Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Thursday, August 3, 2017
Agenda

Welcome
• Joshua Brodsky, Associate Director, Investor Relations and Corporate Communications

Introduction
• Eric Green, Vice President, General Manager, TTR Program

Path to Diagnosis
• Dr. Michael Polydefkis, M.D., Director, Cutaneous Nerve Lab, Professor of Neurology, Johns Hopkins University School of Medicine

Overview of Disease and Patisiran Data
• Jared Gollob, M.D., Vice President, Clinical Research

Commercial Opportunity and Preparation
• Eric Green, Vice President, General Manager, TTR Program

Q&A Session
Reminders

Event will run for approximately 75 minutes

Q&A Session at end of presentation
- Submit questions at top of webcast screen
- Questions may be submitted at any time

Replay, slides and transcript available at www.alnylam.com
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; 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 law, we undertake no obligation to update such statements.
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Q&A Session
RNAi Therapeutics
New Class of Innovative Medicines

- Harness natural pathway
- Catalytic mechanism
- Silence any gene in genome
- Upstream of today’s medicines
- Clinically proven approach
## Alnylam Clinical Development Pipeline

**Focused in 3 Strategic Therapeutic Areas (STArs):**

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases

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<th><strong>HUMAN POC</strong></th>
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*POC, Proof of concept - defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies.*
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**Focused in 3 Strategic Therapeutic Areas (STArs):**

- [ ] Genetic Medicines
- [ ] Cardio-Metabolic Diseases
- [ ] Hepatic Infectious Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease/Condition</th>
<th>HUMAN POC*</th>
<th>EARLY STAGE (IND or CTA Filed-Phase 2)</th>
<th>LATE STAGE (Phase 2-Phase 3)</th>
<th>REGISTRATION/COMMERCIAL</th>
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As of July 2017

*POC, Proof of concept - defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
Alnylam ATTR Amyloidosis Portfolio*
Committed to Continued Innovation for Patients

**patisiran**

**hATTR amyloidosis**

- IV administration
- Phase 2 completed
- Phase 2 Open-Label Extension (OLE) study completed
- APOLLO Phase 3 trial ongoing; fully enrolled with top-line results expected in mid-2017
- APOLLO-OLE study ongoing
- Expanded Access Protocol (EAP) ongoing in the US

**ALN-TTRsc02**

**ATTR amyloidosis**

- ESC “second generation” chemistry
- Expect clamped TTR knockdown with very low volume, quarterly SC dose regimen
- Phase 1 ongoing; initial data presented Dec’16

*In October 2016, Alnylam decided to discontinue development of revusiran, which used STC “first generation” GalNAc chemistry and was being developed for treatment of hATTR with cardiomyopathy*
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Q&A Session
hATTR Amyloidosis: Genotypic–Phenotypic Presentation

- >120 amino acid substitutions have been reported in patients with hATTR amyloidosis\(^1\)
- Presentation can vary by *TTR* mutation, but mixed phenotype is commonly reported\(^2,3\)

**Phenotype**

<table>
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<tr>
<th>Early onset</th>
<th>Late onset</th>
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<tr>
<td>V30M</td>
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<tr>
<td>S50R</td>
<td>I107V</td>
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<tr>
<td>F33L</td>
<td>W41L</td>
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<tr>
<td>S77Y</td>
<td>H88R</td>
</tr>
<tr>
<td>V30M (Early onset)</td>
<td>I68L</td>
</tr>
<tr>
<td>F64L</td>
<td>T60A</td>
</tr>
<tr>
<td>A36P</td>
<td>L111M</td>
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<td>G47A</td>
<td>V122I</td>
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<td>C10R</td>
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<td>I68L</td>
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**Neurologic**

Patients with polyneuropathy may also present with, or develop, cardiomypathy

**Cardiac**

Patients with cardiomyopathy may also present with, or develop, polyneuropathy

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Multiple symptoms of hATTR amyloidosis can complicate diagnosis

Diagnosis of ATTR amyloidosis is often delayed

For many patients diagnosis can take years\(^1\)

Wide variety of symptoms mean underlying cause is hard to detect\(^2\)

**Symptoms at presentation (n=186)\(^3\)**

- **ECG ABNORMALITIES**: 75%
- **ECHOCARDIOGRAPHIC ABNORMALITIES**: 71%
- **URINATION PROBLEMS**: 23%
- **DIZZINESS**: 30%
- **GI PROBLEMS**: 42%
- **CARPAL TUNNEL SYNDROME**: 35%
- **SENSOIMOTOR INVOLVEMENT**: 83%

ECG, electrocardiogram

Path to Diagnosis

Long patient odyssey for majority of patients despite family history
Potential Diagnostic Criteria for Confirmation of hATTR Amyloidosis

Assessments to support diagnosis of hATTR amyloidosis\(^1,2\)

- Onset of symptoms and/or signs
- Family history
- Genetic testing
- Changes in physiologic tests vs baseline
- Biopsy evidence of amyloid

Confirmation of diagnosis is by \(TTR\) genotyping\(^3\) alone or with tissue biopsy\(^4\)

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“Red Flag” Symptom Cluster Recommended for hATTR Amyloidosis Presenting With Polyneuropathy

**Progressive symmetric sensory motor neuropathy**

+ \( \geq 1 \) of

<table>
<thead>
<tr>
<th>Family history</th>
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<tr>
<td>Early autonomic dysfunction</td>
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<tr>
<td>GI complaints</td>
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<tr>
<td>Unexplained weight loss</td>
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<tr>
<td>Cardiac hypertrophy, arrhythmias, ventricular blocks, or cardiomyopathy</td>
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<tr>
<td>Renal abnormalities</td>
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<td>Vitreous opacities</td>
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</table>

**Additional alert signs:**
- Rapid disease progression
- Lack of response to prior therapies

“Red Flag” Symptom Cluster Recommended for hATTR Amyloidosis Presenting With Cardiomyopathy

- Evidence of right-sided heart failure
- Hypotension in person with previous hypertension

+ ≥1 of

Family history

- Low/decreasing QRS voltage on ECG
- Thick interventricular septum, “speckled” myocardium by Echo
- Subendocardial late gadolinium enhancement by CMRI
- Heart failure with preserved ejection fraction (without hypertension)
- Sensory involvement, autonomic dysfunction
- Bilateral carpal tunnel syndrome

Additional alert signs:

- Intolerance of commonly used cardiovascular medication
Case 1: “The Serendipitous Diagnosis”

74 year old woman without significant past medical history

• 4 years prior: presents to GI physician with complaint of diarrhea
  • Physical exam: physician notes a murmur and refers to a cardiologist
  • Continued work-up
    • Echocardiogram: suggestive for amyloid
    • Fat pad biopsy: amyloid
    • Genetic testing: transthyretin Thr60Ala variant

“Stopped seeing physicians, they had nothing to offer”

• Currently:
  • Well controlled class II heart failure
  • Progressive peripheral neuropathy that limits daily function (NIS = 42)
Case 2: “Family History”

63 year old man who enjoyed excellent health

- 3 years prior: knee pain, stopped refereeing hockey games
  - Underwent a TKR but did not recover as expected

- 2 years prior: Foot infection requiring IV antibiotics
  - Toe amputation
  - Noticed numbness in his feet and shortly thereafter his hands.

- 1 year prior: Difficulty with fine motor tasks (buttoning shirt)
  - Difficulty walking up stairs - stair lift installed
  - Neurologist: Dx: advanced sensorimotor neuropathy
    - Patient’s father had been seen a decade earlier with an unexplained progressive neuropathy. He spent the last few years of his life in a nursing home with severe impairment. He died ~8 years after symptom onset.

- Continued work up:
  - Patient underwent a nerve biopsy: amyloid
  - Genetic testing: V30M
  - NIS = 101
Case 3: “Evolving Diagnostic Tools”

A 59-year-old athletic, former Division-1 athlete

- 2 years prior: lagging behind during a family outing
- 1.5-years prior: mild foot drop was noted
- 8 months prior: difficulty walking on uneven ground, difficulty maintaining balance on his bike

Previous evaluation:
- B12, TSH, SPEP/IFE
- Athena sensorimotor neuropathy (GM1, GALOP, MAG, Hu, sulfatide) and CMT genetic panels
- A1C = 6.5%

Dx: Diabetic polyneuropathy

- 2-year history of ED and tendency towards constipation

Continued work up:
- PE: bilateral foot drop; NIS=84
- NCV: Sural responses absent; ↓ Peroneal and tibial CMAP (0.5-1.0mV) with ↓ CV (34-36m/s).
- Median & ulnar motor responses and EMG: normal
Case 3: “Evolving Diagnostic Tools,” continued

**Biopsy Results**

↓ IENFD, SGNFD
Case 3: “Evolving Diagnostic Tools,” continued

Biopsy Results

↓ IENFD, SGNFD

Congo red staining:
• Dermal staining with birefringence
• Amyloid Arrector pili
Case 3: “Evolving Diagnostic Tools,” continued

Biopsy Results

↓ IENFD, SGNFD
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Nerve / muscle bx
Biopsy Results

↓ IENFD, SGNFD

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Nerve / muscle bx

Genetic testing
• hATTR: Leu58His
• No previously known family history
Biopsy Results

↓ IENFD, SGNFD
Congo red staining:
- Dermal staining with birefringence
- Amyloid Arrector pili

Nerve / muscle bx

Genetic testing
- hATTR: Leu58His
- No previously known family history

Conclusions:
- First case of hATTR diagnosed by skin bx
- hATTR can be variable: no pain, little dysautonomia
Conclusions

• **hATTR has a heterogeneous presentation**
  ◦ Diagnosed in their 50’s, 60’s and 70’s
  ◦ Presenting with GI, cardiac and peripheral nerve manifestations
  ◦ Tissue diagnosis by fat pad biopsy, nerve biopsy and skin biopsy.

• **Amyloid deposition in the skin correlates with axon loss**

• **Amyloid burden in skin biopsy correlates with disability**
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Q&A Session
hATTR Amyloidosis: A Multisystemic Disease

**CNS Manifestations**
- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Stroke-like episodes

**GI Manifestations**
- Nausea and vomiting
- Changes in GI motility (i.e., diarrhea, constipation, gastroparesis, early satiety)
- Unintentional weight loss

**Nephropathy**
- Proteinuria
- Renal failure

**Cardiac Manifestations**
- Conduction block
- Cardiomyopathy
- Palpitations and arrhythmia
- Mild regurgitation
- Shortness of breath
- Edema

**Autonomic Neuropathy**
- Orthostatic hypotension
- Recurrent urinary tract infection (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities

**Peripheral Sensory-Motor Neuropathy**
- Neuropathic pain
- Altered sensation (i.e., change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired weakness
- Difficulty walking

**Ocular Manifestations**
- Vitreous opacification
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

**Carpal tunnel syndrome**

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GI, gastrointestinal
hATTR Amyloidosis Spectrum of Disease Genotype-Phenotype Association

- Orphan multi-system disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, GI tract, and other tissues
- Range of clinical presentations including neuropathy and cardiomyopathy, with most patients having a mixed presentation of symptoms

Historical Nomenclature of hATTR Amyloidosis

hATTR amyloidosis previously described by predominant clinical manifestation

Patients with polyneuropathy
aka Familial amyloidotic polyneuropathy (FAP)

Patients with cardiomyopathy
aka Familial amyloidotic cardiomyopathy (FAC)

Sensory neuropathy, motor neuropathy, autonomic dysfunction (eg, GI events)

Cardiac wall thickening, atrial arrhythmias, conduction disease, heart failure

However, many patients present with, or develop, concurrent cardiac and neurologic impairments, such that FAP and FAC terminology can be misleading

Amyloid Polyneuropathy: Clinical Manifestations

Sensory Loss and Thermal Burns

Muscle Weakness and Wasting

Joint Damage

“Mal dos pesinhos”

Photos courtesy of Alejandra Gonzalez Duarte (Mexico), Isabel Conceicao (Portugal) and David Adams (France)
Assessment of Polyneuropathy in hATTR Amyloidosis: Neuropathy Impairment Scores

Higher score indicates worsening of disease

NIS (244 points)
- Sensation (32)
- Reflexes (20)

NIS+7 (270 points)
- Motor strength/weakness (192)
- Reflexes (20)
- Sensation (32)
- VDT + HRdb (7.4)
- Σ 5 NCS (18.6)

mNIS+7 (304 points)
- Motor strength/weakness (192)
- Reflexes (20)
- QST (80)
- Σ 5 NCS (18.6)

mNIS+7_{Ionis} (346.3 points)
- Motor strength/weakness (192)
- Reflexes (20)
- QST (80)
- Σ 5 NCS (18.6)
- HRdb (3.7)

BP, blood pressure; VDT, vibration detection threshold
Multiple Assessments Are Needed to Fully Capture the Multisystemic Burden of hATTR Amyloidosis

Motor function
- NIS-weakness (upper and lower limb, cranial nerves)
- 10-meter walk test
- Grip strength

Nutritional status
- mBMI

Cardiac changes
- Echocardiogram
- Cardiac biomarkers (NT-proBNP, troponin)

QoL and physical functioning
- Norfolk-DN QoL
- EQ-5D

Autonomic symptoms
- (GI symptoms, postural hypotension)
  - COMPASS-31

Disease Pathophysiology
- Nerve fiber density
- Amyloid burden

Ambulation changes
- FAP Stage / PND Score

Activity and social functioning
- R-ODS

These additional clinical assessments can help to understand the full impact of the disease on the patient and enhance measurement of disease response to novel therapeutics.
Assessment of Quality of Life (QoL) in hATTR Amyloidosis: Norfolk QoL-DN Questionnaire

35-item patient-reported questionnaire with 5 question domains:
- Activities of daily living, physical functioning/large-fiber neuropathy, small-fiber neuropathy, autonomic neuropathy, and symptoms
- Maximum impairment: 138

In hATTR amyloidosis with polyneuropathy, significant correlation between Norfolk total QoL score and disease stage, disease duration, NIS, and nerve-fiber function\(^1,2\)

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**Mean total QoL scores across disease stages\(^2\)**

<table>
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<th>Disease Stage</th>
<th>Mean QoL Score</th>
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<td>Healthy volunteers (n=16)</td>
<td>Low</td>
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<tr>
<td>Stage 1 (n=29)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stage 2 (n=16)</td>
<td>High</td>
</tr>
<tr>
<td>Stage 3 (n=16)</td>
<td>Very high</td>
</tr>
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</table>

**Individual domain scores across disease stages\(^1\)**

- Physical functioning/large-fiber neuropathy
- Activities of daily living
- Symptoms
- Small-fiber neuropathy
- