Alnylam Pharmaceuticals Conference Call to Discuss Zilebesiran Collaboration Agreement with Roche

July 24, 2023
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

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam’s expectations, beliefs, goals, plans or prospects including, without limitation, expectations regarding Alnylam’s aspiration to become a leading biotech company and the planned achievement of its “Alnylam P5x25” strategy, Roche participation in the development and commercialization of zilebesiran, the potential for zilebesiran to disrupt the treatment paradigm in hypertension, Alnylam’s expectations regarding the receipt of upfront cash, as well as potential development, regulatory and sales milestones and royalties from Roche, Alnylam’s ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam’s projected commercial and financial performance, should be considered forward-looking statements. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam’s efforts to mitigate the impact of the pandemic; Alnylam's ability to successfully execute on its “Alnylam P5x25” strategy; Alnylam’s ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam’s product candidates; actions or advice of regulatory agencies and Alnylam’s ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam’s product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam’s ability to successfully expand the indication for ONPATTRO or AMVUTTRA in the future; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam’s ability to maintain strategic business collaborations; Alnylam’s dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron, Roche and Vir; the outcome of litigation; the potential impact of a current government investigation and the risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with Alnylam’s most recent periodic report (Quarterly Report on Form 10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. In addition, any forward-looking statements represent Alnylam’s views only as of the date of this presentation and should not be relied upon as representing Alnylam’s views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.
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

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.
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, 2020³

~77MM

~80%

UNCONTROLLED HYPTERTENSION

(>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

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

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.
Zilebesiran: Potential Novel Treatment for Patients with Hypertension

Compelling Phase 1 Data Support Transformative Product Profile

>90% mean serum AGT reduction for 6 months*

>20 mmHg SBP reduction at 6 months*

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
Ongoing Phase 2 Clinical Development Plan

**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

**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
Zilebesiran Late Phase Development Update

Designed to Deliver Robust Label with CV Outcomes Benefits at Launch

Phase 1

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

Phase 2

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

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
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
Financial Considerations
## Accounting Summary for Transaction*

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