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 finalization and audit of our fourth quarter and 2019 fiscal year financial results which could potentially result in changes or adjustments to the selected preliminary financial results presented herein; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; 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; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our ability to obtain regulatory approval for our product candidates, including lumasiran, and to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO® (patisiran) and GIVLAARI™ (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI; 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 and achieve a self-sustainable financial profile in the future; our ability to obtain additional funding to support our business activities and establish and maintain business alliances; our dependence on third parties, including Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, and Ironwood, for assistance with the education about and promotion of GIVLAARI; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance 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 expense and the gain on litigation settlement. 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 gain on litigation settlement because the Company believes this item is a one-time event occurring 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.
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\(^1\)

<table>
<thead>
<tr>
<th>Hereditary ATTR (hATTR) Amyloidosis</th>
<th>(~50,000) patients worldwide*</th>
</tr>
</thead>
</table>

| Wild-Type ATTR (wtATTR) Amyloidosis | \(~200,000 – 300,000\) patients worldwide |

ONPATTRO® Global Launch Update: Year End 2019

Strong Performance with Significant Growth Potential

~$166M

ONPATTRO Global 2019
Net Product Revenues (Preliminary*)

ROL
U.S.
WW (preliminary*)

$26.3M
$38.2M
$46.1M
~$56M

Q1 2019
Q2 2019
Q3 2019
Q4 2019

>750

Patients Worldwide on Commercial ONPATTRO at YE 2019

Expect steady and continued growth with new patient finding, global expansion, and evidence-generating activities

* Preliminary select financial results are unaudited, subject to adjustment, and provided as an approximation in advance of the Company’s announcement of complete financial results in February 2020
Alnylam ATTR Amyloidosis Franchise
Potential to Expand Value to Patients Globally for Many Years to Come

ONPATTRO is approved in the U.S. and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; 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

Novel siRNA Conjugates
Ocular & CNS hATTR Amyloidosis

Vutrisiran
HELIOS A
PN, Mixed

Vutrisiran
HELIOS B
PN, Mixed, & CM (including Wild-Type)

Vutrisiran
HELIOS C
PN, Mixed, CM (including Wild-Type), & Carriers

Vutrisiran
Ocular & CNS hATTR Amyloidosis

PN & Mixed* 2019 – 2021

PN, Mixed, & CM (including Wild-Type)† 2021 – 2023

PN, Mixed, & CM (including Wild-Type)‡ 2023 & Beyond

PN & Mixed* 2019 – 2021

PN, Mixed, & CM (including Wild-Type)† 2021 – 2023

PN, Mixed, & CM (including Wild-Type)‡ 2023 & Beyond

PN, Mixed, & Carriers† 2023 & Beyond
The second RNAi therapeutic is NOW APPROVED IN THE U.S.
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

<table>
<thead>
<tr>
<th>Predominantly</th>
<th>female</th>
</tr>
</thead>
<tbody>
<tr>
<td>commonly misdiagnosed</td>
<td></td>
</tr>
</tbody>
</table>

Patient Population
~3,000

diagnosed in U.S./EU with active disease

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

Cutaneous
- Lesions on sun-exposed skin

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

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

Long-term Complications
- Hepatocellular carcinoma
- Chronic kidney disease
- Hypertension
- Neuropathy


1 Symptoms specific to hereditary coproporphyria and variegate porphyria
GIVLAARI™ (givosiran) Label

**Indication**
GIVLAARI is indicated for the treatment of adults with acute hepatic porphyria (AHP)

**Dosing & Administration**
**Dosing:**
• 2.5 mg/kg via subcutaneous injection once monthly

**Administration:**
• GIVLAARI is intended for subcutaneous use only by a healthcare professional

**Safety**
**Contraindications**
• GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran

**Warnings and Precautions**
• **Anaphylactic Reaction:** Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms. If anaphylaxis occurs, discontinue GIVLAARI and administer appropriate medical treatment.
• **Hepatic Toxicity:** Measure liver function at baseline and periodically during treatment with GIVLAARI. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations.
• **Renal Toxicity:** Monitor renal function during treatment with GIVLAARI as clinically indicated.
• **Injection Site Reactions:** May occur, including recall reactions. Monitor for reactions and manage clinically as needed.

*For additional Important Safety Information on GIVLAARI, see full Prescribing Information*
Launching GIVLAARI Globally
Building on ONPATTRO Capabilities and Playbook

- Agreement in principle in place with Harvard Pilgrim

* Proactive Value Based Agreements*

*Strong Product Profile*

Patient Engagement and Advocacy

HCP Education

Support

Access

Diagnosis
# GIVLAARI™ (givosiran) Market Opportunity

Ultra-Rare Orphan Disease with Significant Disease Burden and Limited Treatment Options

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

### COST BURDEN

- $400–650K average annual expenditure, recurrent attack patients<sup>4</sup> | $400–650K average annual expenditure, recurrent attack patients<sup>4</sup> |

### GIVLAARI | ACUTE HEPATIC PORPHYRIA

>$500M potential market opportunity

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<sup>1</sup> Elder et al. J Inherit Metab Dis 2013;36:949–57

<sup>2</sup> Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database

<sup>3</sup> Gouya, et al. EASL 2018

<sup>4</sup> EXPLORE Natural History Study (includes patients with ≥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.
Multiple Launches Planned in Next 12-24 Months

<table>
<thead>
<tr>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>Partnered programs*: 2020-2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONPATTRO (patisiran)</strong></td>
<td><strong>GIVLAARI (givosiran)</strong></td>
<td><strong>Lumasiran</strong></td>
<td><strong>Vutrisiran</strong></td>
<td><strong>Inclisiran</strong></td>
</tr>
<tr>
<td>ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults*</td>
<td>GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria†</td>
<td>Primary hyperoxaluria type 1</td>
<td>ATTR amyloidosis</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>NDA filed</td>
<td>Rolling NDA initiated</td>
<td>Phase 3 enrolling</td>
<td>NDA filed</td>
<td>Phase 3 enrolling</td>
</tr>
</tbody>
</table>

Robust pipeline fuels sustainable product launches **beyond 2021**, leveraging global commercial infrastructure

* 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
† ONPATTRO is approved in Canada for the polyneuropathy of hATTR amyloidosis in adults, the EU and Switzerland for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, and Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy. For additional information on ONPATTRO, see Full Prescribing Information
† Alnylam has filed for marketing authorization for givosiran in Europe and Brazil and plans to file in Japan and other countries in 2020; For additional information on GIVLAARI, 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

<table>
<thead>
<tr>
<th>Focused in 4 Strategic Therapeutic Areas (STArs):</th>
<th>BREAKTHROUGH DESIGNATION</th>
<th>LATE STAGE (Phase 2-Phase 3)</th>
<th>REGISTRATION</th>
<th>COMMERCIAL</th>
<th>COMMERCIAL RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Medicines</td>
<td></td>
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<tr>
<td>Cardio-Metabolic Diseases</td>
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<tr>
<td>Hepatic Infectious Diseases</td>
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<tr>
<td>CNS/Ocular Diseases</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease</th>
<th>Region</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onpattro</strong> (patisiran)</td>
<td>hATTR Amyloidosis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Global</td>
<td>Blue</td>
</tr>
<tr>
<td><strong>GIVLAARI</strong> (givosiran)</td>
<td>Acute Hepatic Porphyria&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Global</td>
<td>Blue</td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Primary Hyperoxaluria Type 1</td>
<td>Global</td>
<td>Blue</td>
</tr>
<tr>
<td>Inclisiran</td>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patisiran</td>
<td>ATTR Amyloidosis Label Expansion</td>
<td>Global</td>
<td>Blue</td>
</tr>
<tr>
<td>Fitusiran</td>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>ATTR Amyloidosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<sup>1</sup> Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy.

<sup>2</sup> Approved in the U.S. for the treatment of adults with acute hepatic porphyria.

As of January 2020
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

**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**

**Topline results 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

<table>
<thead>
<tr>
<th>Cardiac Safety Data in Entire APOLLO Study Population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of Death/Hospitalization, per 100 py (95% CI)</td>
</tr>
<tr>
<td>Placebo$^2$ (n=77)</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
</tr>
<tr>
<td>Cardiac hospitalization</td>
</tr>
<tr>
<td>Hospitalization and/or death</td>
</tr>
<tr>
<td>Cardiac hospitalization and/or death</td>
</tr>
</tbody>
</table>

