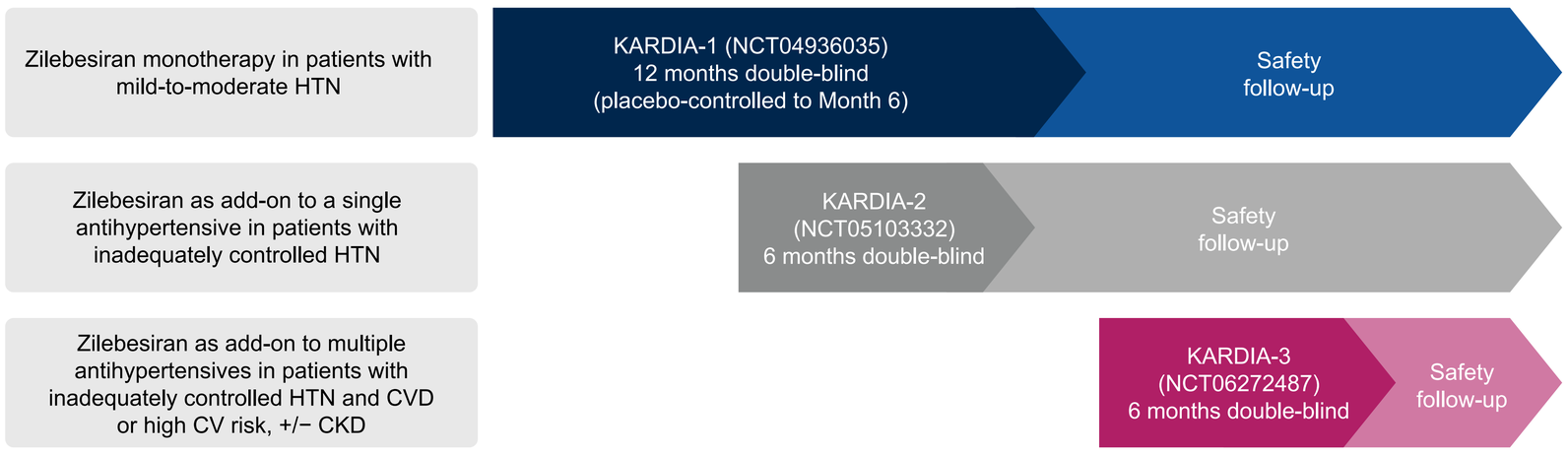
Background

- Hypertension is the strongest modifiable risk factor for CV disease; however, despite the availability of effective antihypertensives, many patients do not meet guideline-recommended blood pressure (BP) targets.[1]
  - Poor adherence to multidrug oral regimens contributes to BP variability and may increase the risk of CV events.[1]
- BP control is also important for patients with CKD, which affects approximately 20% of US adults with hypertension, because controlled BP slows CKD progression and reduces CV risk.[2,3]

Zilebesiran

- Zilebesiran is an investigational, subcutaneously (SC) administered RNA interference therapeutic that targets the synthesis of hepatic AGT, the most upstream precursor of the renin–angiotensin system, which is fundamental in BP regulation.[1]
- Previous Phase 2 studies are shown in **Figure 1**.
  - In KARDIA-1 (NCT04936035), zilebesiran monotherapy as single 150, 300, or 600 mg doses significantly reduced 24-hour mean ambulatory and office systolic blood pressure (SBP) from baseline to Months 3 and 6 compared with placebo in patients with mild-to-moderate hypertension. The only treatment-related adverse events (AEs) reported in ≥5% of patients were injection-site reactions (zilebesiran, 6%; placebo, 0%) and hyperkalemia (zilebesiran, 5%; placebo, 1%); most hyperkalemia events were mild and transient, and did not require intervention.[4]
  - In KARDIA-2 (NCT05103332), a single 600 mg dose of zilebesiran as add-on therapy to a standard-of-care antihypertensive significantly reduced 24-hour mean ambulatory and office SBP from baseline to Month 3 compared with placebo in patients with inadequately controlled hypertension, with effects largely sustained to Month 6. Most instances of hyperkalemia, hypotension, and decline in renal function with add-on zilebesiran treatment were mild, transient, and resolved without intervention.[5]

Figure 1. Overview of Zilebesiran Phase 2 Clinical Trials



CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension.

Study Design

- KARDIA-3 (NCT06272487) is evaluating the efficacy and safety of zilebesiran as add-on therapy in patients who have established CV disease or high CV risk with or without advanced CKD, and hypertension that is uncontrolled despite stable treatment with two to four standard-of-care antihypertensives.

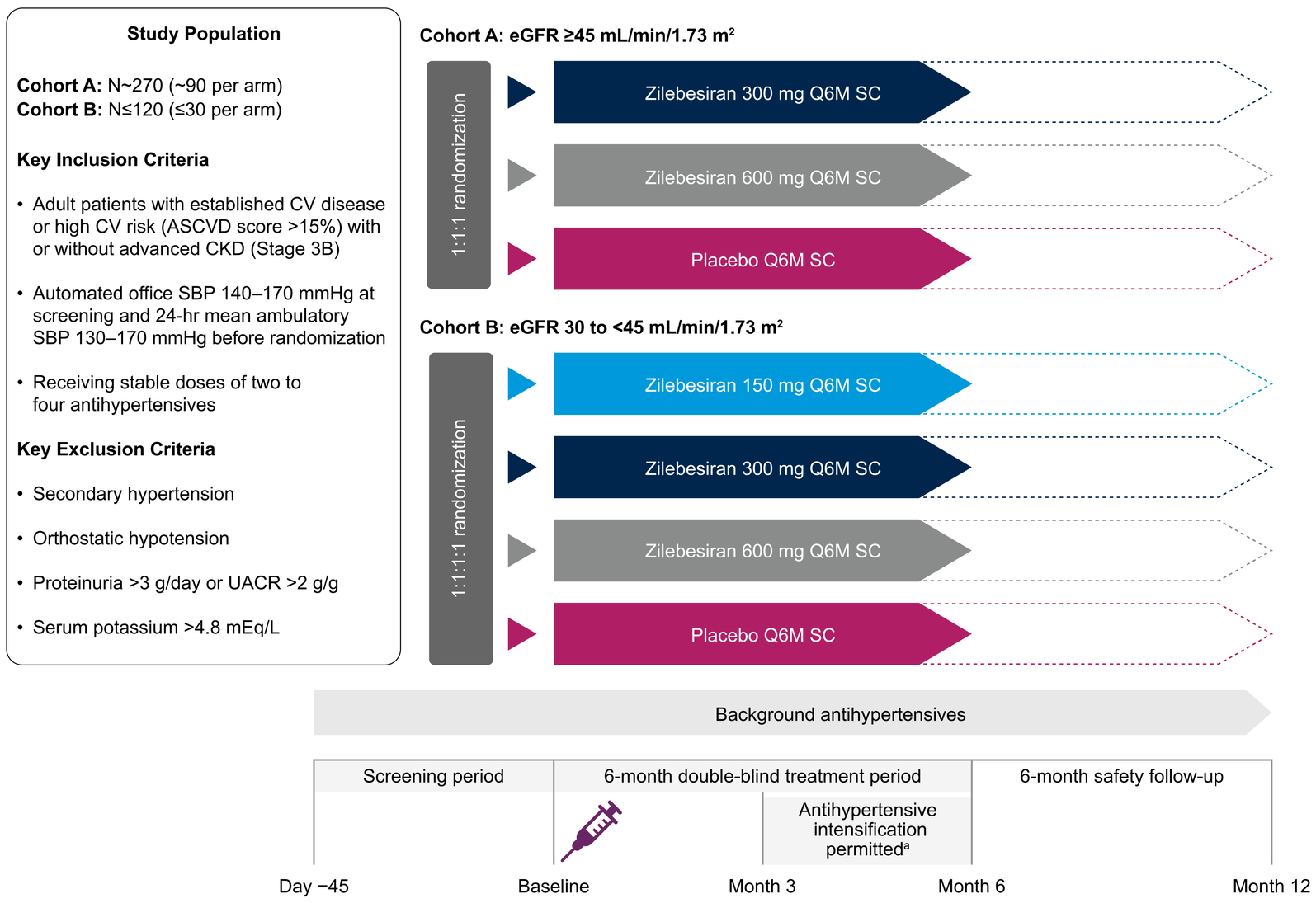
Patient Population

- KARDIA-3 is enrolling adults with seated automated mean office SBP of 140–170 mmHg who are receiving stable therapy with two to four antihypertensives and have one or more of the following characteristics at screening:
  - documented prior CV history, including myocardial infarction, ischemic stroke, or peripheral, coronary, or carotid artery disease
  - a 10-year atherosclerotic CV disease (ASCVD) risk score of >15% as assessed by the American College of Cardiology and American Heart Association ASCVD risk estimator
  - an estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73 m^2 calculated according to the CKD Epidemiology Collaboration equation.

Trial Design

- Patients are being treated in two cohorts (**Figure 2**):
  - Cohort A: approximately 270 patients, eGFR ≥45 mL/min/1.73 m^2
  - Cohort B: up to 120 patients, eGFR 30 to <45 mL/min/1.73 m^2.
- At the start of a 6-month double-blind period, patients are being randomized equally to receive a single SC dose of zilebesiran 300 or 600 mg or placebo in Cohort A, or to receive a single SC dose of zilebesiran 150, 300, or 600 mg or placebo in Cohort B as add-on therapy to a stable background antihypertensive regimen.
  - Cohort B is included in this study to gain additional safety and efficacy data in patients with advanced CKD.

Figure 2. KARDIA-3 Study Design



[a]Antihypertensives may be intensified (defined as an increase in the dose or start of any antihypertensive) in line with investigator judgment for elevated BP.
ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; hr, hour; N, number; Q6M, every 6 months; SBP, systolic blood pressure; SC, subcutaneous; UACR, urine albumin-to-creatinine ratio.

Endpoints

- Study endpoints are shown in **Table 1**.
  - Cohort A will be analyzed based on a statistical model or summarized descriptively, while Cohort B will be summarized descriptively by treatment group.
- Safety will be assessed by monitoring AEs throughout the 6-month double-blind period and in the 6-month safety follow-up period.

Table 1. KARDIA-3 Key Study Endpoints

Endpoint		Time Point Assessed
Primary	Change from baseline in mean seated office SBP	Month 3
Secondary	Change from baseline in mean seated office SBP	Month 6
	Change from baseline in mean seated office DBP	Month 3, Month 6
	Change from baseline in 24-hr, daytime, and nighttime mean ambulatory SBP and DBP	Month 3, Month 6
	Proportion of patients with mean seated office SBP <140 mmHg and/or reduction of ≥10 mmHg without intensification of antihypertensive regimen	Month 6
	Proportion of patients with 24-hr mean ambulatory SBP <130 mmHg and/or reduction of ≥10 mmHg without intensification of antihypertensive regimen	Month 6
	Change from baseline in serum AGT levels	Through Month 6
Exploratory: cardiac and renal biomarkers	Change from baseline in cardiac biomarkers: hscTnT, hsCRP, NT-proBNP	Through Month 6
	Change from baseline in renal biomarkers: UACR	Through Month 6
Safety	Frequency of AEs	Through Month 6

AE, adverse event; AGT, angiotensinogen; DBP, diastolic blood pressure; hr, hour; hsCRP, high-sensitivity C-reactive protein; hscTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

REFERENCES

1. Desai AS *et al. N Engl J Med* 2023;389:228–38.
2. Pugh C *et al. Drugs* 2019;79:365–79.
3. National Kidney Foundation. High blood pressure and chronic kidney disease. 2024. Available from: https://www.kidney.org/news/newsroom/factsheets/High-Blood-Pressure-and-CKD (Accessed April 25, 2024).
4. Bakris GL *et al. JAMA* 2024;331:740–9.
5. Desai AS *et al.* Oral presentation 21475 presented at the American College of Cardiology Annual Scientific Session & Expo, April 7, 2024, Atlanta, GA, USA.

DISCLOSURES

AH, **ZX**, **TZ**, and **IB** are employees of and shareholders in Alnylam Pharmaceuticals.
NP has received research support from Alnylam Pharmaceuticals, Amgen, Bayer, Boehringer Ingelheim, Eggland's Best, Eli Lilly, Merck, Novartis, and Novo Nordisk, has provided consultation for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, CRISPR Therapeutics, Eli Lilly, Esperion, Merck, Novartis, and Novo Nordisk, has been an executive committee member for trials sponsored by Amgen, AstraZeneca, and Novo Nordisk, has been on data and safety monitoring boards for trials sponsored by Johnson & Johnson and Novartis, and has taken part in a medical advisory board for Miga Health.
GLB has received consulting fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, GlaxoSmithKline, inREGEN, Ionis Pharmaceuticals, Janssen, KBP Biosciences, and Novo Nordisk, and is an Editor at the *American Journal of Nephrology*.
MW has received consulting fees from Ablative Solutions, Alnylam Pharmaceuticals, Medtronic, and ReCor.
MB and **SD** are employees of and shareholders in F. Hoffmann-La Roche.
CBG has held grants or contracts from Alnylam Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, FDA, Janssen, Lilly, Novartis, Pfizer, Philips, and Roche, has received consulting fees and speaker fees from AbbVie, Abiomed, Alnylam Pharmaceuticals, Anthos, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cadrenal, Cardionomic, CeleCore Therapeutics, HengRui, Janssen, Medscape, Medtronic Inc., Merck, NIH, Novartis, Novo Nordisk, Pfizer, Philips, REATA, Roche, and Veralox, has participated in advisory boards for Bayer, Cardionomics, Janssen, Merck, Novartis, Novo Nordisk, and Veralox, and holds stocks or stock options in Tenac.io.

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the KARDIA-3 study.
Acknowledgments: Medical writing support provided by Valentina Bart PhD of PharmaGenesis Cardiff, Cardiff, UK, was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice (GPP) guidelines.
Funding: Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

Presented at the 33rd European Meeting on Hypertension and Cardiovascular Protection, May 31–June 3, 2024, Berlin, Germany