Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including expectations regarding our aspiration to become a leading biotech company and the planned achievement of our “Alnylam P²x25” strategy, our ability to attain financial self-sustainability, the drivers of our future growth potential, including the potential of our TTR franchise, our continued confidence in the design and ongoing execution of the APOLLO-B Phase 3 study and the evidence for investigational RNAi therapeutics in ATTR cardiomyopathy, the potential opportunity for RNAi therapeutics in prevalent diseases, and the potential of our engine for sustainable innovation including the potential for improved product profiles to emerge from our IKARIA and GEMINI platforms, as well as the achievement of additional pipeline and regulatory milestones. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on our ability to attract and retain talent and to successfully execute on our “Alnylam P²x25” strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including vutrisiran and patisiran; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for OXLUMO, ONPATTRO (and potentially vutrisiran, if approved) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Annual Report on Form 10-K filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
Alnylam Poised to Become a Top-Tier Biotech

**Leader in RNAi Therapeutics**
- Pioneered new class of innovative medicines
- 4 medicines approved in < 3 years
- Robust clinical pipeline across rare and prevalent diseases
- Global footprint with strong commercial capabilities
- Leading IP estate with fundamental, delivery, and product-specific patent protection
- Strong balance sheet, on path toward financial self-sustainability

**Highly differentiated with proven track record and derisked platform**
- Modular and reproducible approach to drug development
- Historic probability of clinical success multiples higher than industry standards
- Organic product engine capable of sustaining innovation for future growth
- Track record of setting and exceeding 5-year goals
Notable Accomplishments in 2021

- Combined net product revenues of $662 million (83% growth YoY)
- Completed enrollment in two key Phase 3 studies in ATTR amyloidosis with CM
- Advanced multiple investigational products for prevalent diseases (zilebesiran, ALN-HBV02, ALN-HSD)
- Expanding commercial presence into >30 countries
- 2 NDA/sNDA submissions (vutrisiran, lumasiran)
- Maintaining strong financial position:
  - $2.4 billion in cash at year-end 2021
  - $120M+ YoY improvement in non-GAAP operating loss
- Launched new 5-year strategy
- 2 CTA filings (ALN-APP, ALN-XDH)
Continuing Strong Global Commercial Execution
Combined Net Product Revenues ($662M) at Upper End of Guidance Range, with 83% YoY Growth

**Onpattro (patisiran)**
- Combined Net Product Revenues: $475M
- 2021 Revenues: $138.6M
- Q1 2021: 52.5M
- Q2 2021: 61.4M
- Q3 2021: 69.1M
- Q4 2021: 78.5M
- ROW: 102.0M
- U.S.: 49.5M

**Givlaari (givosiran)**
- Combined Net Product Revenues: $128M
- 2021 Revenues: $40.7M
- Q1 2021: 24.7M
- Q2 2021: 30.6M
- Q3 2021: 31.8M
- Q4 2021: 10.4M
- ROW: 24.7M
- U.S.: 6.9M

**Oxlumo (lumasiran)**
- Combined Net Product Revenues: $60M
- 2021 Revenues: $19.2M
- Q1 2021: 9.1M
- Q2 2021: 9.8M
- Q3 2021: 9.7M
- Q4 2021: 5.7M
- ROW: 9.1M
- U.S.: 7.7M

- >2,050 patients as of December 31, 2021
- >350 patients as of December 31, 2021
- >140 patients as of December 31, 2021

- 2021 Revenues: $475M
- 2021 Revenues: $128M
- 2021 Revenues: $60M
Alnylam Clinical Development Pipeline

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

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

### EARLY/MID-STAGE (IND/CTA Filed-Phase 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Disease Area</th>
<th>Status</th>
<th>Royalties</th>
<th>Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leqvio® (inclisiran)</td>
<td>Hypercholesterolemia</td>
<td>Global</td>
<td>Milestones &amp; up to 20% Royalties</td>
<td></td>
</tr>
<tr>
<td>Leqvio® (inclisiran)</td>
<td>Hypercholesterolemia</td>
<td>Global</td>
<td>Milestones &amp; up to 20% Royalties</td>
<td></td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>hATTR Amyloidosis with PN</td>
<td>Global</td>
<td></td>
<td></td>
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<tr>
<td>Patisiran</td>
<td>ATTR Amyloidosis with CM</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>ATTR Amyloidosis with CM</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vutrisiran**</td>
<td>Stargardt Disease</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutisiran*</td>
<td>Hemophilia</td>
<td>Global</td>
<td>15-30% Royalties</td>
<td></td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Severe PH1</td>
<td>Global</td>
<td></td>
<td></td>
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<tr>
<td>Lumasiran</td>
<td>Recurrent Renal Stones</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cemdisiran (+/- Pozelimab)*</td>
<td>Complement-Mediated Diseases</td>
<td>Global</td>
<td>50-50; Milestone/Royalty</td>
<td></td>
</tr>
<tr>
<td>Belcesiran*</td>
<td>Alpha-1 Liver Disease</td>
<td>Ex-U.S. option post-Phase 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALN-HBV02 (VIR-2218)**</td>
<td>Hepatitis B Virus Infection</td>
<td>50-50 option post-Phase 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilebesiran (ALN-AGT)*</td>
<td>Hypertension</td>
<td>Global</td>
<td></td>
<td></td>
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<tr>
<td>ALN-HSD*</td>
<td>NASH</td>
<td>Global</td>
<td>50-50</td>
<td></td>
</tr>
<tr>
<td>ALN-APP*</td>
<td>Alzheimer’s Disease; Cerebral Amyloid Angiopathy</td>
<td>Global</td>
<td>50-50</td>
<td></td>
</tr>
</tbody>
</table>

### LATE STAGE (Phase 2-Phase 3)

- **Global**
- **Milestones & up to 20% Royalties**
- **50-50 option post-Phase 2**
- **Global**
- **15-30% Royalties**

### REGISTRATION/COMMERCIAL (OCE/Phase 4/ISIS/registries)

- **Global**
- **Milestones & up to 20% Royalties**
- **50-50; Milestone/Royalty**
- **Global**
- **15-30% Royalties**

### COMMERCIAL RIGHTS

- **Global**
- **Milestones & up to 20% Royalties**
- **50-50; Milestone/Royalty**
- **Global**
- **15-30% Royalties**

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., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; 4. Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; 5. Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; 6. 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; 7. Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; 8. Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 9. 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; 10. Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; 11. Combispan and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; 12. Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; 13. Vutrisiran* and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; 14. Vutrisiran* and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; 15. As of April 2022
High-Yield Productivity of Alnylam RNAi Therapeutics Platform
Comparison of Historical Industry Metrics to Alnylam Portfolio

Analysis as of November 2021; Past rates of Alnylam and industry respectively may not be predictive of the future

Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners

Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Probability of Success (POS) by Phase Transition

1. Page 7 of the document.
2. Analysis as of November 2021; Past rates of Alnylam and industry respectively may not be predictive of the future.
3. Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners.
# 2022 Expected to Deliver Multiple Catalysts with Value-Creation Potential

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full 18-Month HELIOS-A Phase 3 Results with Vutrisiran</td>
<td>January 21, 2022</td>
</tr>
<tr>
<td>Cemdisiran Phase 2 Data in IgA Nephropathy</td>
<td>Early 2022</td>
</tr>
<tr>
<td>Potential FDA Approval of Vutrisiran</td>
<td>Mid-2022 (PDUFA date July 14, 2022)</td>
</tr>
<tr>
<td>APOLLO-B Phase 3 Results with Patisiran</td>
<td>Mid-2022</td>
</tr>
<tr>
<td>ALN-HSD Phase 1 Part B Topline Results in NASH Patients</td>
<td>Mid-2022</td>
</tr>
<tr>
<td>Vutrisiran Biannual Dose Regimen Data</td>
<td>Late 2022</td>
</tr>
<tr>
<td>ALN-APP Phase 1 Topline Results</td>
<td>Late 2022</td>
</tr>
<tr>
<td>KARDIA-1 Phase 2 Topline Results with Zilebesiran</td>
<td>Late 2022</td>
</tr>
<tr>
<td>ALN-XDH Phase 1 Topline Results</td>
<td>Late 2022</td>
</tr>
</tbody>
</table>

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4
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
Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation

Andreas (Sweden)
Diagnosed with hATTR amyloidosis
ATTR Amyloidosis
Rare, Progressively Debilitating, and Fatal Disease

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

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Hereditary ATTR (hATTR) Amyloidosis

~50,000 patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000 patients worldwide

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Alnylam TTR 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

Intended to be illustrative and not intended to represent specific estimates of patient numbers
HELIOS-A 9-Month Results
Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (N=164)

