Media & Investor Release

Roche and Alnylam report positive topline results from the Phase II KARDIA-2 study in people with hypertension, demonstrating clinically significant blood pressure reductions with zilebesiran when added to standard of care

- **KARDIA-2 study met its primary endpoint, demonstrating clinically significant systolic blood pressure reductions in each treatment arm at month three**
- **Zilebesiran added to a standard of care hypertension medication demonstrated an encouraging safety and tolerability profile in adults with mild to moderate uncontrolled hypertension, and results support the potential for twice-yearly dosing**
- **Roche and Alnylam have initiated the Phase II KARDIA-3 study in adults with uncontrolled hypertension at high cardiovascular risk**
- **KARDIA-2 study results will be presented as a late-breaking abstract in April at the 2024 American College of Cardiology Annual Scientific Session**

Basel, 05 March 2024 - Roche (SIX: RO, ROG; OTCQX: RHHBY) and Alnylam announced today that the Phase II KARDIA-2 study [NCT05103332] of zilebesiran, an investigational RNAi therapeutic in development for the treatment of hypertension (high blood pressure) - the leading cause of cardiovascular disease worldwide[1] - met its primary endpoint. People with mild to moderate hypertension treated with zilebesiran added to a standard of care hypertension medication experienced a clinically and statistically significant reduction in systolic blood pressure at month three. Zilebesiran added to a standard of care demonstrated an encouraging safety and tolerability profile.

“With twice-yearly dosing in combination with standard of care medication, zilebesiran has strong potential to sustain lower blood pressure and reduce the risk of stroke, heart attack and death that can result from inadequate treatment,” said Levi Garraway, M.D., Ph.D., Roche’s Chief Medical Officer and Head of Global Product Development. “We look forward to continuing the zilebesiran Phase II study programme with Alnylam as we seek to provide transformative impact for millions of people living with uncontrolled hypertension.”

Hypertension, or high blood pressure, is the leading cause of cardiovascular disease worldwide and a major risk for premature mortality.[1] It is a growing global health crisis, responsible for around 10 million deaths worldwide each year.[2] Approximately one in three adults are living with hypertension globally, and there remains a significant unmet medical need given the poor rates of adherence to existing treatments.[3] Currently, up to 80% of people with hypertension have blood pressure that remains uncontrolled despite the

availability of several classes of oral hypertension treatments, leaving them at an increased risk of cardiovascular, cerebrovascular, and renal disease.[4-8]

The Phase II KARDIA-2 trial results will be presented as a late-breaking abstract at the 2024 American College of Cardiology Annual Scientific Session (6-8 April 2024, Atlanta, Georgia, USA). The KARDIA-2 results build on the positive Phase II KARDIA-1 [NCT04936035] data, presented at the congress of the American Heart Association Scientific Sessions in November 2023, and published in *JAMA* in February 2024.[9,10] Roche and Alnylam have now initiated the global Phase II KARDIA-3 study [NCT06272487] designed to evaluate the efficacy of zilebesiran when added to two or more hypertension medications in people with uncontrolled hypertension at high cardiovascular risk.

About the KARDIA-2 study[11]

The Phase II KARDIA-2 trial is a randomised, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of zilebesiran, when added to a standard of care, in adults with mild-to-moderate hypertension. This global, multicentre trial enrolled 672 adults with hypertension. Patients who met all inclusion/exclusion criteria during a screening period were randomised into three different cohorts to receive open-label therapy with olmesartan, amlodipine or indapamide as their protocol-specified background hypertension medication during a run-in period of at least four weeks. Following the run-in period, eligible patients were randomised 1:1 to receive zilebesiran 600 mg or placebo in addition to their protocol-specified background hypertension medication for six months. Once the double-blind period has concluded, all patients will complete a safety assessment after six months of treatment.

The primary endpoint is the change from baseline mean systolic blood pressure (SBP) at month three, assessed by 24-hour ambulatory blood pressure monitoring (ABPM). Additional endpoints include the change in 24-hour mean SBP after six months of treatment assessed by ABPM, change in office SBP at months three and six, and change in diastolic blood pressure measured by ABPM and office blood pressure at months three and six. Safety will be assessed throughout the study.

About zilebesiran

Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic targeting angiotensinogen (AGT) in development for the treatment of hypertension in high unmet need populations. AGT is the most upstream precursor in the Renin-Angiotensin-Aldosterone System (RAAS), a cascade which has a demonstrated role in blood pressure regulation and its inhibition has well-established antihypertensive effects. Zilebesiran inhibits the synthesis of AGT in the liver, potentially leading to durable reductions in AGT protein and ultimately, in the vasoconstrictor angiotensin (Ang) II. Zilebesiran utilises Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugate technology, which enables infrequent subcutaneous dosing with increased selectivity and the potential to achieve tonic blood pressure control

demonstrating consistent and durable blood pressure reductions throughout a 24-hour period, sustained up to six months after a single dose of zilebesiran. The safety and efficacy of zilebesiran have not been established or evaluated by the U.S. Food and Drug Administration, European Medicines Agency, or any other health authority. Zilebesiran is being co-developed and co-commercialised by Roche and Alynlam.

Zilebesiran Phase II clinical development overview:

Study	Overview of protocol
KARDIA-1 [NCT04936035]	Evaluated zilebesiran monotherapy in people with mild to moderate hypertension. Met primary endpoint.
KARDIA-2 [NCT05103332]	Evaluated zilebesiran when added to a standard of care hypertension medication in people with mild to moderate hypertension. Met primary endpoint.
KARDIA-3 [NCT06272487]	Designed to evaluate zilebesiran when added to two or more hypertension medications in people with uncontrolled hypertension at high cardiovascular risk.

About hypertension

More than one billion adults are living with hypertension worldwide, which is a major risk factor for cardiovascular disease and premature mortality.[4] Early effects of hypertension can include subtle target organ damage such as left-ventricular hypertrophy and cognitive dysfunction.[12,13] Over time, uncontrolled hypertension can lead to cardiovascular disease including stroke (ischaemic and haemorrhagic), coronary artery disease, heart failure, peripheral artery disease, chronic kidney disease and end-stage renal disease, dementia, and Alzheimer's disease.[5-8]

There remains a significant unmet medical need, as poor rates of adherence to daily medications can result in inconsistent blood pressure control and an increased risk for stroke, heart attack, and premature death.[3] In particular, there are a number of high unmet need settings where novel approaches to hypertension warrant additional development focus, including patients with high cardiovascular risk.[14]

About Roche

Founded in 1896 in Basel, Switzerland, as one of the first industrial manufacturers of branded medicines, Roche has grown into the world's largest biotechnology company and the global leader in in-vitro diagnostics. The company pursues scientific excellence to discover and develop medicines and diagnostics for improving and saving the lives of people around the world. We are a pioneer in personalised healthcare and want to further transform how

healthcare is delivered to have an even greater impact. To provide the best care for each person we partner with many stakeholders and combine our strengths in Diagnostics and Pharma with data insights from the clinical practice.

In recognising our endeavour to pursue a long-term perspective in all we do, Roche has been named one of the most sustainable companies in the pharmaceuticals industry by the Dow Jones Sustainability Indices for the fifteenth consecutive year. This distinction also reflects our efforts to improve access to healthcare together with local partners in every country we work.

Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan.

For more information, please visit www.roche.com.

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F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Group Communications Roche Group Media Relations
Phone +41 61 688 88 88 www.roche.com

Roche Global Media Relations

Phone: +41 61 688 8888 / e-mail: media.relations@roche.com

Hans Trees, PhD
Phone: +41 79 407 72 58

Nathalie Altermatt
Phone: +41 79 771 05 25

Simon Goldsborough
Phone: +44 797 32 72 915

Karsten Kleine
Phone: +41 79 461 86 83

Nina Mählitz
Phone: +41 79 327 54 74

Kirti Pandey
Phone: +49 172 6367262

Dr. Rebekka Schnell
Phone: +41 79 205 27 03

Sileia Urech
Phone: +41 79 935 81 48

Roche Investor Relations

Dr. Bruno Eschli
Phone: +41 61 68-75284
e-mail: bruno.eschli@roche.com

Dr. Sabine Borngräber
Phone: +41 61 68-88027
e-mail: sabine.borngraeber@roche.com

Dr. Birgit Masjost
Phone: +41 61 68-84814
e-mail: birgit.masjost@roche.com

Investor Relations North America

Loren Kalm
Phone: +1 650 225 3217
e-mail: kalm.loren@gene.com