Nathan (USA)
Diagnosed with AHP

Fourth Quarter and Full Year 2021 Financial Results

February 10, 2022
Agenda

Welcome
• Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Overview
• Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

Commercial Highlights
• Tolga Tanguler
  Chief Commercial Officer

Alnylam Pipeline
• Akshay Vaishnaw, M.D., Ph.D.
  President

Financial Summary and Upcoming Milestones
• Jeff Poulton
  Chief Financial Officer

Q&A Session
Alnylam Forward Looking Statements & Non-GAAP Financial Measures

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, including expectations regarding our aspiration to become a leading biotech company and the planned achievement of our “Alnylam P3x25” strategy, our ability to attain financial self-sustainability, the drivers of our future growth potential, including the potential of our TTR franchise, including the potential launch of vutrisiran for the treatment of hATTR amyloidosis patients with polyneuropathy, if approved by the FDA and other regulatory authorities, as well as the potential for investigational RNAi therapeutics in ATTR cardiomyopathy and in Stargardt disease, the potential opportunity for RNAi therapeutics in prevalent diseases, the achievement of additional pipeline and regulatory milestones, the expected range of net product revenues and net revenues from collaborations and royalties for 2022, and the expected range of aggregate annual GAAP and non-GAAP R&D and SG&A expenses for 2022. 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 our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on our ability to attract and retain talent and to successfully execute on our “Alnylam P3x25” strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including patisiran and vutrisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for OXLUMO, ONPATTRO (and potentially vutrisiran, if approved) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

This presentation references non-GAAP financial measures. These measures are not in accordance with, or an alternative to, GAAP, and may be different from non-GAAP financial measures used by other companies. The items included in GAAP presentations but excluded for purposes of determining non-GAAP financial measures for the periods referenced herein are stock-based compensation expenses, unrealized (gains) losses on marketable equity securities, costs associated with our strategic financing collaboration, upfront payment on license and collaboration agreements, change in estimate of contingent liabilities and loss on contractual settlement. We have excluded the impact of stock-based compensation expense, which may fluctuate from period to period based on factors including the variability associated with performance-based grants for stock options and restricted stock units and changes in our stock price, which impacts the fair value of these awards. We have excluded the impact of the unrealized (gains) losses on marketable equity securities because we do not believe these adjustments accurately reflect the performance of our ongoing operations for the period in which such gains or losses are reported, as their sole purpose is to adjust amounts on the balance sheet. We have excluded the impact of the costs associated with our strategic financing collaboration, upfront payment on license and collaboration agreements, change in estimate of contingent liabilities and loss on contractual settlement because we believe these items are non-recurring transactions outside the ordinary course of our business.
Yvonne Greenstreet, MBChB, MBA
Chief Executive Officer

Overview
Notable Accomplishments in 2021

**Combined net product revenues of $662 million (83% growth YoY)**

**Expanded commercial presence into >30 countries**

**APOLLO-B HELIOS-B**

Completed enrollment in two key Phase 3 studies in ATTR amyloidosis w/ CM

**NDA/sNDA submissions (vutrisiran, lumasiran)**

**Maintained strong financial position**
- $2.4 billion in cash at year-end 2021
- $120M+ YoY improvement in non-GAAP operating loss

**Launched new 5-year strategy**

**Advanced multiple investigational products for prevalent diseases (zilebesiran, ALN-HBV02, ALN-HSD)**

**CTA filings (ALN-APP, ALN-XDH)**
Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation
Patients: Over 0.5 million on Alnylam RNAi therapeutics globally
Products: 6+ marketed products in rare and prevalent diseases
Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year
Performance: ≥40% revenue CAGR through YE 2025
Profitability: Achieve sustainable non-GAAP profitability within period
Tolga Tanguler
Chief Commercial Officer
Commercial Highlights
ONPATTRO® (patisiran) Update: Year End 2021

$475M
ONPATTRO Global 2021
Net Product Revenues

>2,050
Patients Worldwide on Commercial
ONPATTRO at YE 2021

Q4 Highlights

<table>
<thead>
<tr>
<th></th>
<th>YoY % Growth</th>
<th>QoQ % Growth</th>
</tr>
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<tbody>
<tr>
<td>U.S.</td>
<td>40%</td>
<td>17%</td>
</tr>
<tr>
<td>ROW</td>
<td>66%</td>
<td>14%</td>
</tr>
<tr>
<td>Global</td>
<td>53%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- Steady patient growth continues across key markets
- U.S. QoQ growth of 17% impacted by:
  - Demand growth +4% due primarily to an increase in patients on therapy
  - Inventory stocking dynamics (+15%)
  - Modest increase in gross to net deductions (-2%)
- ROW growth driven broadly by increased demand from Europe, Canada, and Japan and favorability in gross to net deductions
GIVLAARI® (givosiran) Update: Year End 2021

$128M

GIVLAARI Global 2021 Net Product Revenues

>350

Patients Worldwide on Commercial GIVLAARI at YE 2021

**Q4 Highlights**

<table>
<thead>
<tr>
<th>YoY % Growth</th>
<th>QoQ % Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>81%</td>
</tr>
<tr>
<td>ROW</td>
<td>94%</td>
</tr>
<tr>
<td>Global</td>
<td>84%</td>
</tr>
</tbody>
</table>

- U.S. QoQ growth of 35% impacted by:
  - Demand growth +8% due primarily to an increase in patients on therapy
  - Inventory stocking dynamics (+20%)
  - Decrease in gross to net deductions in Q4 (+6%)

- ROW growth primarily driven by new patient adds in Germany, France, Italy, and Spain
OXLUMO® (lumasiran) Update: Year End 2021

$60M
OXLUMO Global 2021 Net Product Revenues

>140
Patients Worldwide on Commercial OXLUMO at YE 2021

Q4 Highlights

<table>
<thead>
<tr>
<th>QoQ % Growth</th>
<th>U.S.</th>
<th>ROW</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9%</td>
<td>40%</td>
<td>29%</td>
</tr>
</tbody>
</table>

- U.S. QoQ growth of 9% impacted by:
  - Demand growth +15% due primarily to an increase in patients on therapy
  - Inventory stocking dynamics (-6%)
- ROW results favorably impacted by increase in patients on therapy in established markets, geographic expansion, and favorability in gross to net deductions
Akshay Vaishnaw, M.D., Ph.D.
President
Alnylam Pipeline
Patisiran APOLLO-B Phase 3 Study
Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 300
Patient Population
- ATTR amyloidosis; wild-type or any TTR mutation
  - TTR stabilizer naïve and/or TTR stabilizer progressor
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

Concomitant use of local standard of care allowed during study, including TTR stabilizer
† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers
NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

ClinicalTrials.gov Identifier: NCT03997383

1:1 RANDOMIZATION

12-Month Treatment Extension

Enrollment complete
Topline results expected mid-2022

Primary Endpoint
- Change in 6-MWT at 12 months

Key Secondary Endpoints
- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

Patisiran IV q3w† 0.3 mg/kg

Placebo IV q3w†
Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy

- As previously reported, the primary endpoint of change from baseline in mNIS+7 at Month 9 was met\(^1\)

### Patient Population
- N=164
- 18–85 years old
- hATTR amyloidosis with polyneuropathy; any TTR mutation
- NIS 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior tetramer stabilizer use permitted

### 3:1 Randomization

<table>
<thead>
<tr>
<th>Stratification:</th>
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<tbody>
<tr>
<td>TTR V30M vs non-V30M</td>
</tr>
<tr>
<td>Baseline NIS &lt;50 vs ≥50</td>
</tr>
</tbody>
</table>

### Efficacy Assessments

**Primary Endpoint (at Month 9; previously presented\(^1\))**
- Change from baseline in mNIS+7a

**Secondary Endpoints**
- Change from baseline in:
  - mNIS+7 at Month 18
  - Norfolk QOL-DN at Months 9 and 18
  - 10-MWT\(^b\) at Months 9 and 18
  - mBMI\(^d\) at Month 18
  - R-ODS\(^e\) at Month 18

**Selected Exploratory Endpoints**
- Change from baseline in cardiac biomarkers, echocardiographic parameters to Month 18
- Change from baseline in Tc scintigraphy measures to Month 18\(^f\)

**Secondary Endpoint**
- % serum TTR reduction to Month 18

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\(^a\) Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). \(^b\) Higher scores of Norfolk QOL-DN indicate worse quality of life (range, –4 to 136). \(^c\) 10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function. \(^d\) Lower scores of mBMI (weight in kg/m\(^2\) x serum albumin g/L) indicate worse nutritional status. \(^e\) Lower scores of R-ODS indicate more disability (range, 0 to 48). Tc scintigraphy was only performed at select sites, comparison to baseline, not placebo

Rapid and Sustained Reduction in Serum TTR Levels with Vutrisiran

- Vutrisiran achieved a mean steady-state serum TTR reduction from baseline of 88% (SD: 16%)
- TTR reduction with vutrisiran was non-inferior to that observed with the within-study patisiran reference comparator (secondary endpoint) over 18 months

Percent Change from Baseline in Serum TTR Levels

* As assessed by mean trough serum TTR levels; SD, standard deviation; SE, standard error; TTR, transthyretin; Adams, et al. SFNP 2022
Statistically Significant Improvement in Neuropathy Impairment and Quality of Life with Vutrisiran vs External Placebo at Month 18

- Improvement was observed across all prespecified patient subgroups, components, and subdomains of mNIS+7 and Norfolk QOL-DN (data not shown)
- Improvement relative to baseline in mNIS+7 (48.3% [vutrisiran] vs 3.9% [placebo]) and Norfolk QOL-DN (56.8% vs 10.4%)
- Consistent treatment effects in vutrisiran and patisiran groups in HELIOS-A (data not shown)

**mNIS+7 LS Mean Change from Baseline**

Vutrisiran: -2.24 (1.43) n=114  
Placebo (APOLLO): -0.46 (1.60) n=112  
LSMD (95% CI) = -28.55 (−34.00, −23.10) p=6.51 × 10^{-20}

**Norfolk QOL-DN LS Mean Change from Baseline**

Vutrisiran: -3.3 (1.7) n=114  
Placebo (APOLLO): -1.2 (1.8) n=111  
LSMD (95% CI) = -21.0 (−27.1, −14.9) p=1.84 × 10^{-10}
Exploratory Imaging Parameters
Potential Evidence of Reduction in Amyloid Burden

Vutrisiran trended toward improvement in all echocardiographic parameters, compared with external placebo group

Reduced cardiac technetium uptake on scintigraphy imaging shown in majority of assessable vutrisiran patients

- Mean LV Wall Thickness (cm)\(^a\)  
  \[p=0.5228\]
  \[n=51\]  
  \[n=105\]

- Global Longitudinal Strain (%)\(^a\)  
  \[p=0.3182\]
  \[n=48\]  
  \[n=107\]

- Cardiac Output (L/min)\(^a\)  
  \[p=1.144 \times 10^{-5}\]
  \[n=49\]  
  \[n=105\]

- LV End-Diastolic Volume (mL)\(^a\)  
  \[p=4.021 \times 10^{-4}\]
  \[n=50\]  
  \[n=105\]

- Tc Normalized LV Total Uptake (n=47)\(^b\)
  - Improved\(^c\) 68.1
  - Not Improved\(^d\) 31.9

- Tc Heart-to-Contralateral Lung ratio (n=48)\(^b\)
  - Improved\(^c\) 64.6
  - Not Improved\(^d\) 35.4

- Change from Baseline in Tc Perugini Grade (n=57)\(^b\)
  - Improved 28.1
  - Stable 68.4
  - Worsened 3.5

\(^a\) mITT population. P-values are nominal. \(^b\) Patients from the mITT population for whom the relevant 18 month data were available. \(^c\) Improved: <0 increase from baseline. \(^d\) Not improved: ≥0 increase from baseline. Adams, et al. SFNP 2022
HELIOS-A Safety Summary

Majority of AEs mild or moderate in severity

- No drug-related discontinuations or deaths
- Three study discontinuations (2.5%) due to AEs in the vutrisiran arm (two due to death, as previously reported; one due to heart failure), none of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- As previously reported, two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in the vutrisiran group included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
- Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran; all were mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

<table>
<thead>
<tr>
<th>Event</th>
<th>APOLLO Placebo (n=77)</th>
<th>HELIOS-A Vutrisiran (n=122)</th>
<th>HELIOS-A Patisiran (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one event, n (%)</td>
<td>75 (97.4)</td>
<td>119 (97.5)</td>
<td>41 (97.6)</td>
</tr>
<tr>
<td>AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>31 (40.3)</td>
<td>32 (26.2)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>28 (36.4)</td>
<td>19 (15.6)</td>
<td>16 (38.1)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>11 (14.3)</td>
<td>3 (2.5)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>AEs leading to stopping study participation</td>
<td>9 (11.7)</td>
<td>3 (2.5)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (7.8)</td>
<td>2 (1.6)</td>
<td>3 (7.1)</td>
</tr>
</tbody>
</table>

* Data reported during 18-month treatment period.
AE, adverse event; SAE, serious AE. Adams, et al. SFNP 202
Vutrisiran HELIOS·B Phase 3 Study
Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 600
Patient Population
- ATTR amyloidosis; wild-type or any TTR mutation
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

Primary Endpoint
- Composite outcome of all-cause mortality and recurrent CV events (when last patient reaches Month 30)

Select Secondary Endpoints
- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

Vutrisiran SC q3M 25 mg
or
Placebo SC q3M

Enrollment complete
Topline results on 30-month endpoint expected early 2024
Study includes optional interim analysis

ClinicalTrials.gov Identifier: NCT04153149
Stargardt Disease
Promising New Opportunity for Vutrisiran

Description
Rare, inherited, progressive form of blindness caused by accumulation of toxic vitamin A metabolites in retina leading to central vision loss

High unmet medical need with no approved treatments

Incidence of 1 in 8,000-10,000

Therapeutic Hypothesis
- Silence production of TTR in liver
- Reduce circulating TTR / RBP4 / Vitamin A Complex
- Reduce build-up of toxic metabolites in retina
- Halt Progression of vision loss

* >95% of TTR in circulation produced in liver
Zilebesiran Phase 2 Clinical Development Plan

**Monotherapy Phase 2 Study (N ~375)**
- IND opened May 2021
- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- Study initiated **June 2021**

**Add-On Phase 2 Study (N ~800)**
- Evaluate efficacy and safety of zilebesiran as add-on therapy in patients with hypertension despite treatment with a potent RAAS inhibitor, a calcium channel blocker, or a diuretic
- Study initiated **November 2021**
Zilebesiran (ALN-AGT) Interim Phase 1 Results

Results for Investigational Therapy Presented at AHA Scientific Sessions\(^1\)

Encouraging safety and tolerability profile
- Most AEs mild or moderate in severity
- ISRs in 5 of 56 patients (8.9%) were all mild and transient
- No treatment-related SAEs
- No patients required intervention for low blood pressure

Dose-Dependent and Durable Reduction of Serum AGT ≥90% Sustained for 12 Weeks After Single Doses of zilebesiran ≥100 mg

Serum AGT reductions of >90% maintained through six months after single dose of 800 mg

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo (n=28)</th>
<th>10 mg (n=8)</th>
<th>25 mg (n=8)</th>
<th>50 mg (n=8)</th>
<th>100 mg (n=8)</th>
<th>200 mg (n=8)</th>
<th>400 mg (n=8)</th>
<th>800 mg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline in Serum AGT (%)</td>
<td>-0.0%±0.0%</td>
<td>-1.0%±0.0%</td>
<td>-2.0%±0.0%</td>
<td>-3.0%±0.0%</td>
<td>-4.0%±0.0%</td>
<td>-5.0%±0.0%</td>
<td>-6.0%±0.0%</td>
<td>-7.0%±0.0%</td>
</tr>
</tbody>
</table>

Mean 24h blood pressure reduction of >20 mm Hg at Month 6 after a single dose of 800 mg

Sustained Reductions in SBP and DBP\(^2\)

KARDIA-1 Phase 2 Study initiated June 2021
KARDIA-2 Phase 2 Study initiated November 2021

\(^1\) Huang et al, AHA, November 2021; Data cutoff date: 28 May 2021
\(^2\) SBP: systolic blood pressure; DBP: diastolic blood pressure
Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):
- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

<table>
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<tr>
<th>EARLY/MID-STAGE</th>
<th>LATE STAGE</th>
<th>REGISTRATION/ COMMERCIAL¹</th>
<th>COMMERCIAL RIGHTS</th>
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<tbody>
<tr>
<td>(IND/CTA Filed-Phase 2)</td>
<td>(Phase 2-Phase 3)</td>
<td>(CLE/Phase 4/IIS/registries)</td>
<td></td>
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1. Includes marketing application submissions; ² Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU and Japan for the treatment of apheresis in adults with stage 1 or stage 2 polyneuropathy; ³ Approved in the U.S., EU and Japan for the treatment of primary hyperoxaluria type 1; ⁴ Approved in the U.S. and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; ⁵ Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; ⁶ Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; ⁷ 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; ⁸ Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; ⁹ Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; ¹⁰ As of February 2022

- **hATTR Amyloidosis with PN**
- **Acute Hepatic Porphyria**
- **Primary Hyperoxaluria Type 1**
- **Hypercholesterolemia**
- **ATTR Amyloidosis with CM**
- **Stargardt Disease**
- **Hemophilia**
- **Severe PH1**
- **Recurrent Renal Stones**
- **Complement-Mediated Diseases**
- **Alpha-1 Liver Disease**
- **Hepatitis B Virus Infection**
- **Hypertension**
- **NASH**
- **Alzheimer’s Disease; Cerebral Amyloid Angiopathy**
- **Gout**

As of February 2022
## Alnylam Clinical Development Pipeline

### Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

### EARLY/MID-STAGE

**IND/CTA Filed-Phase 2**

<table>
<thead>
<tr>
<th>Early/Mid-stage</th>
<th>Late Stage</th>
<th>Registration/Commercial</th>
<th>Commercial Rights</th>
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<tbody>
<tr>
<td><strong>Genetic</strong></td>
<td><strong>Late Stage</strong></td>
<td><strong>REGISTRATION/COMMERCIAL</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>COMMERCIAL RIGHTS</strong></td>
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<tr>
<td><strong>Cardio-Metabolic</strong></td>
<td></td>
<td><strong>OLE/Phase 4/IIS/registries</strong></td>
<td>Milestones &amp; up to 20% Royalties&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
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<tr>
<td><strong>CNS/Ocular</strong></td>
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### Approved Products

1. **Onpattro**
   - hATTR Amyloidosis with PN
   - Global

2. **Patisiran**
   - ATTR Amyloidosis with CM
   - Global

3. **Vutrisiran**
   - HATTR Amyloidosis with PN
   - Global

4. **Leqvio**<sup>®</sup>(inclisiran)
   - Hypercholesterolemia
   - Milestones & up to 20% Royalties<sup>4</sup>

5. **Leqvio**<sup>®</sup> Global
6. **Leqvio**<sup>®</sup> Global
7. **Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; " Phase 3 study of patisiran in Stargardt Disease expected to initiate in late 2022; " Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; " Osienna is leading and funding development of belcesiran; " Vir is leading and funding development of ALN-HBV02; " Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

### Commercial Rights

- **Global**
- **Milestones & up to 20% Royalties**
- **50-50, Milestone/Royalty**
- **50-50 option post-Phase 2**
- **50-50 option post-Phase 3**
- **Ex-U.S. option post-Phase 3**

### Milestones

- **ALN-HDV**
  - **Hepatitis B Virus Infection**
  - **50-50 option post-Phase 2**

- **ALN-APC**
  - **Alveolar Disease, Cerebral Amyloid Angiopathy**
  - **50-50 option post-Phase 2**

- **ALN-XDH**
  - **Gout**
  - **Global**

### As of February 2022
Jeff Poulton
Chief Financial Officer
Financial Summary and Upcoming Milestones
# Q4 & Full Year 2021 Financial Summary

## Financial Results ($ millions)

<table>
<thead>
<tr>
<th></th>
<th>Q4 2021</th>
<th>Q4 2020</th>
<th>YoY % Change</th>
</tr>
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<tbody>
<tr>
<td>Net Product Revenues</td>
<td>$198.5</td>
<td>$112.8</td>
<td>76%</td>
</tr>
<tr>
<td>Net Revenues from Collaborations</td>
<td>$59.6</td>
<td>$50.7</td>
<td>18%</td>
</tr>
<tr>
<td>Royalty Revenues</td>
<td>$0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Revenues</td>
<td>$258.5</td>
<td>$163.6</td>
<td>58%</td>
</tr>
<tr>
<td>Cost of Goods Sold and Collaborations</td>
<td>$37.7</td>
<td>$23.0</td>
<td>64%</td>
</tr>
<tr>
<td>Gross Margin</td>
<td>$220.9</td>
<td>$140.5</td>
<td>57%</td>
</tr>
<tr>
<td>GM as % of Total Revenues¹</td>
<td>85.4%</td>
<td>85.9%</td>
<td>-</td>
</tr>
<tr>
<td>Non-GAAP R&amp;D Expenses²</td>
<td>$205.2</td>
<td>$153.5</td>
<td>34%</td>
</tr>
<tr>
<td>Non-GAAP SG&amp;A Expenses²</td>
<td>$160.3</td>
<td>$136.7</td>
<td>17%</td>
</tr>
<tr>
<td>Non-GAAP Operating Loss²</td>
<td>($144.7)</td>
<td>($149.7)</td>
<td>(3%)</td>
</tr>
</tbody>
</table>

## FY 2021 vs FY 2020

<table>
<thead>
<tr>
<th></th>
<th>FY 2021</th>
<th>FY 2020</th>
<th>YoY % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net Product Revenues</td>
<td>$662.1</td>
<td>$361.5</td>
<td>83%</td>
</tr>
<tr>
<td>Net Revenues from Collaborations</td>
<td>$181.0</td>
<td>$131.3</td>
<td>38%</td>
</tr>
<tr>
<td>Royalty Revenues</td>
<td>$1.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Revenues</td>
<td>$844.3</td>
<td>$492.9</td>
<td>71%</td>
</tr>
<tr>
<td>Cost of Goods Sold and Collaborations</td>
<td>$140.1</td>
<td>$78.1</td>
<td>80%</td>
</tr>
<tr>
<td>Gross Margin</td>
<td>$704.1</td>
<td>$414.8</td>
<td>70%</td>
</tr>
<tr>
<td>GM as % of Total Revenues¹</td>
<td>83.4%</td>
<td>84.2%</td>
<td>-</td>
</tr>
<tr>
<td>Non-GAAP R&amp;D Expenses²</td>
<td>$708.4</td>
<td>$594.4</td>
<td>19%</td>
</tr>
<tr>
<td>Non-GAAP SG&amp;A Expenses²</td>
<td>$523.3</td>
<td>$469.1</td>
<td>12%</td>
</tr>
<tr>
<td>Non-GAAP Operating Loss²</td>
<td>($527.6)</td>
<td>($648.6)</td>
<td>(19%)</td>
</tr>
</tbody>
</table>

## Financial Results ($ millions)

<table>
<thead>
<tr>
<th></th>
<th>Dec 31, 2021</th>
<th>Dec 31, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash &amp; Investments³</td>
<td>$2,435.6</td>
<td>$1,874.4</td>
</tr>
</tbody>
</table>

¹ GM as a % of Total Net Product Revenues for Q4 2021 is 83.1%, Q4 2020 is 79.6%, FY 2021 is 82.6%, FY 2020 is 79.5% (Q4 2021 excludes $4.0M and FY 2021 excludes $25.1M in Cost of Collaborations and Royalties associated with Net Revenues from Collaborations, respectively).

² Non-GAAP R&D expenses, non-GAAP SG&A expenses and non-GAAP operating loss primarily exclude costs related to stock-based compensation expense and a change in estimate of contingent liabilities.

³ Cash, cash equivalents and marketable securities

See Appendix for a reconciliation between GAAP and non-GAAP measures
## 2022 Full Year Guidance¹

<table>
<thead>
<tr>
<th>Net Product Revenue (ONPATTRO, GIVLAARI, OXLUMO, Vutrisiran)</th>
<th>FY 2021 Actuals</th>
<th>FY 2022 Guidance</th>
<th>Projected 2022 Growth (using mid-point of guidance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$662M</td>
<td>$900M – $1,000M</td>
<td>+44%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Net Revenue from Collaborations &amp; Royalties</th>
<th>FY 2021 Actuals</th>
<th>FY 2022 Guidance</th>
<th>Projected 2022 Growth (using mid-point of guidance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$182M</td>
<td>$175M – $225M</td>
<td>+10%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-GAAP Combined R&amp;D and SG&amp;A Expenses²,³</th>
<th>FY 2021 Actuals</th>
<th>FY 2022 Guidance</th>
<th>Projected 2022 Growth (using mid-point of guidance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1,232M</td>
<td>$1,400M – $1,500M</td>
<td>+18%</td>
<td></td>
</tr>
</tbody>
</table>

1. Our 2022 FY Guidance is based upon January 31, 2022 FX rates of: 1 EUR = 1.12 USD; 1 GBP = 1.34 USD; 1 CHF = 1.08 USD; 1 CAD = 0.79 USD; 1 USD = 115 JPY
2. 2021 Non-GAAP Combined R&D and SG&A Expenses primarily exclude costs related to stock-based compensation expense. See appendix for reconciliation between GAAP and non-GAAP expenses
## Alnylam 2022 Goals

<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Key Milestones</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATISIRAN</strong></td>
<td>hATTR/ATTR Amyloidosis</td>
<td>APOLLO-B Phase 3 Topline Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>File sNDA for ATTR with CM</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>VUTRISIRAN</strong></td>
<td>hATTR/ATTR Amyloidosis</td>
<td>FDA Approval (4/14/22 PDUFA)</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U.S. Launch</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMA Approval</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Stargardt Disease</td>
<td>Biannual Dose Regimen Data</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiate Phase 3 in Stargardt Disease</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ALN-TTRsc04</strong></td>
<td>ATTR Amyloidosis</td>
<td>File IND</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiate Phase 1 Study</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>LUMASIRAN</strong></td>
<td>PH1, Recurrent Renal Stones</td>
<td>Complete Enrollment in Phase 2 Study in Recurrent Renal Stones</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>INCLISIRAN</strong></td>
<td>Hypercholesterolemia</td>
<td>FDA Approval (1/1/22 PDUFA)</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>CEMDISIRAN</strong></td>
<td>Complement-Mediated Diseases</td>
<td>Phase 2 Monotherapy Results in IgA Nephropathy</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiate Phase 3 Combination Study in PNH</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ZILEBESIRAN</strong></td>
<td>Hypertension</td>
<td>Complete KARDIA-1 Enrollment</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complete KARDIA-2 Enrollment</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KARDIA-1 Phase 2 Topline Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ALN-HBV02 (VIR-2218)</strong></td>
<td>Chronic HBV Infection</td>
<td>Phase 2 Combination Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ALN-HSD</strong></td>
<td>NASH</td>
<td>Phase 1 Part B Topline Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ALN-APP</strong></td>
<td>Alzheimer’s Disease</td>
<td>Initiate Phase 1 Study</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 1 Topline Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ALN-XDH</strong></td>
<td>Gout</td>
<td>Initiate Phase 1 Study</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 1 Topline Results</td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td><strong>ADDITIONAL PROGRAMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

*Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4.
Q4 and Full Year 2021 Financial Results

Q&A Session
To those who say “impossible, impractical, unrealistic,” we say:
CHALLENGE ACCEPTED
## Reconciliation of Selected GAAP Measures to Non-GAAP Measures (In thousands)

### Reconciliation of GAAP to Non-GAAP research and development:

<table>
<thead>
<tr>
<th></th>
<th>Three Months Ended</th>
<th>Twelve Months Ended</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>December 31, 2021</td>
<td>December 31, 2020</td>
</tr>
<tr>
<td>GAAP Research and development</td>
<td>$229,050</td>
<td>$168,469</td>
</tr>
<tr>
<td>Less: Stock-based compensation expenses</td>
<td>(18,537)</td>
<td>(14,922)</td>
</tr>
<tr>
<td>Less: Upfront payment on license and collaboration agreements</td>
<td>(5,295)</td>
<td>—</td>
</tr>
<tr>
<td>Non-GAAP Research and development</td>
<td>$205,218</td>
<td>$153,547</td>
</tr>
</tbody>
</table>

### Reconciliation of GAAP to Non-GAAP selling, general and administrative:

<table>
<thead>
<tr>
<th></th>
<th>Three Months Ended</th>
<th>Twelve Months Ended</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>December 31, 2021</td>
<td>December 31, 2020</td>
</tr>
<tr>
<td>GAAP Selling, general and administrative</td>
<td>$186,382</td>
<td>$166,391</td>
</tr>
<tr>
<td>Less: Stock-based compensation expenses</td>
<td>(26,045)</td>
<td>(19,354)</td>
</tr>
<tr>
<td>Less: Change in estimate of contingent liabilities</td>
<td>—</td>
<td>(10,216)</td>
</tr>
<tr>
<td>Less: Costs associated with the strategic financing collaboration</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Less: Loss on contractual settlement</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Non-GAAP Selling, general and administrative</td>
<td>$160,337</td>
<td>$156,721</td>
</tr>
</tbody>
</table>

### Reconciliation of GAAP to Non-GAAP operating loss:

<table>
<thead>
<tr>
<th></th>
<th>Three Months Ended</th>
<th>Twelve Months Ended</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>December 31, 2021</td>
<td>December 31, 2020</td>
</tr>
<tr>
<td>GAAP operating loss</td>
<td>$(194,561)</td>
<td>$(194,223)</td>
</tr>
<tr>
<td>Add: Stock-based compensation expenses</td>
<td>44,582</td>
<td>34,276</td>
</tr>
<tr>
<td>Add: Upfront payment on license and collaboration agreements</td>
<td>5,295</td>
<td>—</td>
</tr>
<tr>
<td>Add: Change in estimate of contingent liabilities</td>
<td>—</td>
<td>10,216</td>
</tr>
<tr>
<td>Add: Costs associated with the strategic financing collaboration</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Add: Loss on contractual settlement</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Non-GAAP operating loss</td>
<td>$(144,684)</td>
<td>$(149,730)</td>
</tr>
</tbody>
</table>

Please note that the figures presented may not sum exactly due to rounding.