Both secondary endpoints met
• Improvement demonstrated in quality of life and 10-meter walk test

Positive exploratory cardiac endpoint result
• Improvement in NT-proBNP biomarker in cardiac subpopulation, relative to placebo (p=0.0016)

Encouraging safety and tolerability profile
• No drug-related discontinuations or deaths; two SAEs deemed drug-related: dyslipidemia, urinary tract infection
  – Include diarrhea, pain in extremity, fall and urinary tract infections
  – Low incidence of injection site reactions (ISRs), all mild and transient
  – No safety signals regarding liver function tests, hematology or renal function related to vutrisiran

Adams et al., AAN, April 2021 as to primary endpoint and safety/tolerability at Month 9; additional data presented by Alnylam in conference call held April 19, 2021

APOLLO refers to the randomized, placebo-controlled Phase 3 study of ONPATTRO (patisiran) in hATTR patients with polyneuropathy (Adams et al, NEJM, 2018). HELIOS-A compares vutrisiran treated hATTR patients with polyneuropathy to the prespecified external placebo group from APOLLO
**HELIOS-A 18-Month Results**

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

- **Placebo (APOLLO):**
  - Baseline: 14.76 (2.0) n=67
  - Month 9: -2.24 (1.43) n=114
  - Month 18: -0.46 (1.60) n=112

- **Vutrisiran:**
  - Baseline: 28.09 (2.28) n=51
  - Month 9: -10.0 (2.7) n=112
  - Month 18: -1.2 (1.8) n=111

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

- **Placebo (APOLLO):**
  - Baseline: 12.9 (2.2) n=65
  - Month 9: -3.3 (1.7) n=114
  - Month 18: -1.2 (1.8) n=111

**Vutrisiran:**
  - Baseline: 19.8 (2.6) n=48
  - Month 9: -3.3 (1.7) n=114
  - Month 18: -1.2 (1.8) n=111

**Safety profile observed with 18 months of treatment consistent with profile at 9 months**

- No drug-related discontinuations or deaths
- Two SAEs deemed drug-related: dyslipidemia, urinary tract infection
- Treatment emergent adverse events occurring in ≥10% of patients receiving vutrisiran included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness

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a mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint.

b At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in external placebo group.

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Adams, et al. SFNP 2022
Exploratory Imaging Parameters

Potential Evidence of Reduction in Amyloid Burden

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

Vutrisiran

Placebo (APOLLO)

Mean LV Wall Thickness (cm)\(^a\)

\(\text{p}=0.5228\)

n=51

n=105

Cardiac Output (L/min)\(^a\)

\(\text{p}=1.144 \times 10^{-5}\)

n=49

n=105

Global Longitudinal Strain (%)\(^a\)

\(\text{p}=0.3182\)

n=48

n=107

LV End-Diastolic Volume (mL)\(^a\)

\(\text{p}=4.021 \times 10^{-4}\)

n=50

n=105

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

\(\text{Tc Normalized LV Total Uptake (n=47)\(^b\)}\)

\(\text{Tc Heart-to-Contralateral Lung ratio (n=48)\(^b\)}\)

\(\text{Improved}\(^c\)\)

\(\text{Not Improved}\(^d\)\)

\(\text{Improved}\(^c\)\)

\(\text{Not Improved}\(^d\)\)

Change from Baseline in Tc Perugini Grade (n=57)\(^b\)

\(\text{Improved}\)

\(\text{Stable}\)

\(\text{Worsened}\)

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

q6M Regimen in Development to Strengthen Leadership Prospects for Future

- Plan to generate TTR reduction and safety data in patients receiving 50mg q6M to support potential sNDA to add biannual dosing regimen aligned with FDA input
- q6M dosing study initiated 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

† Taube 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)
TTR Franchise Phase 3 Program
Randomized, Double-Blind, Placebo-Controlled Studies in ATTR Amyloidosis Patients with Cardiomyopathy

APOLLO.B

**patisiran**

N = 360
hereditary & wild-type
6-minute walk test
12 months

Enrollment complete
Topline results expected **mid-2022**

HELIOS.B

**vutrisiran**

N = 655
hereditary & wild-type
mortality & cardiovascular events
30 months

Enrollment complete
Topline results on 30-month endpoint expected **early 2024**
Study includes optional interim analysis
# Reasons for Confidence in Design and Ongoing Execution of APOLLO-B

Potential to Demonstrate Favorable Impact of Patisiran vs Placebo at 12 Months, as Measured by 6MWT

<table>
<thead>
<tr>
<th>Rigorous Diagnostic Criteria for ATTR with CM</th>
<th>Expertise in Study Design and Execution</th>
<th>Broad Patient Population Enrolled</th>
<th>Unique and Promising MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Positive biopsy or technetium (Tc) scintigraphy with Perugini Grade 2 or 3 uptake</td>
<td>• Positive results in hATTR with PN (APOLLO and HELIOS-A), including on 10-meter walk test</td>
<td>• Target of ~20% hereditary / ~80% wild-type patients</td>
<td>• Excludes patients who anticipate starting tafamidis w/in 12 months</td>
</tr>
<tr>
<td>• Exclusion of AL amyloidosis and other causes of CM</td>
<td>• Conservatively powered; 1:1 randomization, overenrolled with 360 patients</td>
<td>• NYHA Class I, II, and III (clinical evidence of heart failure required)</td>
<td>• APOLO exploratory and post-hoc analyses indicate favorable effects on echo, NT-proBNP, and hospitalization / survival</td>
</tr>
<tr>
<td>• Intraventricular septal wall thickness ≥ 12mm at baseline echo</td>
<td>• Rigorous approach to implementation, training, and oversight of 6MWT</td>
<td>• NT-proBNP &gt;300 ng/L and &lt;8500 ng/L²</td>
<td>• Published post-marketing case series of patisiran with evidence of reduced Tc uptake and increase in 6MWD in hATTR-CM</td>
</tr>
<tr>
<td></td>
<td>• Limited number of baseline 6MWTs per patient to minimize potential training effect of repeat testing</td>
<td>• Up to 30% of patients on tafamidis at entry; all with disease progression on tafamidis</td>
<td>• HELIOS-A exploratory cardiac data, including improvement in Tc scan, show potential evidence for reduced cardiac amyloid burden</td>
</tr>
</tbody>
</table>

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1 Excludes other forms of cardiomyopathy (including hypertensive cardiomyopathy), marked hypertension, and other conditions that impact walking ability; ² Screening NT-proBNP >300 ng/L and <8500 ng/L; ³ Patients with permanent or persistent atrial fibrillation, screening NT-proBNP >600 ng/L and <8500 ng/L; ⁴ Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublised DOI:10.1016/j.jcmg.2020.07.043; ⁵ Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of ATTR amyloidosis with CM. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population.

---

Built on promising MOA of patisiran which has shown consistent exploratory, post hoc and real-world data suggesting benefit in hATTR amyloidosis patients with evidence of cardiac involvement.
Evidence for Investigational RNAi Therapeutics in ATTR Cardiomyopathy

Exploratory & Post-hoc Data from APOLLO

• **55%** Relative reduction in NT-proBNP vs. placebo\(^2\)\(^1\)
• **0.9mm** Mean reduction in LV wall thickness vs. placebo\(^2\)\(^1\)
• **-1.4%** Improvement in global longitudinal strain vs. placebo\(^2\)\(^1\)
• **0.35m/s** Improvement in 10-MWT vs. placebo\(^2\)\(^1\)

Cardiac Safety Data in Entire APOLLO Study Population:

<table>
<thead>
<tr>
<th></th>
<th>Placebo(^6) (n=77)</th>
<th>Patisiran(^5) (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>

\(^1\) 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 treating CM 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; \(^5\) For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; **nominal p<0.01**; \(^6\) Anderson-Gill hazard ratio (HR) 0.49 [0.34, 0.69]; **nominal p<0.01**; \(^7\) nominal p<0.05

 Investigator-Sponsored Study from National Amyloidosis Centre, UK

**Patient with hATTR and CM, receiving patisiran and diflunisal**

*Example Tc-DPD Bone Scintigraphy & Image Analysis conducted as part of study, in this patient showing "unequivocal reduction in cardiac and soft tissue uptake"*\(^3\)

Baseline

12 Months\(^3\)

**Composite Rate of All-Cause Hospitalization and Mortality**

<table>
<thead>
<tr>
<th>Time on Study (Months)</th>
<th>Mean Cumulative Function</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>8</td>
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</tr>
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\(^1\) 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 treating CM 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; \(^5\) For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.49 [0.34, 0.69]; **nominal p<0.01**; \(^6\) nominal p<0.05
Stargardt Disease
Promising New Opportunity for Vutrisiran

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

High unmet medical need with no approved treatments

Therapeutic Hypothesis

Silence production of TTR in liver

Reduce circulating TTR / RBP4 / Vitamin A Complex

Reduce build-up of toxic metabolites in retina

Halt Progression of vision loss

Incidence of 1 in 8,000-10,000

* >95% of TTR in circulation produced in liver
Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation
RNAi Therapeutics Profile Supports Potential Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Safety profile evaluated in clinical trials
- Improved access

1 ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; 2 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; 3 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; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; 4 Leqvio is approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia.
Capabilities Support Potential Expansion to Prevalent Diseases

Sophisticated, Scalable, and Global Medical and Commercial Organizations

**Scalable Capabilities**

**Patient Support:** Experienced patient support teams have enabled >90% adherence in the U.S.

**Customer Engagement:** High-science customer-facing field teams with strong leadership

**Access:** World renowned partnerships with key payers, with VBAs covering >95% of eligible lives in the U.S.

**Diagnosis:** Support for independent diagnostic programs

**Global Footprint:** 23 Direct and 24 distributor markets (and growing) with 50% revenues generated ex-U.S.

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1 ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; 2 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; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; 4 Leqvio is approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia.
Reimagining Treatment of Prevalent Diseases
Highly Differentiated, Infrequently Administered Therapies Against Validated Targets

Hypercholesterolemia*
- Biannually dosed lipid lowering therapy with effective and sustained LDL-C reduction of up to 52%
- Potential to reduce ASCVD risks through lowering of LDL-C at population level

Zilebesiran

Hypertension
- Targets AGT with potential to achieve tonic blood pressure control and improve medication adherence
- Demonstrated >20 mmHg BP reduction in Phase 1, with opportunity to impact CV outcomes at population level

ALN-HBV02 (VIR-2218)

Chronic Hepatitis B Virus (HBV) Infection
- Targets conserved region in X gene, with multi-log reductions in HBsAg levels in Phase 1/2 studies
- Opportunity to be foundational therapy with potential to achieve functional cure

Lumasiran

Recurrent Kidney Stone Disease
- Targets GO1 to lower production of calcium oxalate crystals, source of most kidney stones in adults
- Reductions in kidney stone event rate and nephrocalcinosis in PH1 observed in Phase 3 program

ALN-HSD

Nonalcoholic Steatohepatitis (NASH)
- LOF mutations in HSD17B13 associated with reduced risk of liver injury among NAFLD patients
- Potential to reduce cirrhosis and end-stage liver disease

Gout
- XDH is genetically and clinically validated target for urate lowering
- Potential for more consistent disease management leading to fewer gout flares and less joint damage

Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; Vir is leading and funding development of ALN-HBV02; With the exception of Leqvio® (inclisiran), these are investigational agents and have not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding their safety or effectiveness. * Leqvio® is approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia.
RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure (BP) Control

**Disease Overview**

<table>
<thead>
<tr>
<th>Primary Hypertension&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Hypertension at high CV risk&lt;sup&gt;2&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>~108 Million in U.S.</td>
<td>~38 Million in U.S.</td>
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</tbody>
</table>

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

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

Together, contribute to substantial risk of CV morbidity and mortality

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

Zilebesiran (ALN-AGT) Interim Phase 1 Results
Results for Investigational Therapy Presented at AHA Scientific Sessions

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

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

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

Sustained Reductions in SBP and DBP
Mean 24h blood pressure reduction of >20 mm Hg at Month 6 after a single dose of 800 mg

KARDIA-1 Phase 2 Study initiated **June 2021**
KARDIA-2 Phase 2 Study initiated **November 2021**
Early Evidence of Tonic BP Control Over 24 Hours with Zilebesiran

**Zilebesiran: 24-Hour SBP at Week 6**

![Graph showing 24-hour SBP for Zilebesiran at Week 6](image)

**Losartan: 24-Hour SBP at Week 4a**

![Graph showing 24-hour SBP for Losartan at Week 4](image)

*Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206*

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure
HBV: Global Health Problem Impacting Developed and Developing Countries

Ongoing VIR-2218 Phase 2 Study Evaluating Impact of Concomitant PEG-IFNα in Chronic HBV

VIR-2218 alone or in combination with PEG-IFNα has been generally well tolerated

All VIR-2218 plus PEG-IFNα regimens were associated with clinically meaningful HBsAg reductions (> 2 log10IU/mL on average) by Week 24

Three participants receiving VIR-2218 and PEG-IFNα achieved HBsAg loss by Week 24; 2 of 3 achieved anti-HBs seroconversion

Significant Proportion Achieve HBsAg <10 IU/mL, Including <LOQ

VIR-2218 only
VIR-2218 lead-in
PEG-IFNα (12 wk)
VIR-2218
PEG-IFNα (24 wk)
VIR-2218
PEG-IFNα (648 wk)

Yuen et al., AASLD, November 2021
Multiple Drivers of Future Growth

- TTR Franchise Leadership
- Expansion into Prevalent Diseases
- Engine for Sustainable Innovation
Sources of Sustainable Innovation

Platform Innovation

- Two-decade track record of industry leadership in RNAi
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts
- IKARIA™ enables robust target knockdown with annual dosing potential
- Novel conjugates with variety of ligands for delivery beyond liver

Extrahepatic Delivery

- Potential for delivery to range of organs
- C16 conjugate provides robust CNS knockdown with wide biodistribution and long duration of action
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Human Genetics

- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets (e.g., HSD17B13, Gene X, and more)
Potential to Potently, Durably, Safely and Conveniently Suppress Two Targets

**GEMINI**

**Platform**
- Goal of silencing two gene transcripts using single chemical entity
- Ensures uptake of both siRNAs in same cell
- Potentially simplified development path vs. two entities or combination
- Potential to address polygenic diseases (e.g., cardiometabolic, CNS)

**GEMINI-CVR Program: Reimagining Treatment of CV Disease**
- siRNA 1 targets ANGPTL3 (genetically validated to reduce atherogenic lipids); siRNA 2 targets angiotensinogen (pharmacologically validated to reduce blood pressure)
- Targets support potential to prevent major adverse cardiac outcomes in high-risk individuals
- Biannual or annual subQ injection in office or pharmacy administration
- Targets ≥40% reductions in LDL-C and triglycerides, >10 mmHg reduction in systolic blood pressure and safety profile appropriate for broad use
- Development candidate targeted for 2023
ALN-APP: First Investigational RNAi Therapeutic for CNS

New Potential Approach in Alzheimer’s Disease and Cerebral Amyloid Angiopathy

Proprietary C16 conjugate for delivery to CNS
- IT administration, anticipating infrequent dosing (Q3-6M or less)

**APP is a genetically validated target for two CNS diseases**
- Mutations and duplications in *APP* gene cause Alzheimer’s disease (AD), cerebral amyloid angiopathy (CAA), or both
- Mutations that reduce production of APP cleavage products are protective against AD
- AD (most common cause of dementia) and CAA (second most common cause of intracerebral hemorrhage) represent large populations with high unmet need

Upstream of current approaches: First to target *APP* mRNA
- Expected to comprehensively lower all APP cleavage products, including Aβ, both intra- and extracellularly

CTA filed in late 2021
- Phase 1 initiated in early-onset AD patients in early 2022 with initial human data expected at or around year-end 2022

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**Potential “Firsts” with ALN-APP**
- First siRNA to be delivered to CNS
- First C16 conjugate for CNS delivery
- First development program directly targeting *APP* mRNA
- First CNS collaboration program with Regeneron
Delivering Sustainable Innovation with RNAi Therapeutics

Development Candidate → Phase 1 → Phase 2 → Phase 3 → Global Regulatory Submissions (e.g., NDA, MAA)

- UK Biobank
- Our Future Health
- Literature
- Collaborations (e.g., REGN)
- New Tissues

TRANSFORMATIVE MEDICINES
<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Goal 1</th>
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<tr>
<td>PATISIRAN</td>
<td>hATTR/ATTR Amyloidosis</td>
<td>APOLLO-B Phase 3 Topline Results</td>
<td>File sNDA for ATTR-CM</td>
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<td>VUTRISIRAN*</td>
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<td>CEMDISIRAN* (+/- POZELIMAB)</td>
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<td>ZILEBESIRAN*</td>
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<td>KARDIA-1 Phase 2 Topline Results</td>
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* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4
Nurturing a Culture to Ensure Future Success

- Commitment to People
- Scientific Innovation
- Diversity, Equity, & Inclusion
- Social Responsibility
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED