



Agenda

Welcome

Christine Lindenboom
 Vice President, Investor Relations & Corporate Communications

Q2 2019 Overview

John Maraganore, Ph.D.
 Chief Executive Officer

Commercial/Med Affairs Highlights

Barry Greene
 President

Alnylam Clinical Pipeline

 Akshay Vaishnaw, M.D., Ph.D. President of R&D

Financial Summary and Guidance

- Manmeet Soni Chief Financial Officer
- Jeff Poulton
 Chief Financial Officer (effective Aug 13)

2019 Goals Update

 Yvonne Greenstreet, MBChB, MBA Chief Operating Officer

Q&A Session



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 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; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolic; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally; our ability to successfully expand the indication for ONPATTRO® (patisiran) in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; 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

This presentation contains non-GAAP financial measures, including expenses adjusted to exclude certain non-cash expenses and non-recurring gains outside the ordinary course of the Company's business. These measures are not in accordance with, or an alternative to, GAAP, and may be difference 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 presented 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.



John Maraganore, Ph.D. Chief Executive Officer

Q2 2019 Overview

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Alnylam Snapshot

Sustainable Value Creation Potential



Strong Launch Progress



Productive R&D Engine



Positioned for Future Growth



Strong Balance Sheet

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SAVE THE DATE

Alnylam R&D Day

Friday, November 22, 2019
Westin Times Square
New York City





Barry Greene President

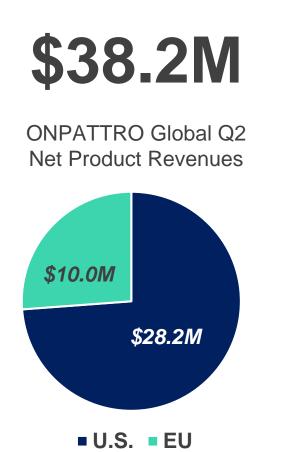
Commercial/Med Affairs Highlights

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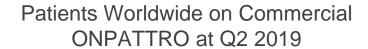


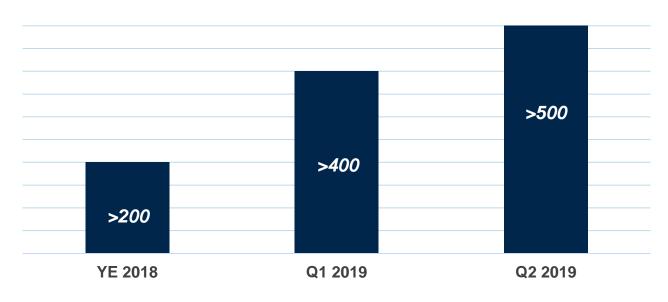
ONPATTRO® Global Launch Update: Q2 2019

Strong Performance with Significant Growth Potential









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

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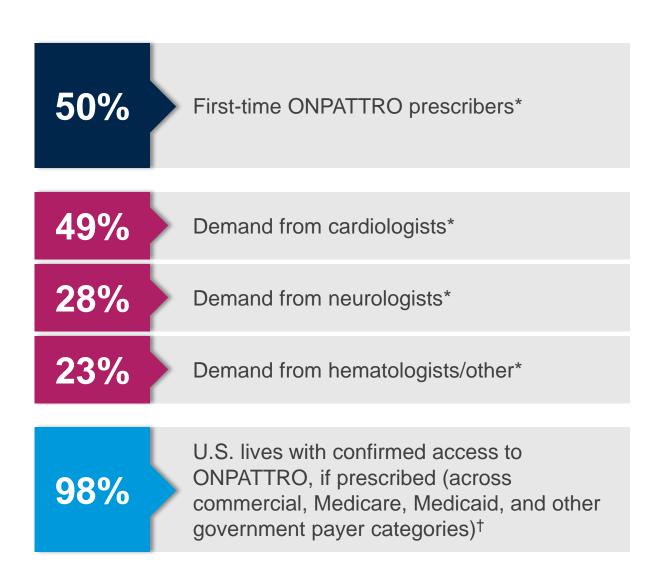


U.S. ONPATTRO Demand, Prescriber Trends, and Market Access

Q2 2019 Selected Metrics







^{*} Based on total Start Forms submitted as of end of Q2 2019. Start Forms are an incomplete picture of U.S. demand.

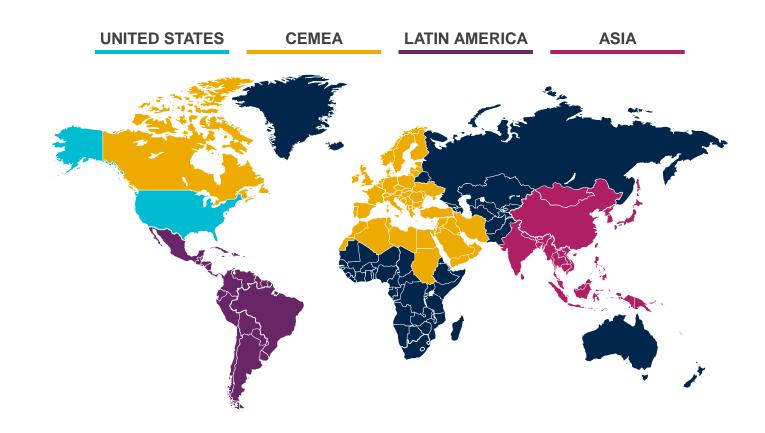
[†] DKP PayerScope® August 1, 2018 through June 30, 2019.



ONPATTRO Global Commercialization

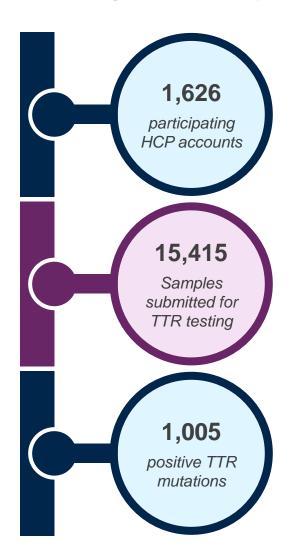
Increasing Access and Value Recognition

- Significant progress with ONPATTRO availability in CEMEA region
 - Favorable and competitively differentiating technology assessments in Germany, France, and Italy
 - Pricing agreement with NICE in England and pricing authorities in Scotland
 - Marketing authorization and commercial availability in Canada
 - Over 10 CEMEA countries now selling ONPATTRO through direct reimbursement, named patient sales, or reimbursed expanded access
- Additional countries and regions advancing
 - Preparing for launch in Japan
 - Latin America plans progressing, starting in Brazil



Alnylam Act – TTR Amyloidosis

No-Charge, Third-Party Genetic Testing and Counseling Program



Reduce barriers to genetic testing and counseling to help people make more informed decisions about their health

Tests and services are performed by independent third parties

Available in U.S. and Canada (genetic counseling service available in U.S.)

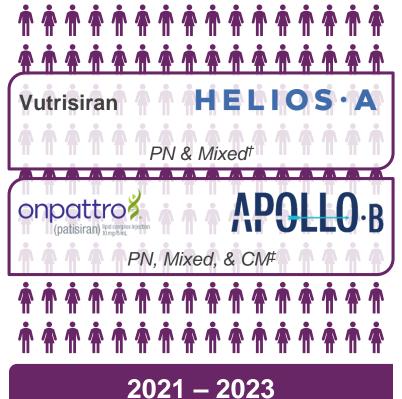
Healthcare professionals who use this program have **no obligation** to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product

