Topline Results from APOLLO-B Phase 3 Study of Patisiran

August 3, 2022

Alnylam®@20

Agenda

Welcome

- Christine Lindenboom
  Senior Vice President, Investor Relations & Corporate Communications

Introduction

- Yvonne Greenstreet, MBChB, MBA
  Chief Executive Officer

ATTR Amyloidosis Overview

- Akshay Vaishnaw, M.D., Ph.D.
  President

APOLLO-B Phase 3 Topline Results

- Pushkal Garg, M.D.
  Chief Medical Officer

Commercialization Strategy

- Tolga Tanguler
  Chief Commercial Officer

Q&A Session

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 but not limited to expectations regarding the potential of our TTR franchise to expand value to patients globally, the safety and efficacy of patisiran for the treatment of ATTR amyloidosis with cardiomyopathy, the expected timing of the presentation of full data from the APOLLO-B study, the filing of an sNDA for patisiran in the U.S. and the potential commercial launch of patisiran, if approved, the evaluation of vutrisiran in the HELIOS-B Phase 3 study for the treatment of patients with ATTR amyloidosis with cardiomyopathy and the expected timing for topline data from that study, the potential market opportunity for patisiran if approved by regulatory authorities to treat ATTR amyloidosis with cardiomyopathy and the broader potential commercial opportunity for investigational RNAi therapeutics in ATTR amyloidosis, our aspiration to become a leading biotech company and the planned achievement of our "*Alnylam P^{5}x25*" strategy, and clinical development milestones in 2022 with value-creation potential. 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 P^{5}x25*" strategy; our ability to discover and develop novel drug candidates and delivery approaches, 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 patisiran and 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 ONPATTRO, AMVUTTRA, and OXLUMO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Yvonne Greenstreet, MBChB, MBA

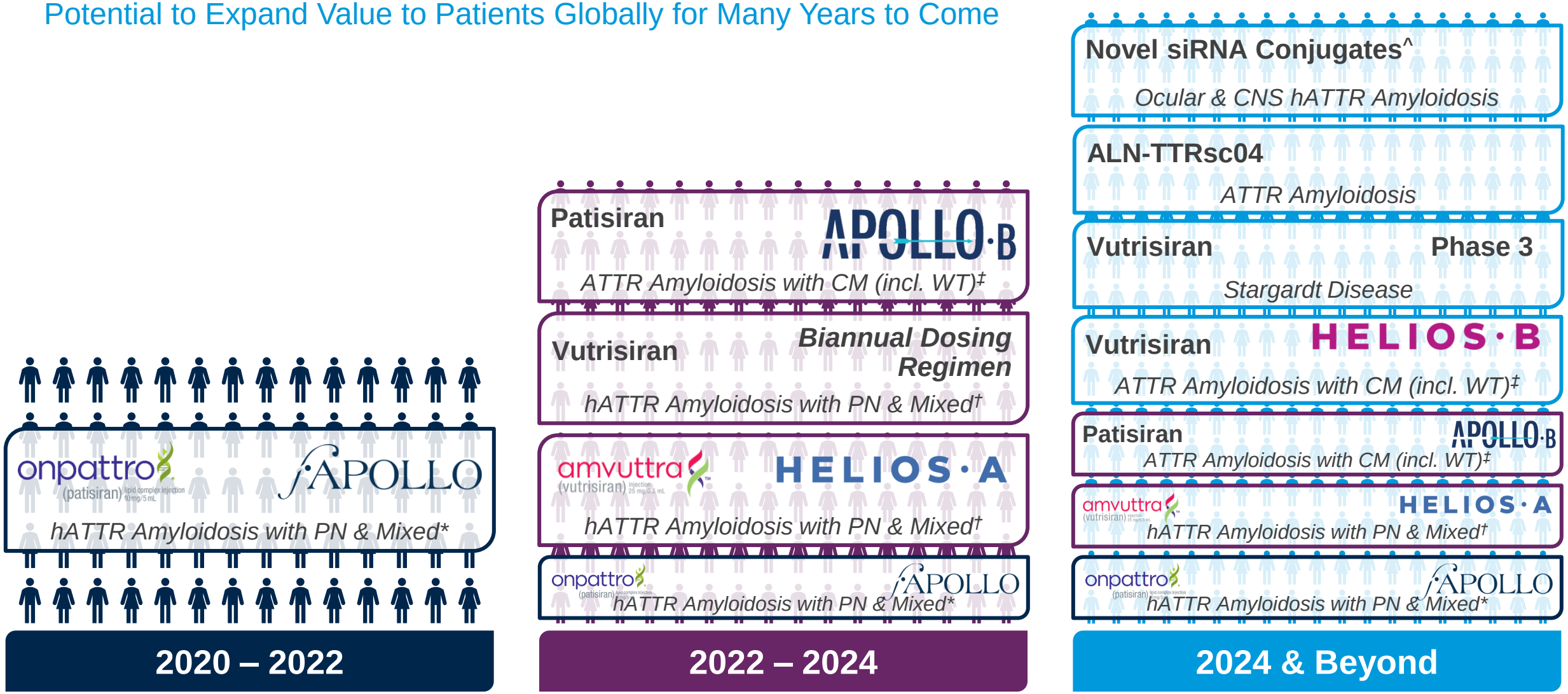
Introduction

APOLLO-B

POSITIVE TOPLINE RESULTS

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; ‡ Patisiran and vutrisiran have 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

† AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults; ^ 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

Akshay Vaishnaw, M.D., Ph.D
President

ATTR Amyloidosis Overview

Catalania (Spain)
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[1]

Hereditary ATTR (hATTR) Amyloidosis

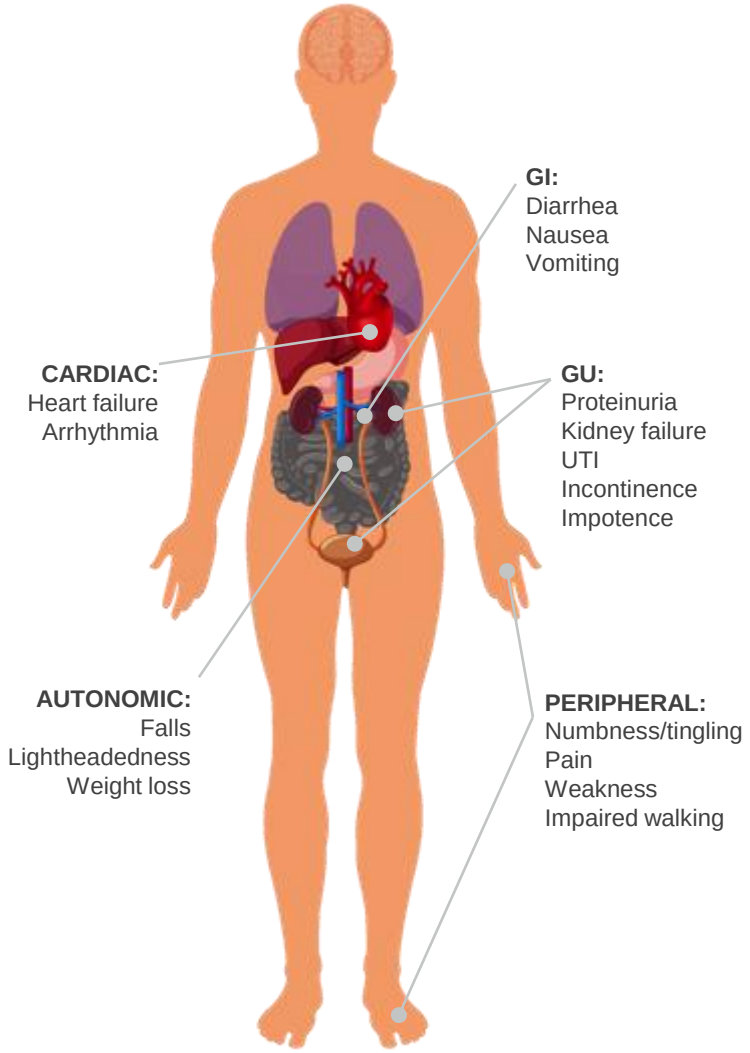
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide

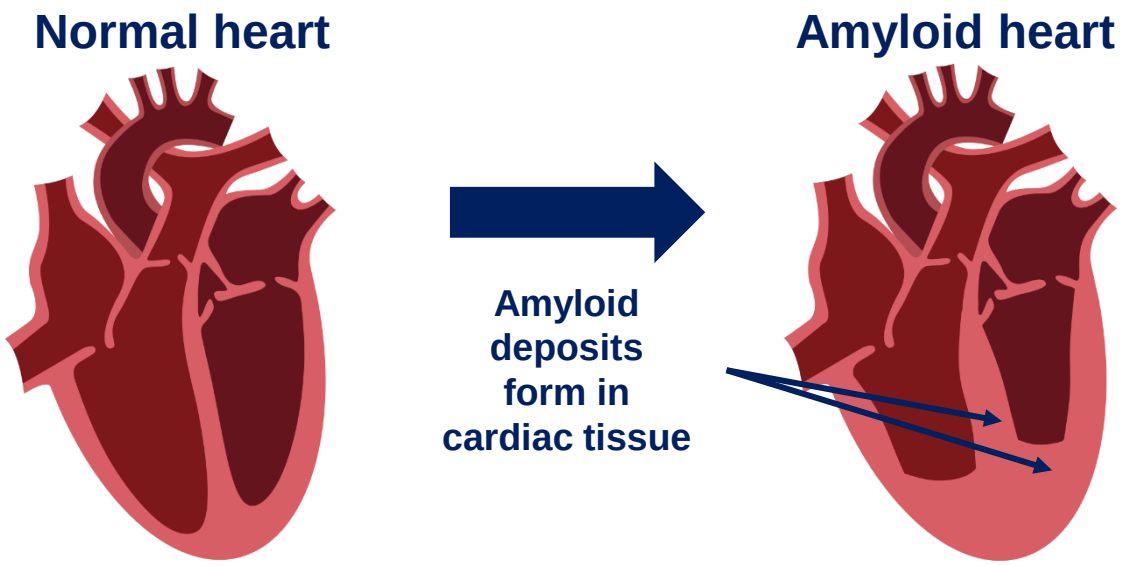


[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy)

Cardiac Manifestations of ATTR Amyloidosis

Amyloid Deposits Accumulating in Heart Can Lead to Substantial Disease Burden



Pathophysiology of disease[1–3]

- Enlarged cardiac walls
- Reduced cavity volumes
- Reduced myocardial elasticity
- Impaired diastolic function
- Impaired systolic function
- Conduction disorders
- Increased NT-proBNP

Patients' experience[1–3]

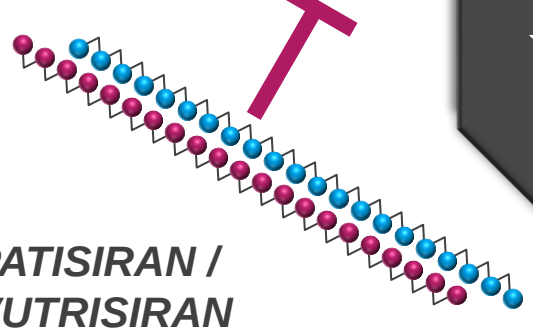
- Progressive heart failure, with poor exercise tolerance and impaired quality of life
- Cardiac arrhythmias
- Cardiomyopathy – a common cause of death

HF, heart failure; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide

1. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 2. Dungu et al. *Heart* 2012;98:1546–54; 3. Castano et al. *Heart Fail Rev* 2015;20:163–78

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease



PATISIRAN / VUTRISIRAN

siRNA sequences selected to silence both variant and wild-type TTR

Production of variant and wild-type TTR in liver*

Reduce
circulating TTR

Prevent or clear
tissue amyloid deposits

Halt or improve
progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Pushkal Garg, M.D.
Chief Medical Officer

APOLLO-B Phase 3 Topline Results

Patisiran APOLLO-B Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N = 360
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - With or without background TTR stabilizer
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Secondary Endpoints

- Cardiomyopathy symptoms and health status (KCCQ)
- Death and hospitalization outcomes*

Selected Exploratory Endpoints

- Cardiac biomarkers

Open-Label Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Positive topline results reported August 2022

Full results to be presented at ISA, September 2022

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

* Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population

APOLLO-B Phase 3 Study – Topline Results

Primary and Secondary Endpoints

Endpoint	p-value
Primary Endpoint	
• 6-minute walk test (6-MWT) (change from baseline at 12 months)	0.0162
Secondary Endpoints	
• Kansas City Cardiomyopathy Questionnaire (KCCQ) (change from baseline at 12 months)	0.0397
• Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT	0.0574
• Composite all-cause mortality and frequency of all-cause hospitalizations and urgent heart failure visits in patients not on tafamidis at baseline	0.9888 (nominal)
• Composite all-cause mortality and frequency of all-cause hospitalizations and urgent heart failure visits in the overall population	0.5609 (nominal)

APOLLO-B Phase 3 Study – Topline Results

Safety Data During 12-Month Double-Blind Period

Safety	Patisiran	Placebo
Adverse Events	165 (91.2%)	168 (94.4%)
Serious Adverse Events	61 (33.7%)	63 (35.4%)
AEs in ≥5% of patisiran patients, seen ≥3% more frequently in patisiran compared with placebo: • Infusion related reactions • Arthralgia • Muscle spasms	 22 (12.2%) 14 (7.7%) 12 (6.6%)	 16 (9.0%) 8 (4.5%) 4 (2.2%)
Deaths (safety analysis)*	5 (2.8%)	8 (4.5%)
Deaths (all-cause mortality efficacy analysis)†	4 (2.2%)	10 (5.6%)

* Safety analysis of deaths include deaths that occurred during the 12-month double blind portion of the study

† Efficacy analysis of deaths presented in accordance with pre-defined statistical analysis plan, which excluded death due to COVID-19, and treated cardiac transplant as death

Next Steps

APOLLO-B Full Results

ISA 2022

Sept 8, 2022
Heidelberg, Germany

Regulatory Submissions – Late 2022 and Beyond

Commercialization – 2023 and Beyond*

HELIOS-B

Vutrisiran HELIOS-B Phase 3 Topline Results – Expected Early 2024

*Assuming regulatory approval(s)

Tolga Tanguler

Chief Commercial Officer

Commercialization Strategy

ATTR Amyloidosis with Cardiomyopathy Remains Significant and Growing Commercial Opportunity

Patisiran Has Potential to be First RNAi Therapeutic to Treat This Progressing and Fatal Disease*

ATTR AMYLOIDOSIS WITH CM LARGE UNMET MEDICAL NEED

GROWING DIAGNOSED & TREATED POPULATION

PATISIRAN POTENTIAL*

>250K Patients Globally Suffer from ATTR Amyloidosis with CM

- Serious disease primarily affecting heart structure and function, patient functional capacity, and quality of life
- Often underdiagnosed, leading to hospitalization and death

Diagnosis & Treatment Rates Rapidly Increasing

- Non-invasive diagnosis options becoming more widely available
- U.S. diagnosis and treatment rates increased significantly in past 5 years
- Large portion remain undiagnosed and untreated

Patients Need More Options

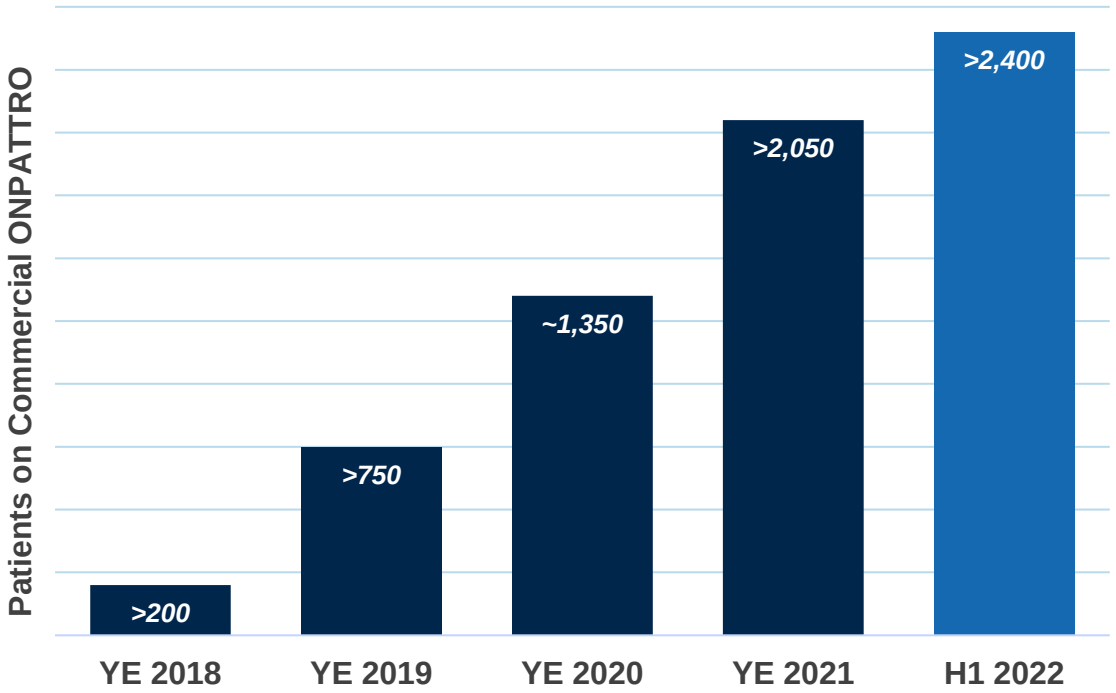
- Patients may experience inadequate treatment response with currently available treatment options
- Patisiran has potential to be first RNAi therapeutic option, targeting disease upstream
- Well-established efficacy and safety profile in hATTR amyloidosis with PN

* Assuming regulatory approval(s)

Well Positioned to Serve Growing Patient Needs

Key Drivers of Potential Commercial Opportunity in ATTR Amyloidosis with Cardiomyopathy

Leadership Established in hATTR Amyloidosis with PN



Scalable Capabilities with Strong Patient-Centric Approach

- Dedicated advocacy, education and treatment support
- Well established patient support and services
- State-of-the-art data analytics
- Highly trained customer facing teams with deep relationships
- Broad geographic footprint
- Successful access and reimbursement execution, including Value Based Agreements

Significant Commercial Potential in ATTR Amyloidosis with Cardiomyopathy*

Initial Entry with Patisiran, and Potential Expansion with Vutrisiran

APOLLO

- Established RNAi therapeutics in hATTR amyloidosis with PN
- Reversal in neuropathy impairment

Strong Foundation

HELIOS-A

- Demonstrated efficacy and safety in hATTR amyloidosis with PN
- Subcutaneous administration with infrequent dosing

Continued Growth in hATTR with PN

APOLLO-B

- First RNAi therapeutic demonstrating impact across a spectrum of disease manifestations
- Encouraging clinical efficacy and safety

Rapid Path to Larger Patient Population

HELIOS-B

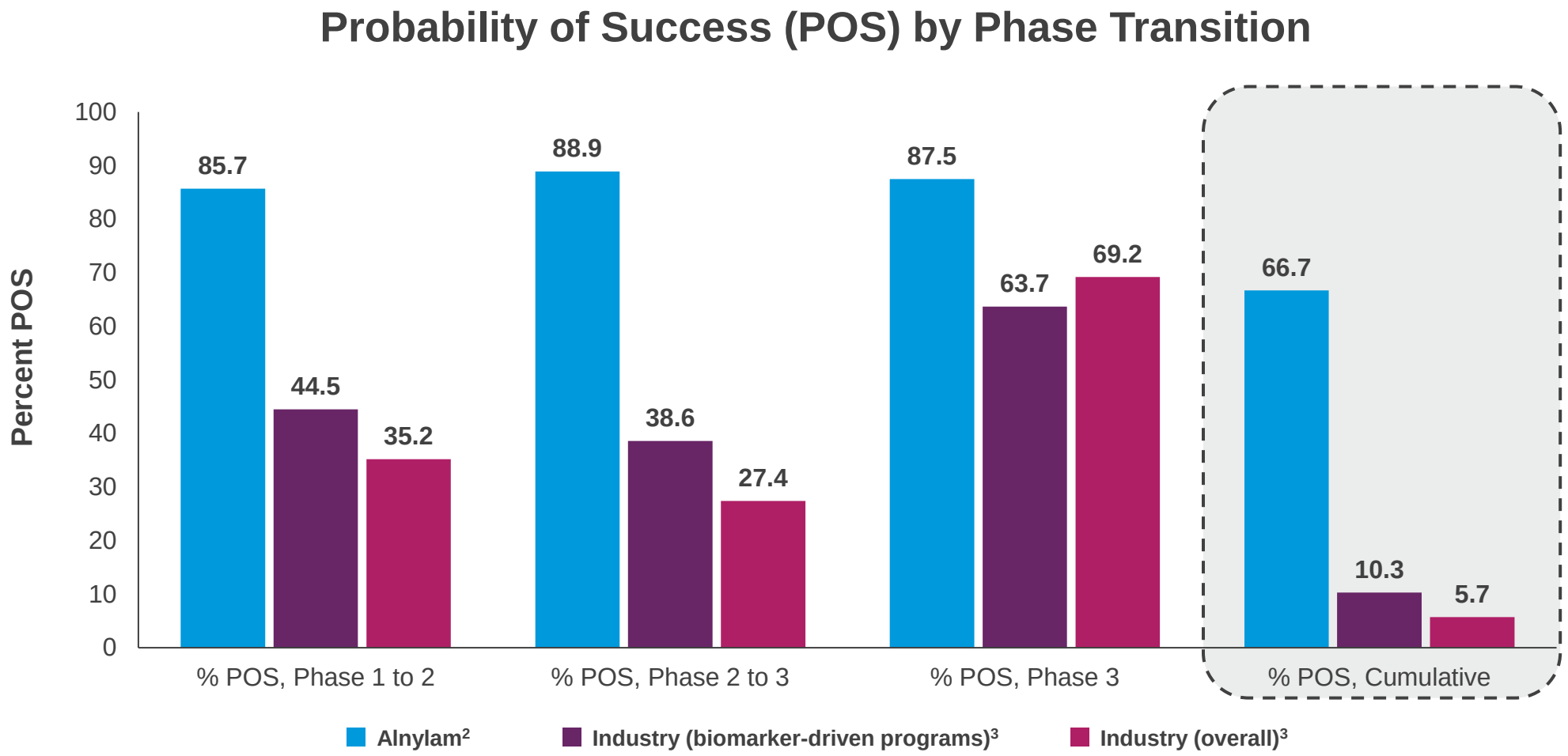
- Potential for a robust efficacy profile, including outcomes data
- Potential best-in-class product profile

Transformative Potential

*Pending label expansion following positive studies, regulatory review and approval

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of November 2021; 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 Alnylam-originated molecules now being developed by partners

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

Alnylam P5X25

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

2022 Expected to Deliver Multiple Catalysts with Value-Creation Potential

Full 18-Month HELIOS-A Phase 3 Results with Vutrisiran	Early 2022 ✓
Cemdisiran Phase 2 Data in IgA Nephropathy	Early 2022 ✓
FDA Approval of Vutrisiran	Mid-2022 ✓
APOLLO-B Phase 3 Results with Patisiran	Mid-2022 ✓
ALN-HSD Phase 1 Part B Topline Results in NASH Patients	Mid-2022
Vutrisiran Biannual Dose Regimen Data	Late 2022
ALN-APP Phase 1 Topline Results	Late 2022
ALN-XDH Phase 1 Topline Results	Late 2022

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

APOLLO-B Phase 3 Topline Results

Q&A Session