ONPATTRO™ (patisiran) and Investigational ALN-TTRsc02 for the Treatment of ATTR Amyloidosis*

September 11, 2018

*ONPATTRO is approved in the U.S. for the polyneuropathy of hereditary ATTR (hATTR) amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. ALN-TTRsc02 is an investigational RNAi therapeutic, in development for the treatment of ATTR amyloidosis.
Agenda

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

Introduction and ONPATTRO (patisiran)
- Eric Green, Vice President, General Manager, TTR Program

A Payer’s Perspective
- Michael Sherman, M.D., M.B.A., Chief Medical Officer and Senior Vice President for Health Services, Harvard Pilgrim Health Care

ALN-TTRsc02
- Rena Denoncourt, Program Leader, ALN-TTRsc02 Program

Q&A Session
Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation
• Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface.

Replay, slides and transcript available at www.alnylam.com/capella
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. 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 portfolio; 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 report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
RNAi Therapeutics: New Class of Innovative Medicines
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now commercial
Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):
- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

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As of September 2018
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As of September 2018
Hereditary ATTR (hATTR) Amyloidosis

Description
Mutations in TTR gene lead to deposition of misfolded protein as amyloid, causing polyneuropathy and other multisystem disease manifestations

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<th>Patient Population*</th>
<th>~50,000 worldwide</th>
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Median survival
4.7 years from diagnosis

GU:
- Proteinuria
- Kidney failure
- UTI
- Incontinence
- Impotence

CARDIAC:
- Heart failure
- Arrhythmia

GI:
- Diarrhea
- Nausea
- Vomiting

AUTONOMIC:
- Falls
- Lightheadedness
- Weight loss

PERIPHERAL:
- Numbness/tingling
- Pain
- Weakness
- Impaired walking

* Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012
The first RNAi therapeutic is NOW APPROVED

onpattro

(patisiran) lipid complex injection
First and Only Therapy Approved for Patients with hATTR Amyloidosis in U.S.

Approved U.S. Indication
For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Data in Label
Includes data from APOLLO primary and select secondary endpoints.

“This approval is part of a broader wave of advances that allow us to treat disease by actually targeting the root cause, enabling us to arrest or reverse a condition, rather than only being able to slow its progression or treat its symptoms...New technologies like RNA inhibitors, that alter the genetic drivers of a disease, have the potential to transform medicine, so we can better confront and even cure debilitating illnesses.”
~ Scott Gottlieb, MD, FDA Commissioner, Press Release, 8/10/2018

ONPATTRO on Market 1st Business Day Post U.S. Approval
ONPATTRO U.S. Label Highlights

Dosing & Administration

Dosing:
• 0.3 mg/kg (patients <100 kg)
• 30 mg (patients ≥100 kg)

Premedication (day of infusion):
• IV dexamethasone, 10 mg
• IV H1 and H2 blockers
• Oral acetaminophen

Administration:
• Should be performed by healthcare professional.

Safety

No contraindications

Warnings and Precautions
• Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs.
• Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

Common adverse reactions are upper respiratory tract infections and infusion-related reactions

No required laboratory monitoring

For additional information about ONPATTRO, please see the full Prescribing Information.
Change From Baseline in mNIS+7

Primary Endpoint: Change from baseline in mNIS+7, a specialized assessment of polyneuropathy in hATTR amyloidosis\textsuperscript{a-d}

- The mean change from baseline in mNIS+7 at 18 months was -6.0 points (improvement) for ONPATTRO-treated patients versus 28.0 points (worsening) for patients who received placebo, a difference of -34 points.

- In a binary analysis of the primary endpoint, 56% of ONPATTRO-treated patients experienced reversal in neuropathy impairment, defined as a change in mNIS+7 of <0 from baseline at 18 months, compared with 4% of placebo-treated patients\textsuperscript{2}

\textsuperscript{a}Possible total score ranges from 0 to 304.
\textsuperscript{b}Improvement defined as a decrease in mNIS+7 compared to placebo.
\textsuperscript{c}Bars represent SEM (standard error of the mean).
\textsuperscript{d}Mean mNIS+7 at baseline was 80.9 with ONPATTRO and 74.6 with placebo.
\textsuperscript{e}95% CI: -20.7, -11.3.
\textsuperscript{f}95% CI: -39.9, -28.1.

hATTR=hereditary transthyretin-mediated
LS=least squares
mNIS=modified Neuropathy Impairment Score

Change From Baseline in Norfolk QoL-DN Score¹

Significant improvement in quality of life vs placebo, as measured by Norfolk QoL-DN²³⁴

- For ONPATTRO-treated patients, the mean change from baseline in Norfolk QoL-DN at 18 months was -6.7 points (improvement) versus 14.4 points (worsening) for patients who received placebo, a difference of -21.1 points.
- At 18 months, 51% of ONPATTRO-treated patients experienced improvement from baseline in QoL compared with 10% of placebo-treated patients².


Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis


ABSTRACT

BACKGROUND

Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin.

METHODS

In this phase 3 trial, we randomly assigned patients with hereditary transthyretin amyloidosis with polyneuropathy, in a 2:1 ratio, to receive intravenous patisiran (0.3 mg per kilogram of body weight) or placebo once every 3 weeks. The primary end point was the change from baseline in the modified Neuropathy Impairment Score-10 (mNIS-10), range, 0 to 304, with higher scores indicating more impairment) at 18 months. Other assessments included the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, and a 10-m walk test (with gait speed measured in meters per second), and modified body-mass index (modified BMI, defined as weight in kilograms divided by square of height in meter squared in grams per liter; lower values indicated worse nutritional status).

RESULTS

A total of 225 patients underwent randomization (148 to the patisiran group and 77 to the placebo group. The mean (SD) baseline mNIS-10 was 80.9 (41.5) in the patisiran group and 74.6 (33.0) in the placebo group; the least-squares mean (LSM) change from baseline was –6.0 (21.7) versus 28.0 (26.6) difference, –34.0 points; P = 0.001) at 18 months. The mean (SD) baseline Norfolk QOL-DN score was 59.6 (28.3) in the patisiran group and 55.5 (24.3) in the placebo group; the least-squares mean (LSM) change from baseline was –7.2 (8.1) versus 14.4 (2.7) difference, –21.1 points; P = 0.001) at 18 months. Patisiran also showed an effect on gait speed and modified BMI. At 18 months, the least-squares mean change from baseline in gait speed was 0.08 (0.15) m per second with patisiran versus –0.28 (0.04) m per second with placebo difference, 0.36 (0.11) m per second, P = 0.001, and the least-squares mean change from baseline in the modified BMI was –3.7 (5.6) versus –13.9 (14.5) difference, 11.2; P = 0.001). Approximately 20% of the patients who received patisiran and 10% of those who received placebo had mild or moderate infusion-related reactions; the overall incidence and types of adverse events were similar in the two groups.

CONCLUSIONS

In this trial, patisiran improved multiple clinical manifestations of hereditary transthyretin amyloidosis. (Funded by Alnylam Pharmaceuticals; APOLLO ClinicalTrials.gov number, NCT01963346.)

The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Adam; at the Department of Neurology, CHU Bordeaux, 78, rue de la Charité Lescar, 33275 Le Corestel-Bordeaux CEDEX, France, or at david.adams@aphp.fr.

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U.S. Commercialization Underway

1. Diagnosis

2. Brand Choice

3. Treatment Experience and Access

Unified Commercial, Market Access, & Medical Affairs teams driving disease education, diagnosis, optimized patient experience, and access to care
Alnylam Act™: No-charge, Third-party Genetic Testing and Counseling Program

Developed to reduce barriers to genetic testing and counseling to help people make more informed decisions about their health.

Alnylam provides financial support for the program, but the tests and services are performed by independent third parties for individuals who may carry gene mutations known to be associated with hATTR amyloidosis.

Genetic counselors provide information and support for people who have, or may be at risk for, genetic conditions.

Genetic testing service 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

At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program.
Ongoing Support from Alnylam Assist™

Alnylam Assist is a comprehensive program dedicated to helping guide patients through treatment with ONPATTRO

- **A dedicated Case Manager**
  Alnylam Assist will connect patients with a dedicated Alnylam Case Manager who can provide personalized support throughout the treatment process.

- **Benefit verification**
  Coverage for ONPATTRO will vary by plan and by patient. Alnylam Assist can help determine patient-specific coverage requirements.

- **Financial assistance for patients**
  Eligible patients may qualify for the Alnylam Assist Quick Start Program, Patient Assistance Program (PAP), or Commercial Copay Program.

- **Treatment coverage**
  Alnylam Assist can explain the requirements and processes for prior authorizations, claims, and appeals.

- **Coding and billing**
  A Field Reimbursement Director can provide education about billing, coding, and the reimbursement process for ONPATTRO.

- **Disease and product education**
  Patient Education Liaisons are available to help patients gain a better understanding of the disease.

- **Ordering assistance**
  Alnylam Assist will help with ordering and facilitation of delivery via specialty distributor or specialty pharmacy.

To learn more about Alnylam Assist, visit www.AlnylamAssist.com.
First-Ever RNAi Therapeutic Approved in the EU

Approved EU Indication
For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy

Data in Label
Includes data from APOLLO primary and secondary endpoints, as well as exploratory cardiac endpoints

“The safety and efficacy of Onpattro was evaluated in a pivotal trial involving 225 patients with hATTR amyloidosis and symptomatic polyneuropathy. The study showed clinically-relevant improvements in the neurological manifestations of the disease and on patients’ quality of life, as well as a positive impact on cardiac parameters.”
~ CHMP Opinion Press Release, 7/27/2018

For additional information about ONPATTRO, please see the Summary of Product Characteristics (SmPC).
Global Disease Education Resources

Health care professionals

Patients and their families

www.hattramyloidosis.de
www.hattramyloidosis.fr
www.hattramyloidosis.it
www.hattramyloidosis.es
www.hattramyloidosis.pt
www.hattramyloidosis.co.uk

www.hATTRbridge.de
www.hATTRbridge.fr
www.hATTRbridge.nl
www.hATTRbridge.es
www.hATTRbridge.pt
www.hATTRbridge.se
www.hATTRbridge.co.uk
Global Progress of ONPATTRO

- **UK**
  - Provide patisiran to eligible adults in UK with hATTR amyloidosis through MHRA Early Access to Medicines Scheme (EAMS)

- **Japan**
  - Increasing presence in Japan
    - Head of Asia and seasoned leadership team on board
  - On track for JNDA filing with Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in mid-2018
    - PMDA decision for approval anticipated June 2019

- **Canada**

- **Switzerland**

- **Additional regulatory submissions by year end**
  - Continued infrastructure build out for global commercialization in 2019 and beyond
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ALN-TTRsc02
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Q&A Session
A Payer’s Perspective

In his role as Senior Vice President & Chief Medical Officer at Harvard Pilgrim Health Care, Dr. Sherman is responsible for Harvard Pilgrim’s medical trend management, network medical management, medical informatics, wellness and health promotion initiatives, care and disease management services, pharmacy services, NCQA accreditation and quality and utilization management programs. He also serves as chair of the board of managers of the Harvard Pilgrim Health Care Institute, which includes the Department of Population Medicine at Harvard Medical School. A leader in driving adoption of outcomes-based provider and pharmaceutical contracts, Dr. Sherman has overseen the execution of over a dozen outcomes-based contracts with major pharmaceutical companies that go beyond the current “pay per pill” paradigm.

Dr. Sherman serves as chair of the Board of Managers of the Harvard Pilgrim Health Care Institute, which encompasses the Department of Population Medicine at Harvard Medical School and on the Advisory Board of the Institute for Clinical and Economic Review (ICER). He also is the current chair for AHIP’s CMO Leadership Council, comprising chief medical officers from health plans throughout the United States, and serves on the board of directors for the Personalized Medicine Coalition.

Prior to joining Harvard Pilgrim, Dr. Sherman held leadership roles at Humana, UnitedHealth Group, and Thomson Medstat (now IBM Truven). He holds a B.A. and an M.S. in biomedical anthropology from the University of Pennsylvania and received his M.D. from Yale and M.B.A. from the Harvard Business School.

Michael Sherman, M.D., M.B.A
Chief Medical Officer and Senior Vice President for Health Services
Harvard Pilgrim Health Care
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Q&A Session
Alnylam’s Commitment to ATTR Amyloidosis Patients

Continued Innovation in ATTR with Investigational ALN-TTRsc02

Development Status for ALN-TTRsc02

- Completed Phase 1 study in healthy volunteers

- Granted Orphan Drug Designation (ODD) in US and Europe for Treatment of Transthyretin-Mediated Amyloidosis (ATTR amyloidosis)
  - Covers both the hereditary and wild-type forms of the disease

- Proactively engaging with regulatory agencies, physicians, and payers to establish a clinical development plan addressing heterogeneous needs of the broad patient population

Potential Product Attributes for ALN-TTRsc02

- POTENT AND SUSTAINED TTR KNOCKDOWN
- INFREQUENT, QUARTERLY SUBCUTANEOUS DOSING
- SIMPLE, FIXED DOSE, SELF-ADMINISTRATION VIA PRE-FILLED SYRINGE

Expect to initiate a Phase 3 pivotal study in hATTR amyloidosis in Late 2018
ALN-TTRsc02 Phase 1 Study*

Phase 1 Study Design

- Screening
- Randomization
- Dosing on Day 1
- Postdose Follow-up (through day 90)
- PD, PK and Safety* Monitoring

ALN-TTRsc02 Achieves Robust and Durable Serum TTR Knockdown (KD)

Mean max TTR KD of 83% after single 25 mg dose

Safety (N=80):
- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity

TTR Reduction Following Single Dose ALN-TTRsc02 Administration

Mean +/- SEM TTR Relative to Baseline

Days since first dose

* Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)
ALN-TTRsc02 Phase 3 HELIOS • A Study
Planned Initiation Late 2018

Alignment reached on pivotal trial design

**Endpoints**
mNIS+7 & Norfolk-QOL (co-primary)
certain cardiac parameters

**Details**
open label
nine months

~120 patients with hATTR amyloidosis

vs.

APOLLO placebo arm results

Reference arm of ~30 patients on patisiran to be included.
No formal comparisons between patisiran and ALN-TTRsc02 planned.

Additional Phase 3 studies, including in wild-type ATTR amyloidosis, planned for 2019
ALN-TTRsc02 Phase 3 HELIOS•A Study
Randomized, Open-label Study in Hereditary ATTR Amyloidosis Patients

Patient Population
N=~150
- hATTR amyloidosis; any TTR mutation
- Neuropathy Impairment Score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

† Stratification factors include: genotype (V30M vs non-V30M) and neuropathy impairment score (NIS: < 50 vs ≥ 50)

* Patisiran-treated patients will receive premedication prior to patisiran infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers. After relevant efficacy assessments have been completed, patients will transition to q3m ALN-TTRsc02 for the remainder of the study

^ Primary efficacy endpoint at 9 months; total treatment period is 18 months. Full set of assessments conducted at 9 and 18 months. Additionally, at 18 months, all-cause death and hospitalization will be assessed.

Trial design is not final and is subject to further diligence and health authority feedback
ALN-TTRsc02 Phase 3 HELIOS·A Study

Key Study Design Elements

Global Footprint
Enrollment with various hATTR amyloidosis mutation types

Similar inclusion and exclusion criteria to APOLLO
Patients with multi-systemic disease manifestations and a range of disease severity

Comprehensive Evaluations
Assessments leveraging well-established tools for thorough evaluations of various aspects of disease burden

Harnessing RNAi with ALN-TTRsc02, the HELIOS-A study will evaluate a 25mg dose administered subcutaneously once every three months
A Transformative and Historic Year for Alnylam and the TTR Programs

- First-ever approval of a RNAi therapeutic in the U.S. and EU in August
- Commercialization ongoing in U.S. and gearing up in EU
- Continued global expansion with regulatory filings in Japan, Canada and Switzerland planned this year
- Continued commitment to ATTR amyloidosis patients with ALN-TTRsc02 entering Late Stage Development later this year

1 Approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; 2 ALN-TTRsc02 is an investigational RNAi therapeutic

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<tr>
<th>ONPATTRO (patisiran) (hATTR Amyloidosis with polyneuropathy)</th>
<th>2018*</th>
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<tr>
<td>Additional APOLLO Phase 3 data</td>
<td>✔</td>
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<td>FDA approval</td>
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<td>U.S. launch</td>
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<td>J-NDA submission</td>
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<td>EMA approval</td>
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<td>EU launch</td>
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<td>Additional ROW submissions</td>
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<th>ALN-TTRsc02 (ATTR Amyloidosis)</th>
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<tr>
<td>Start Phase 3</td>
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Agenda

Welcome
• Christine Lindenboom, Vice President, Investor Relations & Corporate Communications

Introduction and ONPATTRO (patisiran)
• Eric Green, Vice President, General Manager, TTR Program

A Payer’s Perspective
• Michael Sherman, M.D., M.B.A., Chief Medical Officer and Senior Vice President for Health Services, Harvard Pilgrim Health Care

ALN-TTRsc02
• Rena Denoncourt, Program Leader, ALN-TTRsc02 Program

Q&A Session
Thank You