Media & Investor Release

Roche and Alnylam advance zilebesiran into global phase III cardiovascular outcomes trial for people with uncontrolled hypertension

- **Phase III trial informed by comprehensive KARDIA data set generated through three Phase II studies: KARDIA-1, KARDIA-2 and KARDIA-3**
- **In the Phase II KARDIA-3 study, presented today as a late breaker at the European Society of Cardiology Congress 2025, zilebesiran demonstrated clinically meaningful reductions in office systolic blood pressure at month three with continuous control through month six**
- **Zilebesiran, a potential best-in-disease RNAi anti-hypertensive with twice-yearly subcutaneous dosing, demonstrated encouraging safety when combined with two or more antihypertensives**
- **Phase III cardiovascular outcomes trial expected to be initiated by the end of the year**

Basel, 30 August 2025 - Roche (SIX: RO, ROG; OTCQX: RHHBY) and Alnylam (Nasdaq: ALNY) today announced the decision to initiate a Phase III cardiovascular outcomes trial (CVOT) to evaluate the ability of zilebesiran, a RNAi therapeutic, to reduce the risk of major adverse cardiovascular events in patients with uncontrolled hypertension. This decision was informed by the comprehensive KARDIA Phase II programme, including KARDIA 1, KARDIA 2 and the most recent KARDIA-3 study evaluating the efficacy and safety of zilebesiran in patients with uncontrolled hypertension and high cardiovascular (CV) risk, on two to four standard of care antihypertensives. In particular, KARDIA-3 aimed to define the patient population to be investigated in the Phase III CV outcomes trial.

Results of KARDIA-3 showed that a single dose of zilebesiran (300 mg every six months, subcutaneous injection) resulted in clinically meaningful placebo-adjusted reductions of office systolic blood pressure (SBP) in all comers at the month three primary endpoint (-5.0 mmHg; p=0.0431) with sustained benefits out to month six (-3.9 mmHg; 95% CI: [-8.5, 0.7]). There were no additional benefits of the 600 mg dose at month three (-3.3 mmHg; p=0.1830) or month six (-3.6 mmHg; 95% CI: [-8.2, 1.0]). The overall KARDIA-3 study did not meet the pre-specified definition for statistical significance, because of a multiplicity statistical testing approach. However, the study met the aim of identifying the patient population that could potentially benefit the most from zilebesiran and also showed encouraging safety and clinically meaningful placebo adjusted reductions in blood pressure.

As observed in the KARDIA-2 Phase II study, the KARDIA-3 results support a robust benefit of combining zilebesiran with a diuretic, a commonly used antihypertensive. In an analysis of

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patients that were on diuretics and had a baseline BP >140 mm Hg, the placebo-adjusted reduction was -9.2mmHg; (-17.3, -1.2) at month three and -8.3mmHg (-16.4, -0.2) at month six. A precedent for enhanced blood pressure reduction conferred by this type of combination is established in both literature and clinical practice.

“Zilebesiran has the potential to become a best-in-disease treatment for many patients with uncontrolled hypertension. Its blood pressure-lowering effects and twice-yearly dosing could reduce the risk of serious health complications and death,” said Levi Garraway, MD, PhD, Roche’s chief medical officer and head of Global Product Development. “Detailed analysis of our comprehensive Phase II clinical trials have informed our decision to move zilbesiran into Phase III. Despite current treatment options, up to 80% of people with hypertension do not achieve adequate blood pressure control putting them at higher risk of cardiovascular events. Therefore, additional treatment options are needed."

Zilebesiran also demonstrated encouraging safety in patients with comorbidities on multiple background therapies – more than 90% of whom were receiving treatment with an ACE inhibitor or an Angiotensin Receptor Blocker (ARB). These findings reinforce confidence in zilebesiran’s ability to be combined with standard of care antihypertensives.

As a result, the ZENITH (**Z**ileb**E**sira**N** Card**I**ovascular Ou**T**come Study in **H**ypertension) Phase III trial has been submitted to global regulators and is expected to be initiated by the end of 2025. ZENITH will be a CVOT enrolling approximately 11,000 patients and evaluating zilebesiran (300 mg) every six months compared to placebo in patients with uncontrolled hypertension with either established CV disease or at high risk for CV disease on two or more antihypertensives, one being a diuretic.

Hypertension is the primary cause of and number one modifiable risk factor for cardiovascular disease. An estimated one in three adults, over 1,2 billion people worldwide, have hypertension and despite the wide availability of antihypertensives, up to 80% of them do not achieve adequate blood pressure control. Poor adherence to daily oral therapies is an important contributor to poor blood pressure control and CV outcomes. An effective long-acting therapy that provides continuous control of blood pressure may help to reduce the burden of uncontrolled hypertension.

With its growing cardiometabolic portfolio and strong diagnostic expertise, Roche is advancing transformative standards of care to improve the lives of people living with cardiometabolic diseases as well as reducing the significant burden on healthcare systems and society.

About the KARDIA-3 study

KARDIA-3 (NCT06272487), the third phase II study in the KARDIA programme, included two Cohorts (A and B). Cohort A assessed zilebesiran in patients with eGFR ≥ 45 mL/min/1.73m2,

while Cohort B included patients with advanced kidney dysfunction (i.e., eGFR between 30 and <45 mL/min/1.73m2). Cohort A enrolled 270 patients who were randomised to treatment with zilebesiran (300 mg or 600 mg) or placebo. Randomisation was stratified by background diuretic use, baseline blood pressure, and race. The primary endpoint was change in office SBP at month three. Key secondary endpoints were changes in office SBP at month six and change in 24-hour mean ambulatory SBP at months three and six.

At baseline, 144 (53.3%), 96 (35.6%) and 30 (11.1%) patients were on two, three, or over three antihypertensives, respectively, with ~91% of patients taking ACE inhibitors/ARBs, ~66% of patients taking a diuretic, and ~58% of patients taking calcium channel blockers. The mean baseline office and 24-hour mean ambulatory SBP were 143.6 mmHg and 142.4 mmHg, respectively (N= 270).

KARDIA-3 Cohort A Primary Results (Placebo-Adjusted Changes from Baseline):

Cohort A Study population	Endpoint	Month three change (censored)* †	Month six change (all collected) ** †
Overall study population (N=270)	Office SBP (300 mg)	-5.0 (-9.9, -0.2) *p=0.0431*	-3.9 (-8.5, 0.7)
	24-Hour Mean Ambulatory SBP (300 mg)	-3.6 (-7.7, 0.4)	-5.5 (-9.4, -1.5)
Subgroup (N=110) (Diuretics and with baseline SBP≥140mmHg) ***	Office SBP (300 mg)	-9.2 (-17.3, -1.2)	-8.3 (-16.4, -0.2)
	24-Hour Mean Ambulatory SBP (300 mg)	-6.8 (-13.9, -0.2)	-6.6 (-13.3, -0.0)
*** *Post hoc Analysis*	**Censored analysis excludes patients who intensified antihypertensive use within two weeks of visits at month three* ***All collected analysis includes all available patient data, regardless of medication changes, through visits at month six* *The statistical testing procedure, The Hochberg Method, was used for multiplicity control, requiring both doses to have a p<0.05 or one dose to have a p<0.025 to be considered statistically significant. As the primary endpoint was not significant, statistical significance could not be claimed for secondary endpoints.* *†The placebo adjusted SBP changes are shown as LS mean (95% CI)*		

In summary, in the Cohort A overall study population, zilebesiran 300 mg achieved clinically meaningful reductions in office SBP at month three, with sustained benefits out to month six, compared to placebo. No incremental SBP reductions were observed with zilebesiran 600 mg at months three or six. Post-hoc analyses suggest that a greater blood pressure-lowering effect with zilebesiran was observed in patients on diuretic therapy and uncontrolled hypertension at baseline (with office SBP ≥140). Reductions in blood pressure were sustained over six months, and the entire 24-hour period. Incremental reductions were also observed at nighttime, a period during which blood pressure elevation is a strong predictor of cardiovascular risk.

Consistent with prior studies, zilebesiran demonstrated an encouraging safety profile when added to two or more background antihypertensives (over 90% of whom were receiving treatment with an ACE inhibitor or an ARB). Most adverse events were mild or moderate, non-serious, and transient with few requiring intervention; rates of hyperkalaemia, kidney dysfunction and hypotension were low. Across study arms, serious adverse events were observed in 3.8% and 4.5% in zilebesiran and placebo-treated patients, respectively. No deaths were reported during the six-month double-blind period.

Results from KARDIA-3 Cohort B are expected to be presented at an upcoming medical meeting.

About the ZENITH CVOT

The global phase III ZENITH CVOT is an event-driven study that will enroll approximately 11,000 patients in over 30 countries to evaluate zilebesiran 300 mg in patients with uncontrolled hypertension, despite the use of at least two standard of care antihypertensives (one being a diuretic), and with either established cardiovascular disease (CVD) or at high risk for CVD. The primary objective will be to assess the impact of zilebesiran on reducing the risk of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or heart failure (HF) events (hospitalisation for HF or urgent HF visit), compared to placebo.

About Zilebesiran

Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of hypertension to reduce cardiovascular risk in high unmet need populations. Zilebesiran targets angiotensinogen (AGT), the most upstream precursor in the Renin-Angiotensin-Aldosterone System (RAAS), a cascade which has a role in blood pressure (BP) regulation. 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 utilizes Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugate technology, which enables infrequent biannual subcutaneous dosing and increased selectivity. Zilebesiran has demonstrated the ability to provide continuous control of blood pressure with biannual dosing in patients with mild-to-moderate hypertension as a monotherapy and in combination with standard-of-care antihypertensives, as well as in patients with high cardiovascular risk and uncontrolled hypertension despite the use of multiple background therapies. The safety and efficacy of zilebesiran have not been established or evaluated by the FDA, EMA or any other health authority. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

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 of the study demonstrating a clinically significant reduction of systolic

	blood pressure at three months of treatment compared with placebo (>15 mmHg reduction of 24h mean Systolic Blood Pressure (SBP) at 3 months vs. placebo at two highest doses (300mg, 600mg), p<0.0001).
KARDIA-2 [NCT05103332]	Evaluated zilebesiran when added to a standard of care hypertension medication in people with mild to moderate hypertension. Met primary endpoint demonstrating that zilebesiran resulted in clinically and statistically significant additive, placebo-adjusted reductions in 24-hour mean systolic blood pressure (SBP) of up to 12.1 mmHg at month three (measured per ABPM).
KARDIA-3 [NCT06272487]	Evaluated zilebesiran when added to two to four hypertension medications in people with uncontrolled hypertension at high cardiovascular risk. Among individuals with CV disease or at high CV risk who have uncontrolled HTN, a single dose of zilebesiran 300 mg and 600 mg led to respective 5.0 mmHg and 3.3 mmHg reductions in office systolic BP at three months compared with placebo, although statistical significance was not reached.

About Cardiovascular Disease and Hypertension

Cardiovascular disease (CVD) is a global health crisis and a leading cause of death worldwide, responsible for approximately 20 million deaths annually.[1,2] Hypertension is the primary cause of and number one modifiable risk factor for CVD.[3] An estimated 1 in 3 adults worldwide have hypertension, and, despite wide availability of antihypertensives, up to 80% of all patients, and up to a third of treated patients, do not reach and maintain blood pressure (BP) targets.[4] Even when blood pressure appears well managed, continuous control of BP may remain suboptimal, leading to variability in BP during the 24-hour period and in the long-term, putting patients at greater risk of cardiovascular events and end organ damage.[5-11] These patients require novel approaches that not only reduce BP, but also lower overall cardiovascular risk.

About RNAi

RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today.[12] Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.[13] By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines known as RNAi therapeutics is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function upstream of today's medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing or disease pathway proteins, thus preventing them from being made.[12] This is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases.

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.

For over 125 years, sustainability has been an integral part of Roche's business. As a science-driven company, our greatest contribution to society is developing innovative medicines and diagnostics that help people live healthier lives. Roche is committed to the Science Based Targets initiative and the Sustainable Markets Initiative to achieve net zero by 2045.

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

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