- Relative reduction in NT-proBNP vs. placebo$^†$
  - Effect noted as early as 9 months
- Mean reduction in LV wall thickness vs. placebo$^‡$
- Improvement in global longitudinal strain vs. placebo$^‡$
- Improvement in 10-MWT vs. placebo$^†$

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 Regression¹

• Recent uncontrolled case series²
  • Recently published similar findings by Nienhaus *et al.*³
  • 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 Gilmore, OTS Munich 2019
³ Mayo Clinic Proceedings, 2019

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

Baseline

12 Months
Advancing Continued Innovation to Patients with ATTR Amyloidosis

Vutrisiran Opportunity

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

Vutrisiran
4 DOSES PER YEAR

~90% peak TTR KD predicted after repeat dosing

* 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
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

Open-Label Extension

Efficacy Assessments vs. APOLLO placebo arm

Co-Primary Endpoints
• Change in mNIS+7 from baseline
• Change in Norfolk QOL-DN from baseline

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

HELIOS-A Phase 3 study now enrolling
Topline results expected Early 2021

^ Primary endpoint for the study is at 9 months
* ATTR amyloidosis – wild type or any TTR mutation
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

1:1 RANDOMIZATION

Vutrisiran SC q3M 25 mg

or

Placebo SC q3M

Primary Endpoint
• Composite outcome of all-cause mortality and recurrent CV hospitalizations (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
• All-cause mortality
• Recurrent CV hospitalizations
• NT-proBNP

HELIOS-B Phase 3 study now enrolling
Study includes optional interim analysis
Primary Hyperoxaluria Type 1
Lumasiran

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 – 5,000
U.S./EU
Lumasiran Registrational Program
Robust Registrational Program to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

**ILLUMINATE**

- **ILLUMINATE-A**: Double-blind, placebo-controlled trial in PH1 patients at least 6 years old with preserved renal function. Detailed results in March 2020 (OxalEurope).

- **ILLUMINATE-B**: Single arm, open-label study in PH1 patients less than 6 years old with preserved renal function. Topline results expected in mid-2020.

- **ILLUMINATE-C**: Single arm, open-label study in PH1 patients with impaired renal function, including advanced disease. Topline results expected in 2021.

Expanded Access Protocol (EAP) for PH1 patients at least 6 years old with preserved renal function recently initiated in U.S.
Lumasiran **ILLUMINATE•A** Phase 3 Study

**Topline Results**

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent change from baseline in 24-hour urinary oxalate excretion, averaged across months 3 to 6 relative to placebo</td>
<td>$1.69 \times 10^{-14}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute change from baseline in 24-hour urinary oxalate corrected for body surface area (BSA), averaged across months 3 to 6</td>
<td>$1.23 \times 10^{-11}$</td>
</tr>
<tr>
<td>Percent change from baseline in 24-hour urinary oxalate:creatinine ratio, averaged across months 3 to 6</td>
<td>$5.03 \times 10^{-10}$</td>
</tr>
<tr>
<td>Percent change from baseline in plasma oxalate, averaged across months 3 to 6</td>
<td>$2.86 \times 10^{-8}$</td>
</tr>
<tr>
<td>Proportion of patients with 24-hour urinary oxalate level $\leq 1.5x$ ULN at month 6</td>
<td>$8.34 \times 10^{-7}$</td>
</tr>
<tr>
<td>Proportion of patients with 24-hour urinary oxalate level $\leq$ ULN at month 6</td>
<td>0.001</td>
</tr>
<tr>
<td>Absolute change from baseline in plasma oxalate, averaged across months 3 to 6</td>
<td>$3.89 \times 10^{-7}$</td>
</tr>
</tbody>
</table>

**Safety**

- No serious or severe adverse events
- Lumasiran generally well tolerated
- Most common adverse events were injection site reactions
  - All mild and transient
- Overall profile generally consistent with previously reported results from lumasiran Phase 1/2 and OLE studies
### Lumasiran Market Opportunity

Ultra-Rare Orphan Disease with Potential First-in-Class/Best-in-Class Medicine

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>DIAGNOSIS</th>
<th>DISEASE BURDEN</th>
<th>COST BURDEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3–5K patients in U.S./EU&lt;sup&gt;1&lt;/sup&gt;</td>
<td>~50% currently diagnosed&lt;sup&gt;2&lt;/sup&gt;; mean time to diagnosis ~6 years&lt;sup&gt;3&lt;/sup&gt;</td>
<td>30–65% reach end-stage renal disease before diagnosis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>$1M+ average cost (transplant &amp; lifelong immunosuppression)</td>
</tr>
</tbody>
</table>

### LUMASIRAN | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

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Late Stage Partnered Program Opportunities

<table>
<thead>
<tr>
<th>INCLISIRAN</th>
<th>NOVARTIS</th>
<th>FITUSIRAN</th>
<th>SANOFI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td></td>
<td><strong>Hemophilia A or B, with and without inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>Adults WW with high LDL-C; ASCVD leading cause of death WW</td>
<td>~200K</td>
<td>Patients WW with hemophilia A or B, with and without inhibitors</td>
</tr>
<tr>
<td>&gt;50M</td>
<td>Patients in key markets with ASCVD or FH on current SOC not at goal</td>
<td>~75%</td>
<td>Patients switched to emicizumab due to convenience (less freq. dosing, SC)²</td>
</tr>
<tr>
<td>7%</td>
<td>Treated patients statin intolerant</td>
<td>&lt;10%</td>
<td>Emicizumab patients on monthly dosing³</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>Patients treated with statins +/- ezetimibe do not meet goal¹</td>
<td>~90%</td>
<td>Emicizumab patients experienced acute bleeds²</td>
</tr>
<tr>
<td></td>
<td>NDA filed</td>
<td></td>
<td>&gt;70% patients enrolled in ATLAS Phase 3 trials</td>
</tr>
</tbody>
</table>

¹ Boekholt et al. Very Low LDL-C levels and CVD Risk JACC VOL 64:No5 2014:485-94.
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.
Alnylam Early Stage Clinical Development and 2020 IND Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic 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>Complement-Mediated Diseases</td>
<td></td>
<td></td>
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<td>50-50 (Regeneron)</td>
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<tr>
<td>Cemdisiran/Pozelimab Combo²</td>
<td>Complement-Mediated Diseases</td>
<td></td>
<td></td>
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<td>Milestone/Royalty (Regeneron)</td>
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<tr>
<td>ALN-AAT02</td>
<td>Alpha-1 Liver Disease</td>
<td></td>
<td></td>
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<td>Global</td>
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<tr>
<td>ALN-HBV02 (VIR-2218)</td>
<td>Hepatitis B Virus Infection</td>
<td></td>
<td></td>
<td></td>
<td>50-50 option post-Phase 2 (Vir)</td>
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<tr>
<td>ALN-AGT</td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
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<tr>
<td>ALN-HSD</td>
<td>NASH</td>
<td></td>
<td></td>
<td></td>
<td>Milestone/Royalty (Regeneron)</td>
</tr>
<tr>
<td>ALN-LEC</td>
<td>ALECT2 Amyloidosis</td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
</tbody>
</table>

2-4 INDs per year planned from organic product engine

¹ POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
² Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

As of January 2020
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 Aβ 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
Highly Durable Amyloid Precursor Protein (APP) Knockdown in NHP

Single Intrathecal Dose of ALN-APP Supports Bi-Annual or Less Frequent Regimen

CSF sAPPα and sAPPβ Protein Knockdown
(Single Intrathecal Dose in NHP)
Guidance, Goals, & Perspective
3 STArs
3 Marketed Products
10 Clinical Programs
4 Late Stage Programs
<table>
<thead>
<tr>
<th>Product</th>
<th>2020 Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alnylam 2020 Goals</strong></td>
<td><strong>2020</strong>*</td>
</tr>
<tr>
<td><strong>Early</strong></td>
<td><strong>Mid</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Global Commercial Execution</th>
<th>Brazil Approval</th>
<th>Additional Country Launches</th>
<th>Complete APOLLO-B Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>onpattro</strong>&lt;br&gt;(ATR Amyloidosis)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>GIVLAARI</strong>&lt;br&gt;(Givosiran)&lt;br&gt;(Acute Hepatic Porphyria)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>VUTRISIRAN</strong>&lt;br&gt;(ATR Amyloidosis)</td>
<td>Complete HELIOS-A Enrollment</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>LUMASIRAN</strong>&lt;br&gt;(Primary Hyperoxaluria Type 1)</td>
<td>File 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 3 new INDs; Present clinical data</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PARTNERED PROGRAMS</strong></th>
<th><strong>FDA Approval</strong></th>
<th><strong>MAA Filing</strong></th>
<th><strong>ORION-4 CVOT Phase 3 Enrollment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCLISIRAN</strong>&lt;br&gt;(Hypercholesterolemia)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>FITUSIRAN</strong>&lt;br&gt;(Hemophilia)</td>
<td>Support Sanofi on ATLAS Phase 3</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

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

Alnylam programs biomarker-driven at all stages of development (100%).

1. 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%).
A Top Priority for Alnylam

Path to Self-Sustainability

Strong 2019 YE balance sheet of ~$1.5B*

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

2019 projected to be peak non-GAAP NOL year

Non-GAAP Net Operating Income/Loss ($1,000s)

Actual Results
Illustrative Growth (not to scale)

# Late Stage Programs: 2 1 4 6 6 6
# Commercial Products: 0 0 0 1 2 4

* Preliminary selected 2019 financial results are unaudited, subject to adjustment, and are provided as an approximation in advance of the Company’s announcement of complete financial results for Q4 and FY 2019 in Feb. 2020
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>2</td>
<td>8+</td>
</tr>
<tr>
<td>Approved Products</td>
<td>Approved Products</td>
</tr>
<tr>
<td>6</td>
<td>10+</td>
</tr>
<tr>
<td>Late Stage Programs</td>
<td>Late Stage Programs</td>
</tr>
<tr>
<td>4</td>
<td>4+</td>
</tr>
<tr>
<td>STArs</td>
<td>STArs</td>
</tr>
<tr>
<td>~1K</td>
<td>~2.5K</td>
</tr>
<tr>
<td>Employees</td>
<td>Employees</td>
</tr>
<tr>
<td>~1K</td>
<td>~2.5K</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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ONPATTRO Net Product Revenues</td>
<td>$46.1M</td>
<td>$110.6M</td>
</tr>
<tr>
<td>Total Revenues</td>
<td>$70.1M</td>
<td>$148.1M</td>
</tr>
<tr>
<td>Total GAAP Operating Costs and Expenses</td>
<td>$286.4M</td>
<td>$789.4M</td>
</tr>
<tr>
<td>• R&amp;D Expenses</td>
<td>$160.8M</td>
<td>$453.8M</td>
</tr>
<tr>
<td>• SG&amp;A Expenses</td>
<td>$120.4M</td>
<td>$322.7M</td>
</tr>
<tr>
<td>• Cost of Goods Sold</td>
<td>$5.2M</td>
<td>$12.9M</td>
</tr>
<tr>
<td>Non-GAAP Expenses</td>
<td></td>
<td></td>
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<tr>
<td>• Non-GAAP R&amp;D Expenses†</td>
<td>$138.1M</td>
<td>$399.7M</td>
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<tr>
<td>• Non-GAAP SG&amp;A Expenses†</td>
<td>$97.1M</td>
<td>$268.2M</td>
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<tr>
<td>GAAP Net Loss</td>
<td>$208.5M</td>
<td>$609.9M</td>
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<tr>
<td>Non-GAAP Net Loss</td>
<td>$162.5M</td>
<td>$510.7M</td>
</tr>
<tr>
<td>Shares Outstanding</td>
<td>111.3M</td>
<td>101.2M</td>
</tr>
</tbody>
</table>

### 2019 Financial Guidance
(affirmed as of 10/31/2019)

- **$550M to $575M**
  - Non-GAAP R&D Expenses†
- **$390M to $400M**
  - Non-GAAP SG&A Expenses†
- **$1,738.3M**
  - Current cash, cash equivalents, and marketable debt securities expected to support company operations for multiple years based on current operating plan

### Select Q4 & FY 2019 Preliminary Results

- **~$56M / ~$166M**
  - ONPATTRO global net product revenues (Q4/FY’19; preliminary)
- **~$0.2M**
  - GIVLAARI global net product revenues (Q4’19; preliminary)
- **~$1.5B**
  - Year-end cash, cash equivalents, marketable debt and equity securities, and restricted investments (preliminary)

---

1. Non-GAAP operating expenses exclude stock-based compensation expenses
2. Non-GAAP net loss excludes stock-based compensation expenses, a gain on the change in fair value of a liability obligation, and a gain on litigation settlement
3. Preliminary select financial results are unaudited, subject to adjustment, and provided as an approximation in advance of the Company’s announcement of complete financial results in February 2020
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED