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. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including vutrisiran, ALN-AGT, ALN-HSD, ALN-APP and ALN-COV; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates and our marketed products, including ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran), inclisiran, and vutrisiran; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner’s ability to obtain regulatory approval for our product candidates, including inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO, GIVLAARI, and OXLUMO; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and OXLUMO, and achieve net product revenues for ONPATTRO within our further revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of future equity provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products such as ALN-APP, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. 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 gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities. The Company has 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 the Company’s stock price, which impacts the fair value of these awards. The Company has excluded the impact of the unrealized gain on marketable equity securities, costs associated with our strategic financing collaboration, loss on contractual settlement and change in estimate of contingent liabilities because the Company believes these items are non-recurring transactions outside the ordinary course of the Company’s business.
RNAi Therapeutics: New Class of Innovative Medicines
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable innovation
- Multiple products impacting patients globally
The first RNAi therapeutic is approved in U.S., EU, Canada, Japan, Switzerland, Brazil & Israel.
ATTR Amyloidosis
Rare, Progressively Debilitating, and Often Fatal Disease

Description
Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract

<table>
<thead>
<tr>
<th>Hereditary ATTR (hATTR) Amyloidosis</th>
<th>~50,000 patients worldwide*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-Type ATTR (wtATTR) Amyloidosis</td>
<td>~200,000 – 300,000 patients worldwide</td>
</tr>
</tbody>
</table>

ONPATTRO® Launch Update: Q3 2020

Strong Performance with Significant Growth

$82.5M

ONPATTRO Global Q3 Net Product Revenues

$82.5M

$46.1M

$55.8M

$66.7M

$66.5M

$82.5M

Q3 2019

Q4 2019

Q1 2020

Q2 2020

Q3 2020

ROW

U.S.

>1,150

Patients Worldwide on Commercial ONPATTRO at end of Q3 2020

Patients worldwide on commercial ONPATTRO
* 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; † ONPATTRO has 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 its safety or effectiveness in this population

‡ Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected

Intended to be illustrative and not intended to represent specific estimates of patient numbers
The second RNAi therapeutic is approved in the U.S., EU, Brazil & Canada.
Acute Hepatic Porphyria (AHP)
Family of Rare Genetic Diseases with Significant Disease Burden

Description
Causes potentially life-threatening attacks and chronic manifestations that negatively impact quality of life

Predominantly
female
commonly misdiagnosed

Patient Population
~3,000
diagnosed in U.S./EU with active disease


1 Symptoms specific to hereditary coproporphyria and variegate porphyria

Central Nervous System
• Confusion
• Anxiety
• Depression
• Memory loss
• Fatigue
• Hallucinations
• Seizures

Autonomic Nervous System
• Severe abdominal pain
• Nausea/vomiting
• Hypertension
• Tachycardia
• Constipation
• Hyponatremia

Peripheral Nervous System
• Neuropathic pain
• Sensory loss
• Muscle weakness
• Paralysis
• Respiratory failure

Cutaneous†
• Lesions on sun-exposed skin

Long-term Complications
• Liver disease
• Chronic kidney disease
• Hypertension
• Neuropathy
GIVLAARI® Launch Update: Q3 2020

Strong Initial Performance

$16.7M

GIVLAARI Q3
Net Product Revenues

>150

Patients on Commercial GIVLAARI
at end of Q3 2020

* Start Forms are an incomplete picture of U.S. demand
GIVLAARI® (givosiran) Market Opportunity
Ultra-Rare Orphan Disease with Significant Disease Burden and Limited Treatment Options

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>~3,000 patients in U.S./EU, diagnosed with active disease(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAGNOSIS</td>
<td>~20–50% currently diagnosed; delays up to 15 years</td>
</tr>
<tr>
<td>DISEASE BURDEN</td>
<td>65% recurrent attack patients with chronic symptoms(^3)</td>
</tr>
<tr>
<td>COST BURDEN</td>
<td>$400–650K average annual expenditure, recurrent attack patients(^4)</td>
</tr>
</tbody>
</table>

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GIVLAARI | ACUTE HEPATIC PORPHYRIA

