Media & Investor Release

Roche and Alnylam report positive topline results from Phase 2 study KARDIA-1 of zilebesiran, an investigational RNAi therapeutic in development to treat hypertension in patients at high risk of cardiovascular disease

- **Zilebesiran met primary endpoint demonstrating greater than 15 mmHg reduction of systolic blood pressure at three months of treatment compared to placebo**
- **Study met key secondary endpoints showing consistent and sustained reductions of systolic blood pressure at six months**
- **Zilebesiran demonstrated an encouraging safety and tolerability profile in adult patients with mild-to-moderate hypertension**
- **Full study results to be presented at an upcoming scientific conference**

Basel, 7 September 2023 - Roche (SIX: RO, ROG; OTCQX: RHHBY) and Alnylam announced today that the Phase 2 study KARDIA-1 of zilebesiran, an investigational RNAi therapeutic targeting liver-expressed angiotensinogen (AGT), met the primary endpoint. Zilebesiran demonstrated a clinically significant reduction in 24-hour mean systolic blood pressure (SBP) at month three, achieving a placebo-subtracted reduction greater than 15 mmHg with both 300 and 600 mg doses ($p < 0.0001$). The study also met key secondary endpoints showing consistent and sustained reductions of SBP at six months supporting quarterly or biannual dosing. In addition, the study showed that zilebesiran was associated with a potent and durable reduction of serum AGT levels through month six while demonstrating an encouraging safety and tolerability profile.

“These early results indicate the potential for zilebesiran to achieve sustained blood pressure reduction with quarterly or biannual dosing,” said Levi Garraway, M.D., Ph.D., Roche’s Chief Medical Officer and Head of Global Product Development. “Also, these data underscore the potential of this investigational medicine to provide transformative impact for many people living with uncontrolled hypertension.”

The Phase 2 trial KARDIA-1 is a randomised, double-blind, placebo-controlled, multi-centre global dose-ranging study designed to evaluate the efficacy and safety of zilebesiran as monotherapy in adults with mild-to-moderate hypertension. The study enrolled 394 adults representing a diverse patient population with untreated hypertension or who were on stable therapy with one or more anti-hypertensive medications (after a washout period).

Hypertension is a growing global health crisis responsible for around 10 million deaths worldwide each year. Approximately one in three adults are living with hypertension globally, with up to 80% of individuals remaining uncontrolled despite the availability of several

classes of oral anti-hypertensive treatments leaving them at an increased risk of cardiovascular, cerebrovascular and renal disease.

Earlier this year, Roche entered the partnership with Alnylam to co-develop and co-commercialise zilebesiran. The KARDIA study program also includes the Phase 2 study KARDIA-2 of zilebesiran used in combination with one of three standard classes of anti-hypertensive medications which completed enrollment in June 2023. The topline results of KARDIA-2 are expected in early 2024.

About the KARDIA-1 study

The Phase 2 KARDIA-1 trial enrolled 394 adults with untreated hypertension or who were on stable therapy with one or more anti-hypertensive medications. Any patients taking prior anti-hypertensive medications completed at least a two- to four-week wash-out before randomisation. Patients were randomised to one of five treatment arms during a 12-month double blind (DB) period and DB extension period: 150 mg zilebesiran subcutaneously once every six months; 300 mg zilebesiran subcutaneously once every six months; 300 mg zilebesiran subcutaneously once every three months; 600 mg zilebesiran subcutaneously once every six months; or placebo. Patients who received placebo were randomised to one of the four initial zilebesiran dose regimens beginning at Month 6. The primary endpoint is defined as the change from baseline in SBP at Month 3, assessed by 24-hour ambulatory blood pressure monitoring (ABPM). Key secondary and exploratory endpoints in this study include additional measures of blood pressure reduction at six months, time-adjusted change in blood pressure, and change in daytime average and night-time average blood pressure.

The study met the primary endpoint demonstrating a dose-dependent, clinically significant reduction in 24-hour mean systolic blood pressure (SBP) measured by ABPM at month 3, achieving a placebo-subtracted reduction greater than 15 mmHg ($p < 0.0001$) with both 300 mg and 600 mg doses. The study also met key secondary endpoints including change in 24-hour mean SBP as measured by ABPM at month 6 as well as change in office SBP at month 3 and month 6, for all zilebesiran arms, compared to placebo.

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 (BP) regulation and its inhibition has well-established anti-hypertensive 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 Stabilisation Chemistry Plus (ESC+) GalNAc-conjugate technology. It enables infrequent subcutaneous dosing with increased selectivity and the potential to achieve tonic blood

pressure control demonstrating consistent and durable blood pressure reduction 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 FDA, EMA or any other health authority. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

About hypertension

Hypertension, or high blood pressure, is the leading cause of cardiovascular disease worldwide, and a major risk for premature mortality. Early effects of hypertension can include subtle target organ damage such as left-ventricular hypertrophy and cognitive dysfunction. 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.

There remains a significant unmet medical need, especially given the poor rates of adherence to existing daily oral medications, resulting in inconsistent blood pressure control and an increased risk for stroke, heart attack and premature death. 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.

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 thirteenth 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.

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