Glaucienne
Living with AHP (Brazil)

Alnylam Pharmaceuticals
January 2021
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, the broad availability of safe and effective vaccine(s), 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; the finalization and audit of our fourth quarter and 2020 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, including vutrisiran, patisiran, fitisiran, cemdisiran, ALN-AGT, ALN-HSD, ALN-AAT02 (DCR-A1AT) and ALN-HBV02 (VIR-2218); 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, or our partners’, product candidates and marketed products, including ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran), Leqvio® (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 in the U.S., and our, or our partners’, ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO, GIVLAARI, OXLUMO and Leqvio in the EU; our, or our partners’, ability to successfully launch, market and sell our approved products globally, including ONPATTRO, GIVLAARI, OXLUMO and Leqvio, 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 guidance 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 Leqvio, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products such as ALN-APP and ALN-HTT; 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.
## Our Last 5-Year Strategy

<table>
<thead>
<tr>
<th>GOAL</th>
<th>TARGET</th>
<th>ACHIEVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategic Therapeutic Areas (STArs)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Marketed Products</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Clinical Programs</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Late Stage Programs</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Our New 5-Year Strategy

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
RNAi Therapeutics: New Class of Innovative Medicines
Clinically and Commercially Established Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome with siRNAs
- Potent and durable mechanism of action
- Product engine for sustainable innovation
- Multiple products impacting patients globally
TRANSFORMATIONAL MEDICINES

ROBUST & HIGH-YIELD R&D PIPELINE

ORGANIC PRODUCT ENGINE
TRANSFORMATIONAL MEDICINES

ROBUST & HIGH-YIELD R&D PIPELINE

ORGANIC PRODUCT ENGINE
RNAi Therapeutics: Transformational Medicines for Rare & Prevalent Diseases
Four Global Approvals in Just Over 2 Years
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>
</tr>
</thead>
<tbody>
<tr>
<td>~50,000 patients worldwide*</td>
</tr>
</tbody>
</table>

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


ONPATTRO® Launch Update: Q4 and Year-End 2020

Strong Year 2 Performance with Continued Growth

~$306M

ONPATTRO Global 2020
Net Product Revenues (Preliminary*)

~$1,350

Patients Worldwide on Commercial
ONPATTRO at YE 2020

* 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 2021
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 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.

* 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.

† 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
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$^{1,2}$

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

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

Cutaneous $^f$
- Lesions on sun-exposed skin

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

Long-term Complications
- Liver disease
- Chronic kidney disease
- Hypertension
- Neuropathy

$^1$ Elder et al. J Inherit Metab Dis 2013;36:849–57; $^2$ Data on file, IBM MarketScan Commercial Claims and Medicare Supplemental Database

$^f$ Symptoms specific to hereditary coproprophyria and variegate porphyria
GIVLAARI® Launch Update: Q4 and Year-End 2020

Strong Year 1 Performance with Continued Growth

~$55M

GIVLAARI Global 2020
Net Product Revenues (Preliminary*)

Q4 2019: $0.2M
Q1 2020: $5.3M
Q2 2020: $11.0M
Q3 2020: $16.7M
Q4 2020: ~$22M*

~200

Patients Worldwide on Commercial GIVLAARI at YE 2020

Q1 2020: >50
Q2 2020: >100
Q3 2020: >150
Q4 2020: ~200

* 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 2021.
### 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(^1,2)</td>
<td>~20–50% currently diagnosed; delays up to 15 years</td>
<td>65% recurrent attack patients with chronic symptoms(^3)</td>
<td>$400–650K average annual expenditure, recurrent attack patients(^4)</td>
</tr>
</tbody>
</table>

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 ≥ 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.

>$500M potential market opportunity
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./EU¹

¹ Includes patients that are presymptomatic, subclinical, or symptomatic
The third RNAi therapeutic is
NOW APPROVED IN THE EU & U.S.
### 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</td>
<td>~50%</td>
<td>30–65%</td>
<td>$1M+</td>
</tr>
<tr>
<td>potentially symptomatic patients in U.S./EU</td>
<td>currently diagnosed(^1); mean time to diagnosis ~6 years(^2)</td>
<td>reach end-stage renal disease before diagnosis(^2)</td>
<td>average cost (transplant &amp; lifelong immunosuppression)</td>
</tr>
</tbody>
</table>

---

**OXLUMO | PRIMARY HYPEROXALURIA TYPE 1**

>$500M potential market opportunity

---


### Additional Alnylam and Partner Launches Planned Over Next 12-24 Months

**Compelling Commercial Profile of Existing and Emerging Medicines**

<table>
<thead>
<tr>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2020</th>
<th>2022-2023</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONPATTRO</strong></td>
<td><strong>GIVLAARI</strong></td>
<td><strong>OXLUMO</strong></td>
<td><strong>Leqvio® (inclisiran)</strong></td>
<td><strong>Vutrisiran</strong></td>
</tr>
<tr>
<td>ONPATTRO is approved in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults</td>
<td>GIVLAARI is approved in the U.S. for the treatment of adults with acute hepatic porphyria</td>
<td>OXLUMO is approved in the U.S. for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients</td>
<td>Leqvio is approved in the EU for the treatment of adults with hypercholesterolemia or mixed dyslipidemia</td>
<td>ATTR amyloidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CRL in U.S. related to inspection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. ONPATTRO is approved in U.S. and Canada for the PN of hATTR amyloidosis in adults, and in 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.
4. Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics. Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful.
5. Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval.

---

Robust pipeline fuels sustainable product launches **beyond 2021**, leveraging global commercial infrastructure.
Mayah
Living with PH1 (USA)

TRANSFORMATIONAL MEDICINES

ROBUST & HIGH-YIELD R&D PIPELINE

ORGANIC PRODUCT ENGINE
Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

<table>
<thead>
<tr>
<th>Genetic Medicines</th>
<th>Cardio-Metabolic Diseases</th>
<th>Infectious Diseases</th>
<th>CNS/Ocular Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>nattressa</td>
<td>hATTR Amyloidosis^2</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>GIVLAARI</td>
<td>Acute Hepatic Porphyria^2</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>OXLUMO</td>
<td>Primary Hyperoxaluria Type 1^4</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>Leqvio® (inclisiran)</td>
<td>Hypercholesterolemia</td>
<td>Milestones &amp; up to 20% Royalties^5</td>
<td></td>
</tr>
<tr>
<td>Patisiran</td>
<td>ATTR Amyloidosis</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>ATTR Amyloidosis</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>Fitusiran</td>
<td>Hemophilia</td>
<td>15-30% Royalties</td>
<td></td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Severe PH1</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent Renal Stones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cemdisiran</td>
<td>Complement-Mediated Diseases</td>
<td>50-50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complement-Mediated Diseases</td>
<td>Milestone/Royalty</td>
<td></td>
</tr>
<tr>
<td>ALN-AAT02 (DCR-A1AT)^7</td>
<td>Alpha-1 Liver Disease</td>
<td>Ex-U.S. option post-Phase 3</td>
<td></td>
</tr>
<tr>
<td>ALN-HBV02 (VIR-2218)^8</td>
<td>Hepatitis B Virus Infection</td>
<td>50-50 option post-Phase 2</td>
<td></td>
</tr>
<tr>
<td>ALN-AGT</td>
<td>Hypertension</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>ALN-HSD</td>
<td>NASH</td>
<td>50-50</td>
<td></td>
</tr>
</tbody>
</table>

^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, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; ^3 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; ^4 Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; ^5 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; ^6 Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; ^7 Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development; ^8 Vir is leading and funding development of ALN-HBV02

As of January 2021
High-Yield Productivity of Alnylam RNAi Therapeutics Platform
Comparison of Historical Industry Metrics to Alnylam Portfolio

Probability of Success (POS) by Phase Transition

1 Analysis as of December 2020; 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%); figures include ALNY-originated molecules now being developed by partners
3 Wong et al., Biostatistics (2019) 20, 2, pp. 273–286
Vutrisiran HELIOS·A Phase 3 Study
Randomized, Open-Label Study in Hereditary ATTR Amyloidosis Patients

N ~ 164
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

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

Positive topline results
Full data presentation and NDA filing expected early 2021
HELIOS-A Positive Topline Results
Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (N=164)

Positive results for all Month 9 primary and secondary efficacy endpoints, relative to APOLLO placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy Impairment (mNIS+7) Primary</td>
<td>3.54 x 10^{-12}</td>
</tr>
<tr>
<td>Quality of Life (Norfolk QoL-DN) Key Secondary</td>
<td>5.43 x 10^{-9}</td>
</tr>
<tr>
<td>Gait Speed (10-MWT) Secondary</td>
<td>3.10 x 10^{-5}</td>
</tr>
</tbody>
</table>

Evidence of reversal of disease manifestations
• Majority of patients showed improvement in neuropathy impairment and QOL, relative to baseline

Positive exploratory cardiac endpoint result
• Improvement in NT-proBNP biomarker, relative to placebo (p<0.0001*); additional cardiac data at Month 18 in Late 2021

Encouraging safety and tolerability profile
• No drug-related discontinuations or deaths; two SAEs deemed drug-related: dyslipidemia, urinary tract infection
• Treatment emergent AEs in ≥10% of vutrisiran patients all common in disease natural history and occurred at similar or lower rates than placebo comparator group
  − Include diarrhea, pain in extremity, fall and urinary tract infections
• Low incidence of injection site reactions (ISRs), all mild and transient
• No liver related safety concerns

* Nominal p-value
Opportunity for Biannual Vutrisiran Dosing Regimen
Plan to Further Strengthen Market Leadership

- Plan to generate TTR reduction and safety data in patients receiving 50mg q6M to support sNDA to add biannual dosing regimen aligned with FDA input
- Expect start of q6M dosing study in early 2021

**Phase 1 Study – Healthy Volunteers**

- Mean max TTR reduction of >80% after single dose of either 25mg or 50mg†

**Pharmacodynamic Modeling**

- After repeat dosing, ~90% peak TTR reduction predicted with both 25mg q3M and 50mg q6M vutrisiran regimens

---

† 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: XVIIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)
RNAi Therapeutics Opportunity for ATTR Amyloidosis
Potential for Broad Impact of TTR Silencing Across Disease Spectrum

1 Solomon S, et al. Circulation 2018
ATTR Amyloidosis Franchise Phase 3 Program
Randomized, Double-Blind, Placebo-Controlled Studies in ATTR Amyloidosis Patients with Cardiomyopathy

**APOLLO·B**

- **patisiran**
  - N ~ 300
  - hereditary & wild-type
  - 6-minute walk test
  - 12 months

  Enrollment completion expected **early 2021**
  Topline results expected **mid-2022**

**HELIOS·B**

- **vutrisiran**
  - N ~ 600
  - hereditary & wild-type
  - mortality & cardiovascular events
  - 30 months

  Enrollment ongoing
  Study includes planned interim analysis

Enrollment completion expected **early 2021**
Topline results expected **mid-2022**
Encouraging Evidence for RNAi Therapeutics in ATTR Cardiomyopathy\(^1\)

Results from Exploratory Endpoints in APOLLO\(^2\)O2 and Matched Control Case Series\(^3\)

- **55%** Relative reduction in NT-proBNP vs. placebo\(^2,\dagger\)
- **0.9mm** Mean reduction in LV wall thickness vs. placebo\(^2,\ddagger\)
- **-1.4%** Improvement in global longitudinal strain vs. placebo\(^2,\ddagger\)
- **0.35m/s** Improvement in 10-MWT vs. placebo\(^2,\dagger\)

---

\(^{1}\) Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of cardiac amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; \(^{2}\) Solomon S, et al. Circulation 2018; \(^{3}\) Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; \(^{4}\) 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; \(^{†}\) nominal p<0.01; \(^{‡}\) nominal p<0.05
RNAi Therapeutics Profile Supports Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Established safety profile
- Improved access

RARE
- ONPATTRO-PN
- GIVLAARI
- OXLUMO
- Vutrisiran-PN

SPECIALTY
- Flutisiran
- ALN-AAT02
- ALN-APP
- ALN-HTT
- ONPATTRO-CM
- Vutrisiran-CM
- Cerdelisiran

PREVALENT
- Leqvio® (inclisiran)
- ALN-HBV02 (VIR-2218)
- ALN-AGT
- ALN-HSD
- ALN-XDH
- ALN-KHK
RNAi Therapeutics to Reimagine Treatment of Hypertension
Opportunity for Tonic Blood Pressure Control

**Disease Overview**

<table>
<thead>
<tr>
<th>Primary Hypertension¹</th>
<th>Hypertension at high CV risk²</th>
</tr>
</thead>
<tbody>
<tr>
<td>~108 Million</td>
<td>~38 Million</td>
</tr>
<tr>
<td>in U.S.</td>
<td>in U.S.</td>
</tr>
</tbody>
</table>

>71% of patients have uncontrolled hypertension (>130/80 despite treatment)³

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

Together, contribute to substantial risk of CV morbidity and mortality

---


² Estimated from multiple sources and internal estimates: Dorans, JAhA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD

ALN-AGT Interim Phase 1 Results
Potent, Highly Durable Efficacy and Encouraging Safety

Encouraging safety and tolerability profile
- Most AEs mild or moderate in severity

Dose-Dependent AGT Lowering\(^1\)
>95% AGT Knockdown following Single Injection

Dose-Dependent Reductions in SBP and DBP\(^2\)
>15 mmHg Systolic BP Reduction at Week 8 following Single Injection

Initiate KARDIA-1 and -2 Phase 2 Studies in mid-2021

\(^1\) Data transfer date: 08 Dec 2020
\(^2\) Data access date: 19 Nov 2020; SBP: systolic blood pressure; DBP: diastolic blood pressure
Mayah
Living with PH1 (USA)

TRANSFORMATIONAL MEDICINES

ROBUST & HIGH-YIELD R&D PIPELINE

ORGANIC PRODUCT ENGINE
Over 25 Preclinical Programs in Four Tissues Feeding Sustainable Innovation

**Alnylam**
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- Many others

**Alnylam/Regeneron**
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5

**Alnylam/Regeneron**
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

**Alnylam/Regeneron**
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4

**Alnylam/Vir**
- ALN-COV
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

2-4 INDs per year from organic product engine (4+ planned by end’25)
Alnylam Platform Expands Opportunities for Novel RNAi Therapeutics

- **Human Genetics**
  - Biobank
  - REGENERON

- **New Tissues**
  - Target 1
  - Target 2
  - Linker

- **Bis-RNAi™**

- **Reversir™**

- **Novel Administration**
  - BBB penetration

- **Novel mAb Combos**

- **Target 1**
- **Target 2**
- **Linker**
Guidance, Goals & Financials
### Alnylam 2021 Goals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>onpattro</strong>&lt;sup&gt;®&lt;/sup&gt; (ATTR Amyloidosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Commercial Execution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete APOLO-B Phase 3 Enrollment</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**GIVLAARI®&lt;/span&gt; (givosiran) (Acute Hepatic Porphyria)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Commercial Execution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan Approval</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>**OXLUMO®&lt;/span&gt; (olumasiran) (Primary Hyperoxaluria Type 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Commercial Execution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil Approval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILLUMINATE-C Phase 3 Topline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### VUTRISIRAN (ATTR Amyloidosis)

<table>
<thead>
<tr>
<th>Event</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELOS-A Phase 3 Topline – 9 Month Endpoint</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>File NDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate q6M Dose Regimen Study</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>HELOS-A Phase 3 Topline – 18 Month Endpoint (incl. cardiac)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HELOS-B Phase 3 Enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### ALN-AGT (Uncontrolled Hypertension)

<table>
<thead>
<tr>
<th>Event</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate KARDIA-1 and -2 Phase 2 Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ADDITIONAL CLINICAL PROGRAMS

Continue to advance early/mid-stage pipeline; File 2-4 new INDs; Present clinical data

### PARTNERED PROGRAMS

#### Leqvio® (inclisiran) (Hypercholesterolemia)

FVA Approval (guidance pending)

Support, as Needed, Novartis on Global Commercial Execution

Support, as Needed, Novartis on ORION-4 CVOT Phase 3 Enrollment

#### FITUSIRAN (Hemophilia)

Support, as Needed, Sanofi on ATLAS Phase 3 Studies

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4.
Transition to Self-Sustainable Financial Profile
Alnylam Entering Period of Projected Growth on Path to Profitability

Strong 2020 YE balance sheet of $1.9B*  
• $2B strategic partnership with Blackstone anchors path toward self-sustainable financial profile without need for future equity financing

Focused on key levers  
• Topline growth  
• Disciplined investment

2019 was peak non-GAAP operating loss year

* Including cash, cash equivalents, marketable securities; Preliminary selected 2020 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 FY2019 in Feb. 2021
## 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>$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 as of 12/31/2019</td>
</tr>
</tbody>
</table>

Guidance and cash expectations as of November 5, 2020

1 GM as % of Product Sales for Q3 2020 is 78.0%, 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.

Building a Top-Five Biotech
Potential for Significant Transformation of Alnylam over Next 5 Years

### 2020
- Rare Diseases
- Initial Indications
- 4 STArs
- ~20 Markets
- ~1K Employees
- CMOs

### 2025
- Rare & Prevalent Diseases
- Multiple Indications
- 4+ STArs
- Global
- ~2.5K Employees
- Norton + CMOs

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.
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED