Alnylam Pharmaceuticals Conference Call to Discuss Zilebesiran Collaboration Agreement with Roche

July 24, 2023

Agenda

Welcome

- Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Introduction

- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

Hypertension Overview & Zilebesiran Program

- Pushkal Garg, M.D.
  Chief Medical Officer

Roche Partnership Details

- Evan Lippman
  Chief Corporate Development and Strategy Officer

Financial Considerations

- Jeff Poulton
  Chief Financial Officer

Q&A Session

Alnylam Forward Looking Statements

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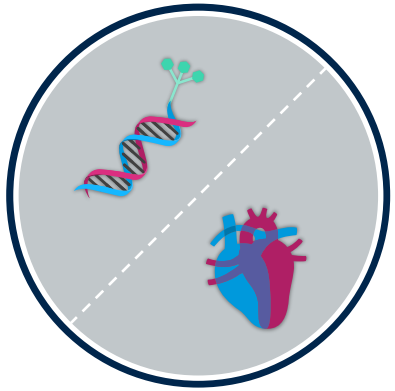
Yvonne Greenstreet, MBChB, MBA

Chief Executive Officer

Introduction

Alnylam + Roche Partnership

Reimagining Treatment of Hypertension



Partnership to realize full potential of zilebesiran as innovative treatment for hypertension

- Enables robust development plan with outcomes data at launch, optimizing commercial potential
- Significant economics enables Alnylam investment across broad pipeline
- Builds go-to-market expertise and commercial capabilities
- Advances *Alnylam P^{5}x25* strategy

Strong Portfolio Potential Beyond Ultra Rare/Specialty Diseases

ULTRA RARE

GIVLAARI®
OXLUMO®

RARE/SPECIALTY

ONPATTRO®: hATTR w/ PN[1]
AMVUTTRA® : hATTR w/ PN[2]
Patisiran: ATTR w/ CM[3]
Vutrisiran: ATTR w/CM[3]

ALN-TTRsc04
Fitusiran
Belcesiran

PREVALENT

Leqvio®[4]
Zilebesiran
ALN-HBV02 (VIR-2218)
ALN-APP

ALN-HSD
ALN-PNP
ALN-KHK

1 ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; 2 AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults and in the EU and Japan for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; 3 Patisiran and vutrisiran have not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding their safety or effectiveness in this population; 4 Leqvio is approved in the U.S. for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce low-density lipoprotein cholesterol, and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia.

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Pushkal Garg, M.D.

Chief Medical Officer

Hypertension Overview & Zilebesiran

Uncontrolled Hypertension is a Global Health Crisis

Hypertension is Highly Prevalent and Carries Substantial Risk of CV Morbidity and Mortality

Primary Hypertension[1] in 7 Major Markets, 2020

~219MM

High CV Risk with Hypertension[2] in 7 Major Markets, 2020[3]

~77MM

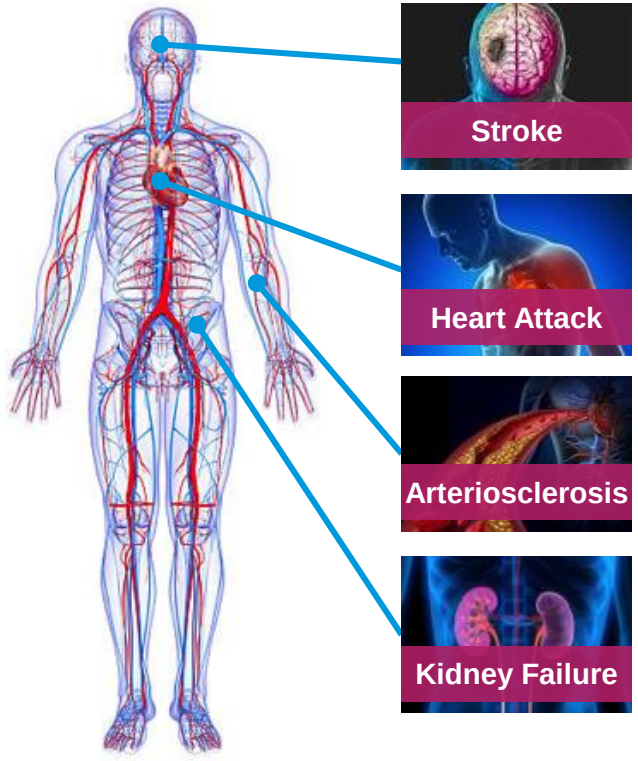
~80%

UNCONTROLLED HYPERTENSION
(>130/80 mmHg despite treatment)[4]

Hypertension risk further exacerbated by **variability in BP control**, **lack of nighttime dipping**, and **poor medication adherence**

Together, contribute to substantial risk of CV morbidity and mortality

Potential complications of uncontrolled hypertension



BP, blood pressure; CV, cardiovascular; MM, million; mmHg, millimeters of mercury

1. Extrapolated for 7 major markets (7MM) based on proportion of US hypertension population with prior history of CVD or Framingham Risk Score of >10%, excluding patients with history of stroke and women of child-bearing potential; 2. Estimated from multiple sources and internal estimates: Dorans et al. J Am Heart Assoc 2018;7:e008888; Al Kibria et al. Hypertens Res. 2019;42:1631–43; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD; 3. Excluding stroke and WOCBP; 4. https://www.who.int/news-room/fact-sheets/detail/hypertension.

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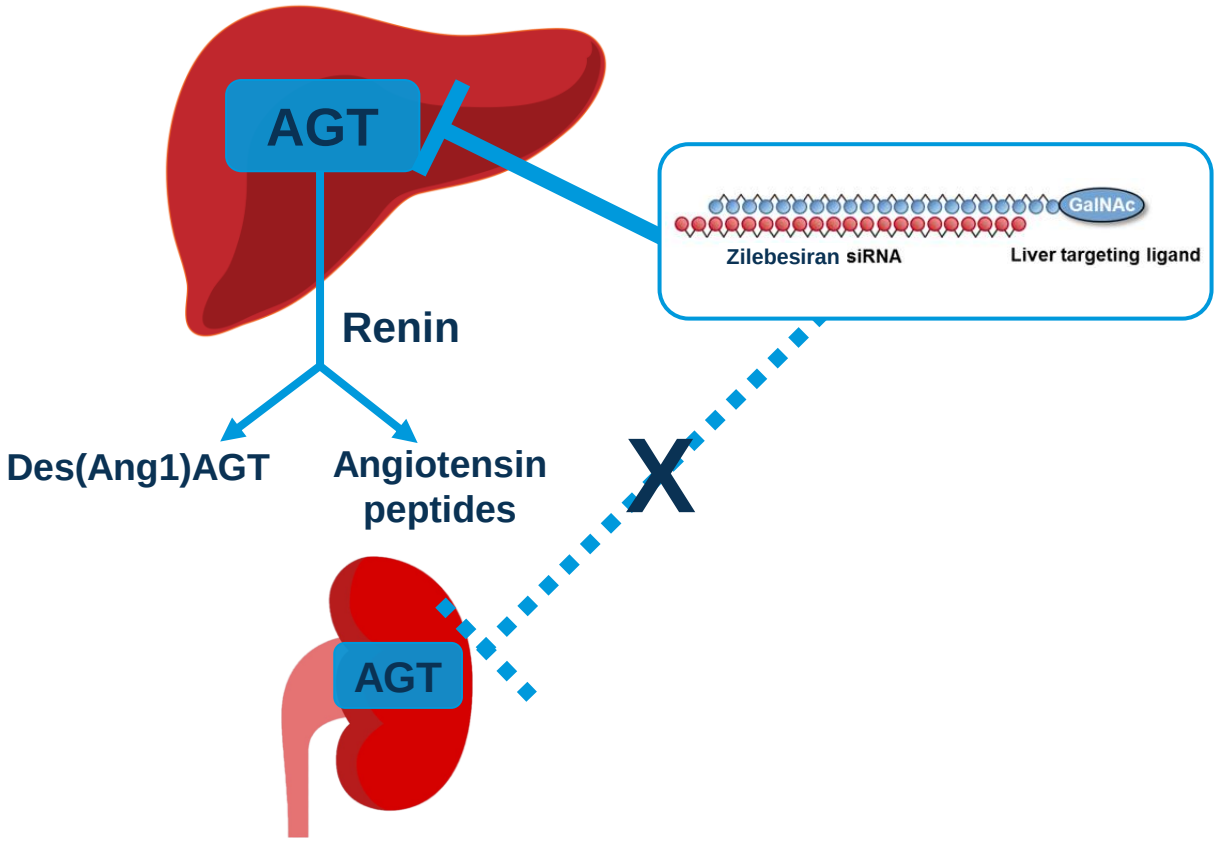
Therapeutic Hypothesis for Zilebesiran

Liver-specific AGT Knockdown



Potential Mechanistic Advantages

- **Liver-specific silencing of AGT**
- **Prolonged duration of action**
  - Consistent and durable BP response
  - Infrequent dose administration, with potential for improved adherence
- **Improved RAAS inhibition**
  - Potentially avoiding RAAS escape phenomena

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-Acetylgalactosamine; q3M; every 3 months; RAAS, renin angiotensin aldosterone system; siRNA, small interfering ribonucleic acid.
The safety and efficacy of zilebesiran in patients with hypertension have not been established or reviewed by any regulatory agency.

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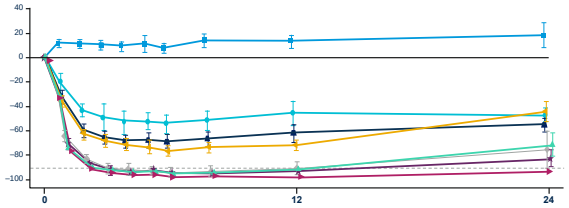
Zilebesiran: Potential Novel Treatment for Patients with Hypertension

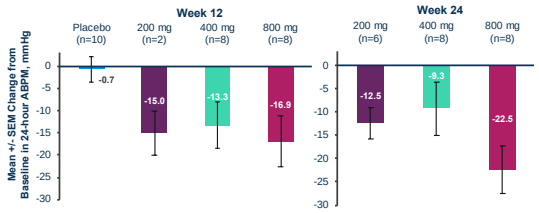
Compelling Phase 1 Data Support Transformative Product Profile

Serum AGT Lowering



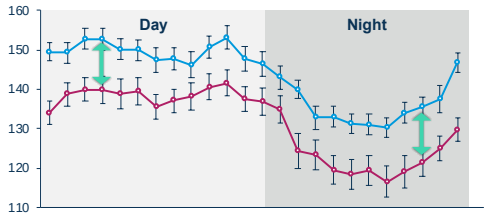
>90% mean serum AGT reduction for 6 months*

Blood Pressure Reduction



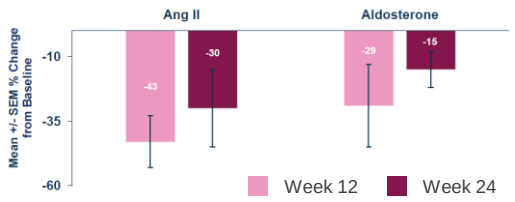
>20 mmHg SBP reduction at 6 months*

Consistent BP Reduction



Tonic BP control demonstrated over 24hr*

Change in RAAS Biomarkers



Durable reduction in Ang II & aldosterone*

Phase 1 Safety Summary

- Zilebesiran generally well tolerated; no treatment-related SAEs
- All AEs were mild or moderate in severity and resolved without intervention
- No patient required intervention for low blood pressure, and there were no elevations in liver enzymes, serum creatinine or potassium during study

* After single dose of zilebesiran 800mg

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Ongoing Phase 2 Clinical Development Plan

KARDIA-1

Monotherapy Phase 2 Study (N = 394)

- Evaluate efficacy and safety of zilebesiran as monotherapy in patients with mild-to-moderate hypertension
- Exploring multiple doses and dosing regimens
- Enrollment completed December 2022; topline results expected mid-2023; full results to be presented at future medical conference

KARDIA-2

Combination Phase 2 Study (N = 672)

- Evaluate efficacy and safety of zilebesiran as concomitant therapy
- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Enrollment completed June 2023; topline results expected early 2024

ARB, angiotensin receptor blocker.
KARDIA-1: NCT04936035
KARDIA-2: NCT05103332

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Zilebesiran Late Phase Development Update

Designed to Deliver Robust Label with CV Outcomes Benefits at Launch

Phase 1 ✓ → **Phase 2** → **Phase 3** → ★

Multicenter Phase 1 study evaluating safety, tolerability, and PK/PD in patients with mild-to-moderate hypertension

KARDIA

Phase 2 program evaluating zilebesiran as monotherapy and in combination in patients with mild-to-moderate hypertension

NEW: KARDIA-3

- Multi-agent combination study (2+ background standard of care therapies) in patients with uncontrolled hypertension and high CV risk
- *Expected initiation in 2024*

Phase 3 Cardiovascular Outcomes Trial (CVOT)

NEW: Phase 3 Study:

- Uncontrolled hypertensive patients at high CV risk
- MACE-type endpoint

Launch with label to reduce cardiovascular morbidity and mortality

CV: cardiovascular
MACE: major adverse cardiac events

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Evan Lippman

Chief Corporate Development and Strategy Officer

Roche Partnership Details

Transaction Summary

Furthers Innovation, Provides Access to Expertise, and Delivers Attractive Economics

Global leader delivering transformational RNAi therapeutics to patients through focused research, development and commercialization efforts

Innovative market builder with global reach, capability depth and strong history of success across multiple therapeutic areas

Collaboration Overview

- Joint development:
  - Alnylam leads global development and U.S. regulatory activities for primary indication
  - Development cost split: 40% Alnylam / 60% Roche
- U.S. commercialization and Ex-U.S. License
  - U.S. commercialization by both parties with Roche as lead.
  - U.S. profits and losses shared 50/50.
  - Alnylam to receive low double-digit tiered royalties on ex-U.S. sales

Financials

- Up to $2.8 billion in upfront fee and development, regulatory and sales milestones to Alnylam
  - Upfront cash payment of $310 million
  - Substantial development milestones

Bringing an Innovative Therapy Forward to Hypertension Patients Globally

Opportunity to Bring Industry Leading Expertise & Full Resources for Potential Blockbuster Success

- Enormous patient impact and product potential
- Alnylam expertise and track record of success in RNAi
- Roche extensive global footprint and proven history of market innovation

- Alnylam responsible for global development and U.S. regulatory activities, maintaining position as leading RNAi therapeutics company
- Enables Alnylam investment in broader commercial capabilities and sales force reach, building upon TTR expertise

- Deal supports growth and expansion into prevalent indications
- Transaction economics allows significant pipeline, program and capability investment

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Jeff Poulton

Chief Financial Officer

Financial Considerations

Accounting Summary for Transaction*

Transaction Consideration	P&L Impact
$310 million upfront payment	Recognized in collaboration revenue as performance obligations are met (i.e., development through approval, manufacturing tech transfer)
Development milestones	Recognized in collaboration revenue as performance obligation is met (i.e., development through approval)
Commercial milestones	Recognized as collaboration revenue when earned
40 / 60 global development cost share	Alnylam books 100% of R&D expense; 60% reimbursement of R&D opex recognized in collaboration revenue as incurred
50 / 50 U.S. profit split	Recognized in collaboration revenue
Tiered low double-digit royalties on ex-U.S. sales	Recognized as royalty revenue

*Preliminary and subject to change

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Q&A Session

Thank You!

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