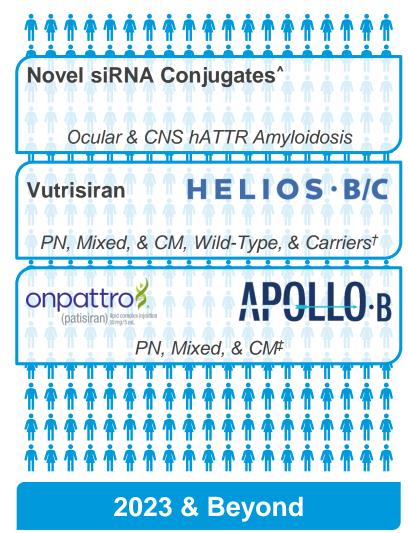
More information regarding this program available at: **www.alnylamact.com**

Alnylam ATTR Amyloidosis Franchise

Potential to Expand Value to Patients Globally for Many Years to Come







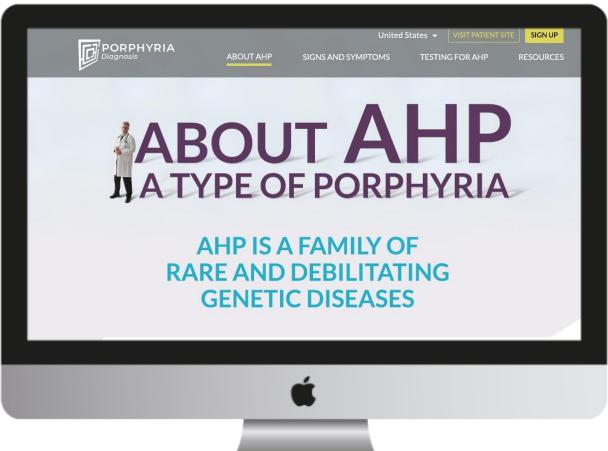
^{*} ONPATTRO is approved in the U.S. for the treatment of the polyneuropathy of hATTR amyloidosis in adults, in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; † 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; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not vet selected.



Driving AHP Awareness

Education Initiatives Tailored to Physician and Patient Communities



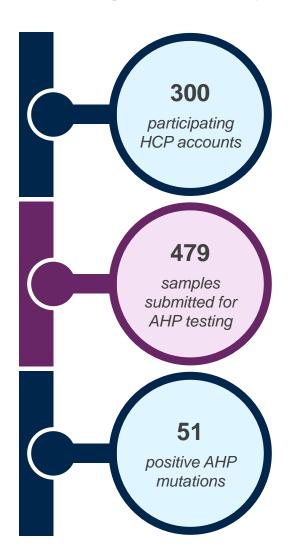




PorphyriaDiagnosis.com

Alnylam Act – Acute Hepatic Porphyria

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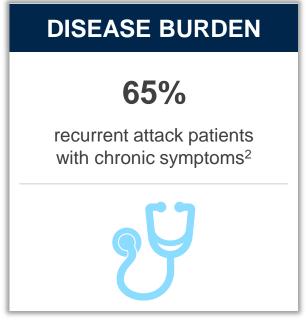


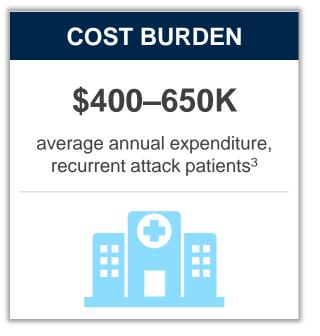
Givosiran Market Opportunity

Ultra-Rare Orphan Disease with Significant Disease Burden and Essentially No Competition

~1,000 ~5,000 recurrent attacks sporadic attacks patients in U.S./EU1







GIVOSIRAN | ACUTE HEPATIC PORPHYRIA

>\$500M potential market opportunity

¹ ORPHANET; The Porphyrias Consortium

² Gouva et al. EASL 2018

³ 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.



Akshay Vaishnaw, M.D., Ph.D. President of R&D

Alnylam Clinical Pipeline



Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

Genetic Medicines	Cardio-Metabolic Diseases						
Hepatic Infectious Diseases	CNS/Ocular Diseases	HUMAN POC ¹	BREAKTHROUGH DESIGNATION	EARLY STAGE (IND or CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 4)	REGISTRATION/ COMMERCIAL ³	COMMERCIAL RIGHTS
onpattro (patisiran) led center insector	hATTR Amyloidosis²	2	9			•	Global
Givosiran	Acute Hepatic Porphyria		Q			•	Global
Patisiran	ATTR Amyloidosis Label Expansion				•		Global
Fitusiran	Hemophilia and Rare Bleeding Disorders				•		15-30% royalties
Inclisiran	Hypercholesterolemia				•		Milestones & up to 20% royalties
Lumasiran	Primary Hyperoxaluria Type 1		9		•		Global
Vutrisiran	ATTR Amyloidosis				•		Global
Cemdisiran	Complement-Mediated Diseases			•			50-50
Cemdisiran/Pozelimab Combo ⁴	Complement-Mediated Diseases			•			Milestone/Royalty
ALN-AAT02	Alpha-1 Liver Disease			•			Global
ALN-HBV02 (VIR-2218)	Hepatitis B Virus Infection			•			50-50 option rights post-Phase 2
ALN-AGT	Hypertension						Global

¹ POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

² Approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, in the EU 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

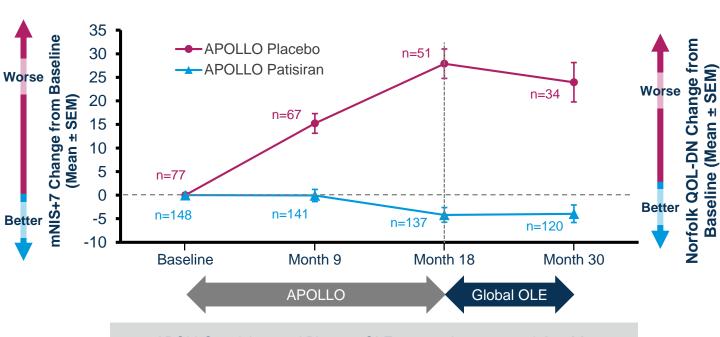
³ Includes marketing application submissions

⁴ 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 August 2019

Patisiran Global OLE Results

Durable Improvement in mNIS+7 and Norfolk QOL-DN in Patients with Longest Patisiran Experience

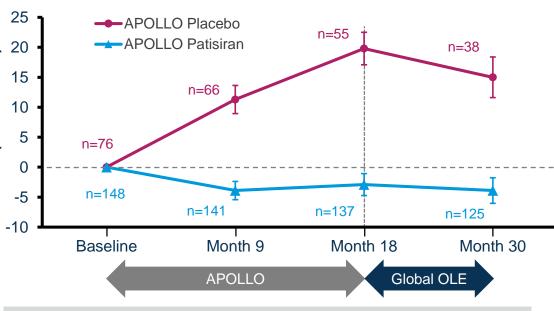
Integrated Change in mNIS+7 from APOLLO and Global OLE^a



APOLLO patisiran and Phase 2 OLE groups demonstrated **durable improvement in neuropathy** versus their parent study baselines, as demonstrated by mean negative change from baseline in mNIS+7

Rapid trajectory of disease progression among APOLLO placebo patients halted once patisiran treatment was initiated in the Global OLE, however patients did not return to parent study baseline

Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE



Durable improvement in QOL observed in the APOLLO patisiran group compared with parent study baseline, after additional 12 months of patisiran treatment in the Global OLE

APOLLO placebo patients experienced an **improvement in QOL** over the 12 months of patisiran treatment; however, their QOL did not return to their baseline values due to the deterioration experienced while on placebo during APOLLO

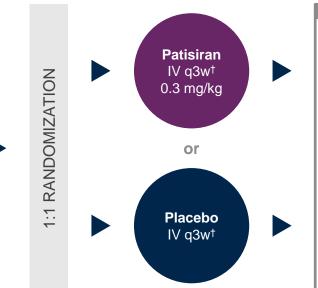
^a For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alternative treatment are treated as missing QOL, quality of life; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire

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-MWD at 12 months

Key Secondary Endpoints

- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

12-Month
Treatment
Extension

APOLLO·B

Expected to initiate in mid-2019

^{*} Subject to protocol finalization; concomitant use of local standard of care allowed during study, including TTR stabilizer

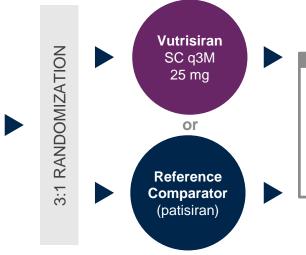
[†] To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWD: 6-Minute Walk Distance

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



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 initiated

HELIOS-B Phase 3 outcomes study for ATTR* cardiomyopathy expected to initiate in late 2019

[^] Primary endpoint for the study is at 9 months

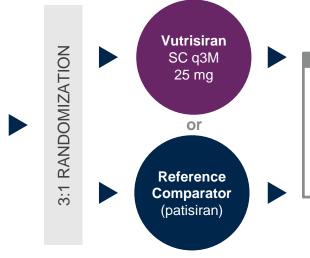
^{*} ATTR amyloidosis - wild-type or any TTR mutation

Vutrisiran HELIOS • A Phase 3 Study

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18-Month Efficacy

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Open-Label Extension



Efficacy Assessments vs. APOLLO placebo arm

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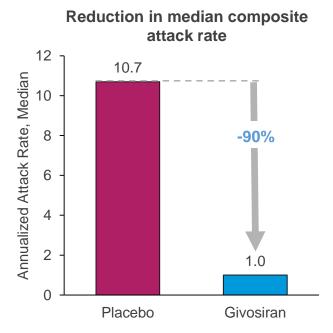
^{*} ATTR amyloidosis - wild-type or any TTR mutation

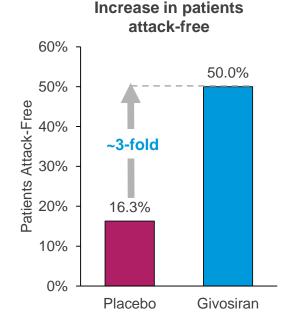


Givosiran ENVISION Phase 3 Study

Givosiran Meets Primary Endpoint with Encouraging Profile in High Unmet Need Disease

Primary Endpoint*	Givosiran (N=46)	Placebo (N=43)	Rate Ratio	P-Value
Composite [†] Annualized Attack Rate, Mean	3.2	12.5	0.26	6.04 x 10 ⁻⁹





Adverse Event, n of patients (%)	Placebo (N = 46)	Givosiran (N = 48)		
Adverse Event (AE)	37 (80.4%)	43 (89.6%)		
Serious Adverse Event (SAE)	4 (8.7%)	10 (20.8%)		
Deaths	0 (0.0%)	0 (0.0%)		
Discontinuations Due to AEs	0 (0.0%)	1 (2.1%)		

- Three SAEs in givosiran patients reported as study drug related
 - 1 pyrexia, 1 abnormal liver function test, and 1 chronic kidney disease
- Common AEs (>10% in either arm)
 - More common in givosiran than placebo: nausea, injection site reaction, chronic kidney disease, fatigue
 - More common in placebo than givosiran: headache, vomiting, urinary tract infection, pyrexia
- ALT elevations >3x ULN occurred in 7 givosiran patients compared to 1 placebo
 - Majority of ALT elevations mild to moderate in severity; occurred after the first 3 to 5 doses of givosiran
 - One givosiran-treated patient discontinued due to ALT >8x ULN, a protocoldefined stopping rule; the elevation subsequently resolved; in remaining 6 patients, all events resolved with continued dosing (n=5) or after a brief pause in dosing (n=1)
- Mild and mostly reversible increases in serum creatinine and decreases in eGFR were seen more commonly in givosiran than placebo; none led to discontinuation
- 93/94 (99%) patients enrolled into Open Label Extension (OLE) study

Completed primary analysis as of April 13, 2019; see Balwani, et al., EASL Meeting, April 13, 2019 for full ENVISION study results

^{*} Efficacy endpoints evaluated in AIP patients, unless otherwise noted

[†] Attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home

Givosiran Regulatory Status Update

FDA & EMA Filings Accepted



Givosiran New Drug Application and Marketing Authorisation Application accepted for filing by FDA and EMA



Granted Priority Review by FDA

• Currently no plan to hold advisory committee meeting to discuss application



PDUFA date set for February 4, 2020

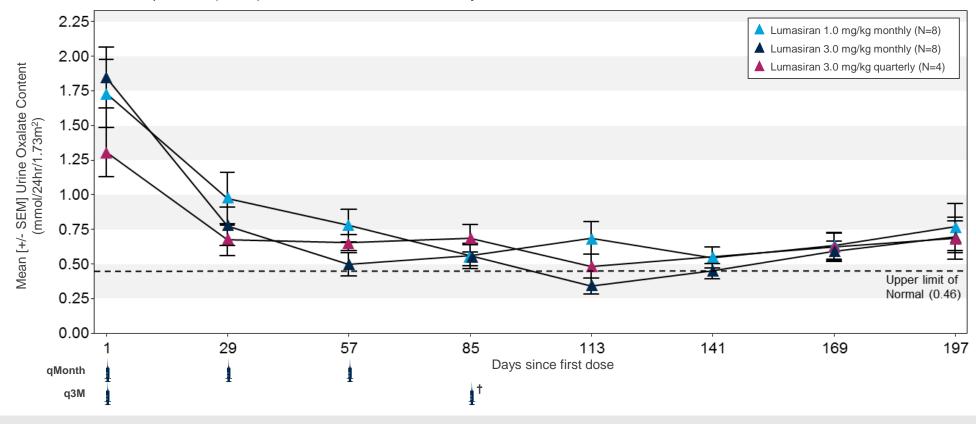


Expanded Access Program initiated

Lumasiran Phase 1/2 Study Final Results*

75% Mean Maximal Reduction in Urinary Oxalate Relative to Baseline After Lumasiran Dosing

All patients (N=20) achieved reductions in urinary oxalate to <1.5xULN



Part B Safety (N=20):

- · No discontinuations from study treatment
- · Majority of AEs mild or moderate, unrelated to study drug
- AEs reported in >3 lumasiran patients: pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); rhinitis, nephrolithiasis (N=4 each)
- No drug-related SAEs; SAEs included: kidney stones, vomiting, gastroenteritis (N=1 each); and 1 patient with abdominal pain, fever, and vomiting
- Self-limiting ISRs in 3 lumasiran patients (15%), all mild or moderate and did not affect dosing

^{*} Only data points with at least 3 contributing patients are represented; placebo data not shown due to limited valid collections

[†] Patients randomized (3:1 drug:placebo) to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized; Day 1 relative to first lumasiran dose; patient randomized to placebo 3 mg/kg quarterly received single dose of lumasiran on Day 1

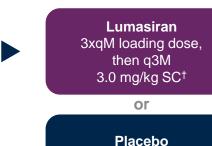
Lumasiran ILLUMINATE • A Phase 3 Study

Randomized, Double-Blind Study in Primary Hyperoxaluria Type 1 Patients

ENROLLMENT COMPLETEDPatient Population

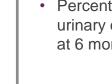
- Adults & children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m²
- Confirmed alanine glyoxalate aminotransferase (AGXT) mutations
- eGFR >30 mL/min/1.73m²





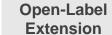
3xqM loading dose,

then q3M SC



Primary Endpoint

 Percent change in 24-hour urinary oxalate excretion at 6 months





FDA Breakthrough and EMA PRIME Designations

Topline ILLUMINATE-A results expected in late 2019

ILLUMINATE-C expected to initiate in late 2019

NDA submission planned in **early 2020** (assuming positive results)

Topline ILLUMINATE-B results expected in **mid-2020**

ORION Phase 3 Program for Inclisiran

Largest Study Program for an RNA Therapeutic

	ORION-9	ORION-10	ORION-11
Study Population	Heterozygous FH	ASCVD (LDL-C >70 mg/dL)	ASCVD (LDL-C >70 mg/dL) & risk equivalent (LDL-C >100 mg/dL)
Number of Patients	482	1,561	1,617

7th IDMC review completed – recommendation to continue without modification

- Substantially all randomized patients in Phase 3 studies treated with four doses of inclisiran or placebo
- >3,500 patient-years of inclisiran safety data accumulated in ORION program
 - Additional safety data continues to accrue at rate of five patient-years per day

Sequential release of topline data readouts by The Medicines Company for ORION-11, -9, and -10 expected to start in second half of Q3





Manmeet Soni Chief Financial Officer

Financial Summary and Guidance

Financial Summary and Updated Guidance

	Three Months	Ended June 30,	Six Months Ended June 30,		
Financial Results	2019	2018	2019	2018	
ONPATTRO Net Product Revenues	\$38.2M	n/a	\$64.5M	n/a	
Total Revenues	\$44.7M	\$29.9M	\$78.0M	\$51.8M	
Total GAAP Operating Costs and Expenses	\$281.0M	\$222.3M	\$503.1M	\$391.6M	
R&D Expenses	\$163.9M	\$137.6M	\$293.0M	\$2 <i>34.4</i> M	
SG&A Expenses	\$112.8M	\$84.7M	\$202.4M	\$157.1M	
Cost of Goods Sold	\$4.3M	n/a	\$7.7M	n/a	
Non-GAAP Expenses					
Non-GAAP R&D Expenses*	\$148.6M	\$126.0M	\$261.6M	\$212.7M	
Non-GAAP SG&A Expenses*	\$97.4M	\$74.1M	\$171.1M	\$137.1M	
GAAP Net Loss	\$219.5M	\$163.6M	\$401.4M	\$304.8M	
Non-GAAP Net Loss**	\$198.3M	\$161.9M	\$348.2M	\$283.5M	

Second Quarter 2019 Cash & Shares

- Cash \$1.97B
 - Includes \$44.8M in restricted investments
- Shares Outstanding 111.1M

See Appendix for a reconciliation between GAAP and non-GAAP measures.

2019 Updated Financial Guidance

- Annual Non-GAAP Operating Expenses:
 - Non-GAAP R&D Expenses* in the range of \$550M to \$575M (from \$550M to \$590M)
 - Non-GAAP SG&A Expenses* in the range of \$390M to \$400M (from \$390M to \$410M)
- Current cash, cash equivalents, and marketable debt securities expected to support company operations for multiple years based on current operating plan

^{*} Non-GAAP operating expenses exclude stock-based compensation expenses.

^{**} 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.



Jeff Poulton Chief Financial Officer (effective Aug 13) Welcoming Remarks



Yvonne Greenstreet, MBChB, MBA
Chief Operating Officer
2019 Goals Update



Alnylam 2019 Goals

2019*

y is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4		Early	Mid	Late
	Commercial Execution	Ø	Ø	
onpattro 🐔 📃	Japan Launch			
(patisiran) lipid complex injection 10 mg/5 mL	Additional Country Launches	⋖	Ø	
(ATTR Amyloidosis)	Start APOLLO-B Cardiomyopathy Phase 3			
VUTRISIRAN	HELIOS-A Polyneuropathy Phase 3 Enrollment	€	Ø	
(ATTR Amyloidosis)	Start HELIOS-B Cardiomyopathy Phase 3			
	ENVISION Phase 3 Topline Results	€		
GIVOSIRAN (Acute Hepatic Porphyria)	File NDA		⋖	
(Acute riepatic Forpriyria)	File MAA		⋖	
	Complete ILLUMINATE-A Phase 3 Enrollment		Ø	
(Drimary Hypercycluria Type 1)	ILLUMINATE-A Phase 3 Topline Results			
(Primary Hyperoxaluria Type 1)	Start ILLUMINATE-B & C Phase 3 Studies	€		
ADDITIONAL CLINICAL PROGRAMS	Continue to advance early/mid-stage pipeline; File new INDs; Present clinical data	Ø	Ø	•
	PARTNERED PROGRAMS			
INCLISIRAN	ORION-9, 10, & 11 Phase 3 Topline Results			
(Hypercholesterolemia)	File NDA			
FITUSIRAN (Hemophilia and RBD)	Support Sanofi on ATLAS Phase 3	Ø	Ø	•

Q2 2019 Financial Results Q&A Session





Q2 2019 Financial Results Appendix



Alnylam Pharmaceuticals, Inc.

Reconciliation of Selected GAAP Measures to Non-GAAP Measures (In thousands, except per share amounts)

	Three Months End June 30,			led		Six Montl June			
		2019		2018		2019		2018	
Reconciliation of GAAP to Non-GAAP Research and development:									
GAAP Research and development	\$	163,890	\$	137,582	\$	293,017	\$	234,439	
Less: Stock-based compensation expenses		(15,282)		(11,616)		(31,407)		(21,753)	
Non-GAAP Research and development	\$_	148,608	\$_	125,966	\$	261,610	\$	212,686	
Reconciliation of GAAP to Non-GAAP Selling, general and administrative:									
GAAP Selling, general and administrative	\$	112,769	\$	84,679	\$	202,377	\$	157,126	
Less: Stock-based compensation expenses		(15,321)		(10,625)		(31,228)		(20,072)	
Non-GAAP Selling, general and administrative	\$_	97,448	\$_	74,054	\$_	171,149	\$	137,054	
Reconciliation of GAAP to Non-GAAP Operating expenses:									
GAAP Operating expenses	\$	280,985	\$	222,261	\$	503,067	\$	391,565	
Less: Stock-based compensation expenses		(30,603)		(22,241)		(62,635)		(41,825)	
Non-GAAP Operating expenses	\$_	250,382	\$_	200,020	\$_	440,432	\$	349,740	
Reconciliation of GAAP to Non-GAAP Net loss:									
GAAP Net loss	\$	(219,481)	\$	(163,560)	\$	(401,396)	\$	(304,774)	
Add: Stock-based compensation expenses		30,603		22,241		62,635		41,825	
Less: Change in fair value of liability obligation		(9,422)		_		(9,422)		_	
Less: Gain on litigation settlement				(20,564)				(20,564)	
Non-GAAP Net loss	\$_	(198,300)	\$_	(161,883)	\$_	(348,183)	\$	(283,513)	
Reconciliation of GAAP to Non-GAAP Net loss per common share-basic and diluted:									
GAAP Net loss per common share - basic and diluted	\$	(2.02)	\$	(1.63)	\$	(3.75)	\$	(3.04)	
Add: Stock-based compensation expenses		0.28		0.22		0.59		0.42	
Less: Change in fair value of liability obligation		(0.09)		_		(0.09)		_	
Less: Gain on litigation settlement				(0.20)				(0.21)	
Non-GAAP Net loss per common share - basic and diluted	\$	(1.83)	\$	(1.61)	\$	(3.25)	\$	(2.83)	