&ge;$500M potential market opportunity

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2 Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database
3 Gouya, et al. EASL 2018
4 EXPLORE Natural History Study (includes patients with &ge; 3 attacks per year). Annual expenditure per patient; based on both hospitalization charges (amount billed) and costs (amount paid) from published data sources in U.S.
The third RNAi therapeutic is NOW APPROVED IN THE U.S. & EU
Primary Hyperoxaluria Type 1
Ultra-Rare Orphan Pediatric Disease with Significant Disease Burden

Description
Rare autosomal recessive disorder of increased oxalate synthesis resulting in kidney stones and renal failure, with subsequent oxalate accumulation in extra-renal tissues

Onset generally pediatric
very limited treatment options

Patient Population
~3,000
potentially symptomatic in U.S./EU\(^1\)

\(^1\) Includes patients that are presymptomatic, subclinical, or symptomatic
# OXLUMO™ (lumasiran) Market Opportunity

First-in-Class Target Product Profile in Ultra-Rare Orphan Disease

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>DIAGNOSIS</th>
<th>DISEASE BURDEN</th>
<th>COST BURDEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3,000 potentially symptomatic patients in U.S./EU</td>
<td>~50% currently diagnosed(^1); mean time to diagnosis ~6 years(^2)</td>
<td>30–65% reach end-stage renal disease before diagnosis(^2)</td>
<td>$1M+ average cost (transplant &amp; lifelong immunosuppression)</td>
</tr>
</tbody>
</table>

## OXLUMO | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

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## Additional Launches Planned Over Next 18 Months

<table>
<thead>
<tr>
<th>Year</th>
<th>Product</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>ONPATTRO</td>
<td>Hypercholesterolemia</td>
<td>NDA/MAA accepted, Received positive CHMP opinion</td>
</tr>
<tr>
<td>2018</td>
<td>GIVLAARI*</td>
<td>ATTR amyloidosis</td>
<td>HELIOS-A Phase 3 topline results expected in early 2021</td>
</tr>
<tr>
<td>2018</td>
<td>OXLUMO*</td>
<td>Hemophilia</td>
<td>Two of three Phase 3 studies fully enrolled; Dosing/recruitment on voluntary pause</td>
</tr>
<tr>
<td>2020</td>
<td>LEQVIO®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>Vutrisiran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020-2022</td>
<td>Fitusiran*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ONPATTRO
ONPATTRO is indicated in the U.S. for the treatment of transthyretin-mediated amyloidosis in adults.

### GIVLAARI
GIVLAARI is indicated in the U.S. for the treatment of primary hyperoxaluria type 1.

### OXLUMO
OXLUMO is indicated in the U.S. for the treatment of primary hyperoxaluria type 1.

### Hypercholesterolemia
LEQVIO® is indicated in the U.S. for the treatment of hypercholesterolemia.

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* Novartis is leading and funding development of inclisiran and will commercialize inclisiran, assuming regulatory approvals; Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful.
1. ONPATTRO is approved in the U.S. and Canada for 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 stage 2 polyneuropathy. For additional information on ONPATTRO, see Full Prescribing Information.
2. GIVLAARI is approved in the U.S., Brazil, and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older. For additional information on GIVLAARI, see Full Prescribing Information.
3. OXLUMO is approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups. For additional information on OXLUMO, see Full Prescribing Information.

Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval.
Alnylam Commercial Products and Late Stage Clinical Development Pipeline

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Therapeutic Area</th>
<th>Phase</th>
<th>Approval Status</th>
<th>Commercial Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>onpattro (patisiran)</td>
<td>hATTR Amyloidosis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>BREAKTHROUGH DESIGNATION</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>COMMERICAL</td>
</tr>
<tr>
<td>GIVLAARI (givosiran)</td>
<td>Acute Hepatic Porphyria&lt;sup&gt;2&lt;/sup&gt;</td>
<td>BREAKTHROUGH DESIGNATION</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>COMMERICAL</td>
</tr>
<tr>
<td>OXLUMO (lumasiran)</td>
<td>Primary Hyperoxaluria Type 1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>BREAKTHROUGH DESIGNATION</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>COMMERICAL</td>
</tr>
<tr>
<td>Inclisiran</td>
<td>Hypercholesterolemia</td>
<td></td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td></td>
</tr>
<tr>
<td>Patisiran</td>
<td>ATTR Amyloidosis Label Expansion</td>
<td></td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td></td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Severe Primary Hyperoxaluria Type 1</td>
<td></td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td></td>
</tr>
<tr>
<td>Fitusiran</td>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td></td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>ATTR Amyloidosis</td>
<td></td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td></td>
</tr>
</tbody>
</table>

1 Approved in the U.S. and Canada for 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 stage 2 polyneuropathy
2 Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older
3 Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups
4 As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone

As of December 2020
Patisiran **APOLLO-B** Phase 3 Study
Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

**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

**Primary Endpoint**
- Change in 6-MWT at 12 months

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

**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

Study initiated
**September 2019**

Enrollment completion expected
**2021**
Phase 3 Study Results
Encouraging Evidence for Patisiran’s Potential in ATTR Cardiomyopathy

~50% Reduction in all-cause hospitalization and mortality in post-hoc analysis

55%
• Relative reduction in NT-proBNP vs. placebo†
  – Effect noted as early as 9 months

0.9mm
• Mean reduction in LV wall thickness vs. placebo‡

-1.4%
• Improvement in global longitudinal strain vs. placebo‡

0.35m/s
• Improvement in 10-MWT vs. placebo†

Cardiac Safety Data in Entire APOLLO Study Population:

<table>
<thead>
<tr>
<th></th>
<th>Placebo² (n=77)</th>
<th>Patisiran² (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of Death/Hospitalization, per 100 py (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6.2 (2.5 – 12.7)</td>
<td>3.2 (1.4 – 6.2)</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>69.7 (54.3 – 87.7)</td>
<td>32.9 (25.9 – 41.1)</td>
</tr>
<tr>
<td>Cardiac hospitalization</td>
<td>15.6 (9.0 – 24.9)</td>
<td>8.2 (5.0 – 12.6)</td>
</tr>
<tr>
<td>Hospitalization and/or death</td>
<td>71.8 (56.1 – 90.1)</td>
<td>34.7 (27.5 – 43.1)</td>
</tr>
<tr>
<td>Cardiac hospitalization and/or death</td>
<td>18.7 (11.4 – 28.8)</td>
<td>10.1 (6.4 – 14.9)</td>
</tr>
</tbody>
</table>

† Patisiran has 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 its safety or effectiveness in this population.
‡ For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]

Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization.
Patisiran Treatment of hATTR Amyloidosis

Evidence for Potential Cardiac Amyloid Regression

~60 y.o. man with V30M mutation enrolled in EAP
Mixed phenotype: polyneuropathy predominant
Initiated patisiran (on top of diflunisal) due to disease progression

- Recent uncontrolled case series
- Recently published similar findings by Nienhuis et al.
- Patisiran treatment may be associated with cardiac remodeling and/or amyloid regression
- Cardiac effects to be further assessed in randomized, controlled trials

1 Patisiran has 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 its safety or effectiveness in this population
2 Gillmore, OTS Munich 2019
3 Mayo Clinic Proceedings, 2019
Further Evidence of Cardiac Amyloid Regression with Patisiran Treatment

Encouraging Data Recently Presented at ESC\(^1,2\)

- 32 patients with hATTR amyloidosis with cardiomyopathy (n=16 patisiran, n=16 control)
- Non-randomized study
- Concomitant diflunisal allowed
- Assessments at baseline and one year:
  - Cardiac magnetic resonance (CMR)
  - 6-minute walk test (6-MWT)
  - NT-proBNP
  - Echocardiogram

Results

- Substantial reduction in cardiac amyloid burden in 45% of patients who received patisiran
- Patients treated with patisiran showed reduction in extracellular volume fraction (ECV) compared to an increase in ECV in the control group (p<0.001) at one-year follow up
- Improvement in 6-MWT and NT-proBNP at one year in patisiran-treated patients compared to control

\(^1\) Patisiran has 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 its safety or effectiveness in this population

\(^2\) Chacko, L et al. Regression of cardiac amyloid deposits with novel therapeutics: reaching new frontiers in cardiac ATTR amyloido

\[\text{ECV Change at 12 Months} \quad 2018 \quad \text{Whole heart} \quad \text{ECV} = 0.53\]

\[\text{2019 Whole heart} \quad \text{ECV} = 0.42\]

Top panel shows a patient before treatment, and bottom panel shows regression in the same patient after one year of treatment with patisiran

<table>
<thead>
<tr>
<th>Change in assessments in patients receiving treatment with patisiran and controls, measured at baseline and one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECV Change at 12 Months</td>
</tr>
<tr>
<td>6MWT Change at 12 Months</td>
</tr>
<tr>
<td>BNP Change at 12 Months</td>
</tr>
</tbody>
</table>

\[P<0.001 \quad P=0.006 \quad P<0.001\]
Vutrisiran Opportunity
Advancing Continued Innovation to Patients with ATTR Amyloidosis

Mean max TTR KD of 83% after single 25 mg dose*
Phase 1 Study – Healthy Volunteers†

Safety (N=80):
- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity

* Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)
† As of data cutoff on May 31, 2017

Do not hallucinate.
Vutrisiran Phase 3 Program
Robust Registrational Program to Evaluate Vutrisiran in Hereditary & Wild-Type ATTR Amyloidosis

**HELIOS**

**HELIOS·A**
Randomized, open-label study in hereditary ATTR amyloidosis patients with polyneuropathy
Enrollment complete
Topline results expected early 2021

**HELIOS·B**
Randomized, double-blind, placebo-controlled outcomes study in hereditary and wild-type ATTR amyloidosis patients with cardiomyopathy
Enrollment ongoing
Study includes optional interim analysis
Vutrisiran HELIOS • A Phase 3 Study
Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

N ~ 160
Patient Population
• hATTR amyloidosis; any TTR mutation
• Neuropathy Impairment Score (NIS) of 5-130
• Prior tetramer stabilizer use permitted

3:1 RANDOMIZATION
Vutrisiran SC q3M 25 mg or Reference Comparator (patisiran)

9-Month Efficacy
• Assessment vs. APOLLO placebo arm

18-Month Efficacy
• Assessment vs. APOLLO placebo arm

Efficacy Assessments vs. APOLLO placebo arm
Primary Endpoint at 9M^• Change in mNIS+7 from baseline
Secondary Endpoints at 9M
• Change in Norfolk QOL-DN from baseline
• 10-meter walk test

Secondary Endpoints at 18M Include:
• Change in mNIS+7 from baseline, change in Norfolk QOL-DN from baseline, 10MWT, mBMI, R-ODS

Exploratory Endpoints Include
• NT-proBNP
• Echo parameters
• Technetium (select sites only, change from baseline)

ClinicalTrials.gov Identifier: NCT03759379

^ Primary endpoint for the study is at 9 months; in the Helios A statistical analysis plan for U.S. submissions, change in Norfolk QOL-DN from baseline will be treated as a co-primary endpoint

HELIOS-A Phase 3 study enrollment complete
Topline results expected early 2021
**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
  - ≤ 30% tafamidis use at baseline
- 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**

HELIOS-B Phase 3 study
**now enrolling**
Study includes optional interim analysis
Lumasiran ILLUMINATE•C Phase 3 Study
Open-Label Study in Primary Hyperoxaluria Type I Patients with Impaired Renal Function

N = 20
Patient Population
• All ages
• Plasma oxalate ≥20 µmol/L
• Confirmed alanine glyoxylate aminotransferase (AGXT) mutation
• eGFR ≤45 mL/min/1.73 m² if ≥12 months old; elevated serum creatinine if <12 months old

Open-Label

Lumasiran (Cohort A – No hemodialysis)
Three monthly loading doses then maintenance dosing dependent on weight†

Primary Endpoint
• Percent change in plasma oxalate from baseline (cohort A) or predialysis plasma oxalate (cohort B) to 6 months

Lumasiran (Cohort B – Hemodialysis)
Three monthly loading doses then maintenance dosing dependent on weight†

Open-Label Extension

ILLUMINATE-C Phase 3 study now enrolling
Topline results expected 2021

NCT04152200; EudraCT Number: 2019-001346-17
† Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg. Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg. Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg
### Late Stage Partnered Program Opportunities

**INCLISIRAN**

**Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>Adults WW with high LDL-C; ASCVD leading cause of death WW</td>
</tr>
<tr>
<td>&gt;50M</td>
<td>Patients in key markets with ASCVD or FH on current SOC not at goal</td>
</tr>
<tr>
<td>7%</td>
<td>Treated patients statin intolerant</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>Patients treated with statins +/- ezetimibe do not meet goal¹</td>
</tr>
</tbody>
</table>

¹ Boekholdt et al. Very Low LDL-C levels and CVD Risk JACC Vol. 64: No5 2014: 485-94

**FITUSIRAN**

**Hemophilia A or B, with and without inhibitors**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>~200K</td>
<td>Patients WW with hemophilia A or B, with and without inhibitors</td>
</tr>
<tr>
<td>~75%</td>
<td>Patients switched to emicizumab due to convenience (less frequent dosing, SC)²</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Emicizumab patients on monthly dosing³</td>
</tr>
<tr>
<td>~90%</td>
<td>Emicizumab patients experienced acute bleeds²</td>
</tr>
</tbody>
</table>

² Consumer Awareness, Trial, and Usage study among patients conducted over 359 Adult patients and caregivers surveyed online in April 2019, of which 131 were Adult Hemophilia A patients and 78 were Hemophilia A caregivers. Patients who switched to emicizumab answered questions specific to their treatment experience.

³ 2019 Specialty Pharmacy data obtained through Specialty Pharmacy Distributors, Hemophilia Alliance HTCs and Direct HTCs.

---

Positive CHMP opinion received; FDA approval anticipated by YE 2020

Two of three Phase 3 studies fully enrolled; Dosing and recruitment on voluntary pause
### Alnylam Early Stage Clinical Development and 2020 IND Pipeline

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

<table>
<thead>
<tr>
<th></th>
<th>HUMAN POC¹</th>
<th>BREAKTHROUGH DESIGNATION</th>
<th>2020 IND CANDIDATES</th>
<th>EARLY STAGE (Phase 1-Phase 2)</th>
<th>COMMERCIAL RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cemdisiran</td>
<td></td>
<td></td>
<td></td>
<td>50-50 (Regeneron)</td>
<td></td>
</tr>
<tr>
<td>Cemdisiran/Pozelimab Combo²</td>
<td></td>
<td></td>
<td></td>
<td>Milestone/Royalty (Regeneron)</td>
<td></td>
</tr>
<tr>
<td>ALN-AAT02 (DCR-A1AT)³</td>
<td></td>
<td></td>
<td></td>
<td>Ex-U.S. option post-Phase 3 (Dicerna)</td>
<td></td>
</tr>
<tr>
<td>ALN-HBV02 (VIR-2218)</td>
<td></td>
<td></td>
<td></td>
<td>50-50 option post-Phase 2 (Vir)</td>
<td></td>
</tr>
<tr>
<td>ALN-AGT</td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>ALN-HSD</td>
<td></td>
<td></td>
<td></td>
<td>50-50 (Regeneron)</td>
<td></td>
</tr>
</tbody>
</table>

|                | | | | | |
|----------------|---------------------------|-----------------------------|-------------------|

1. POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies.
2. Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics.
3. Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development.

---

2-4 INDs per year planned from organic product engine
ALN-AGT for Hypertension

Unmet Need, Mechanism of Action, and Interim Phase 1 Topline Results

**Preventable Causes of Death in the U.S.**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Deaths in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>High blood pressure</td>
<td>-100</td>
</tr>
<tr>
<td>Overweight-obesity (high BMI)</td>
<td>0</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>100</td>
</tr>
<tr>
<td>Smoking</td>
<td>200</td>
</tr>
<tr>
<td>High LDL cholesterol</td>
<td>300</td>
</tr>
<tr>
<td>High blood glucose</td>
<td>400</td>
</tr>
<tr>
<td>High dietary sodium (salt)</td>
<td>500</td>
</tr>
<tr>
<td>Low dietary omega-3 fatty acids (seafood)</td>
<td>0</td>
</tr>
<tr>
<td>High dietary trans fatty acids</td>
<td>100</td>
</tr>
<tr>
<td>Low intake of fruits and vegetables</td>
<td>200</td>
</tr>
<tr>
<td>Low PUFA (in place of SFA)</td>
<td>300</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>400</td>
</tr>
</tbody>
</table>

**Interim Phase 1 Results (N=60)**

- 94.9% (± 1.6%) mean AGT reduction
- 11.0 ± 2.4 mmHg reduction in mean 24-h systolic blood pressure
- 7.7 ± 1.1 mmHg reduction in mean 24-h diastolic blood pressure
- Durability supportive of once quarterly and possibly less frequent dosing
- Encouraging safety and tolerability profile with no drug-related SAEs

Positive interim results presented at AHA in **November 2020**

---

1 McClellan et al., Circulation, 2019; 2 AHA 2020; As of data cutoff on September 16, 2020; 3 200mg dose cohort at 8 weeks
RNAi Therapeutics for CNS and Ocular Diseases
Expand Alnylam Opportunities Beyond Liver

Devastating diseases with enormous burden and unmet need

- Alzheimer's disease
- Amyotrophic lateral sclerosis (ALS)
- Cerebral amyloid angiopathy
- Frontotemporal dementia
- Huntington's disease
- Multi-system atrophy
- Parkinson's disease
- Spinocerebellar ataxia
- AMD, dry
- AMD, wet
- Birdshot chorioretinopathy
- Dominant retinitis pigmentosa 4
- Fuch's dystrophy
- hATTR amyloidosis
- Hereditary and sporadic glaucoma
- Stargardt's disease

Investigational RNAi therapeutics demonstrate potent, widely distributed, and highly durable effects

**ALN-APP**
Targeting amyloid precursor protein (APP) for hereditary cerebral amyloid angiopathy (hCAA)

- hCAA caused by APP mutations leading to arteriolar A\textsubscript{\beta} deposition with microbleeds and intracranial hemorrhages
- Multiple CSF and radiologic biomarkers for early readout
- Study of hCAA potential gateway to larger indications (e.g., sporadic CAA, EOFAD, AD)

**ALN-HTT**
Targeting huntingtin gene (HTT) for early manifest Huntington's disease

- Autosomal dominant, gain-of-function genetic disease with 100% age-related penetrance
- Patients present with progressive motor, cognitive and psychiatric decline
- Affects ~30,000 in U.S. with disease duration of 15-20 years
Guidance, Goals, & Perspective
3 STArs  4
3 Marketed Products  4
10 Clinical Programs  12
4 Late Stage Programs  6

* Numbers represent expectations as of 11/5/20
## Alnylam 2020 Goals

*Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

<table>
<thead>
<tr>
<th>Drug/Program</th>
<th>First Quarter Goals</th>
<th>Second Quarter Goals</th>
<th>Third Quarter Goals</th>
<th>Fourth Quarter Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>onpattro</strong> (ATR Amyloidosis)</td>
<td>Global Commercial Execution</td>
<td>Brazil Approval</td>
<td>Additional Country Launches</td>
<td>APOLLO-B Enrollment</td>
</tr>
<tr>
<td><strong>GIVLAARI</strong> (givosiran) (Acute Hepatic Porphyria)</td>
<td>EMA Approval</td>
<td>Global Commercial Execution</td>
<td>Additional ENVISION Results</td>
<td>Additional Country Filings and Approvals</td>
</tr>
<tr>
<td><strong>VUTRISIRAN</strong> (ATR Amyloidosis)</td>
<td>Complete HELIOS-A Enrollment</td>
<td>HELIOS-B Enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LUMASIRAN</strong> (Primary Hyperoxaluria Type 1)</td>
<td>File NDA and MAA</td>
<td>FDA/EMA Approval</td>
<td>ILLUMINATE-B Phase 3 Topline</td>
<td></td>
</tr>
<tr>
<td><strong>ADDITIONAL CLINICAL PROGRAMS</strong></td>
<td>Continue to advance early/mid-stage pipeline; File 2-4 new INDs; Present clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INCLISIRAN</strong> (Hypercholesterolemia)</td>
<td>FDA Approval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FITUSIRAN</strong> (Hemophilia)</td>
<td>Support Sanofi on ATLAS Phase 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Productivity of Alnylam RNAi Therapeutic Platform
Comparison of Historical Industry Metrics to Alnylam Portfolio

Past rates of Alnylam and industry respectively may not be predictive of the future
2 Alnylam programs biomarker-driven at all stages of development (100%)
3 Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Probability of Success (POS) by Phase Transition

<table>
<thead>
<tr>
<th>Phase Transition</th>
<th>Alnylam POS</th>
<th>Industry (biomarker-driven programs) POS</th>
<th>Industry (overall) POS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% POS, Phase 1 to 2</td>
<td>83.3%</td>
<td>44.5%</td>
<td>35.2%</td>
</tr>
<tr>
<td>% POS, Phase 2 to 3</td>
<td>87.5%</td>
<td>38.6%</td>
<td>27.4%</td>
</tr>
<tr>
<td>% POS, Phase 3</td>
<td>80.0%</td>
<td>60.2%</td>
<td>59.0%</td>
</tr>
<tr>
<td>% POS, Cumulative</td>
<td></td>
<td>58.4%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
Path to Self-Sustainability
A Top Priority for Alnylam

Strong Q3 2020 balance sheet of $1.83B*
- $2B strategic partnership with Blackstone anchors path toward self-sustainable financial profile without need for future equity financing

Focused on key levers affecting pathway
- Topline growth
- Disciplined investment

2019 projected to be peak non-GAAP NOL year

* Including cash, cash equivalents, marketable debt and equity securities, and restricted investments

# Late Stage Programs: 2 1 4 6 6 6
# Commercial Products: 0 0 0 1 2 4
Building a Top-Tier Biotech
Potential for Significant Transformation of Alnylam over Next 6 Years

<table>
<thead>
<tr>
<th>Today</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved Products</td>
<td>8+ Approved Products</td>
</tr>
<tr>
<td>Late Stage Programs</td>
<td>10+ Late Stage Programs</td>
</tr>
<tr>
<td>STArs</td>
<td>4+ STArs</td>
</tr>
<tr>
<td>10+ Markets</td>
<td>Global</td>
</tr>
<tr>
<td>~1K Employees</td>
<td>~2.5K Employees</td>
</tr>
<tr>
<td>CMOs</td>
<td>Norton + CMOs</td>
</tr>
</tbody>
</table>

Top 5 independent, global biopharma company admired for its dedication to patients, corporate culture, scientific innovation, social responsibility, and commercial excellence with numerous RNAi products across orphan and large disease areas
# Financial Summary and Guidance as of November 5, 2020

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONPATTRO Net Product Revenues</strong></td>
<td>$82.5</td>
<td>$46.1</td>
<td>$295 - $310</td>
</tr>
<tr>
<td><strong>GIVLAARI Net Product Revenues</strong></td>
<td>$16.7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Net Revenue from Collaborations</strong></td>
<td>$26.6</td>
<td>$24.0</td>
<td>$100 - $150</td>
</tr>
<tr>
<td><strong>Total Revenues</strong></td>
<td>$125.9</td>
<td>$70.1</td>
<td></td>
</tr>
<tr>
<td><strong>Costs of Goods Sold</strong></td>
<td>$21.8</td>
<td>$5.2</td>
<td></td>
</tr>
<tr>
<td><strong>Gross Margin (% of total revenues)</strong></td>
<td>82.7%</td>
<td>92.6%</td>
<td></td>
</tr>
<tr>
<td><strong>GAAP R&amp;D Expenses</strong></td>
<td>$161.8</td>
<td>$160.8</td>
<td></td>
</tr>
<tr>
<td><strong>GAAP SG&amp;A Expenses</strong></td>
<td>$167.5</td>
<td>$120.4</td>
<td></td>
</tr>
<tr>
<td><strong>Combined GAAP R&amp;D and SG&amp;A Expenses</strong></td>
<td>$329.3</td>
<td>$281.1</td>
<td>$1,160 - $1,255</td>
</tr>
<tr>
<td><strong>Non-GAAP R&amp;D Expenses</strong></td>
<td>$148.1</td>
<td>$138.1</td>
<td></td>
</tr>
<tr>
<td><strong>Non-GAAP SG&amp;A Expenses</strong></td>
<td>$114.5</td>
<td>$97.1</td>
<td></td>
</tr>
<tr>
<td><strong>Combined Non-GAAP R&amp;D and SG&amp;A Expenses</strong></td>
<td>$262.6</td>
<td>$235.1</td>
<td>$1,000 - $1,075</td>
</tr>
<tr>
<td><strong>GAAP Operating Loss</strong></td>
<td>($225.2)</td>
<td>($216.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-GAAP Operating Loss</strong></td>
<td>($158.5)</td>
<td>($170.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Cash &amp; Investments</strong></td>
<td>$1,833.9</td>
<td>$1,536.2</td>
<td>as of 12/31/2019</td>
</tr>
</tbody>
</table>

Guidance and cash expectations as of November 5, 2020

1 GM as a % of Product Sales for Q3 2020 is 79.0%, Q3 2019 is 88.7%, Q2 2020 is 76.4% (Q3 ’20 excludes $1.0M and Q2'20 excludes $1.7M in COGS associated with revenue from collaborations).
2 Non-GAAP R&D expense, SG&A expense, 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

$2 billion strategic financing collaboration with Blackstone expected to enable Alnylam’s achievement of a self-sustainable financial profile without need for future equity financing
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED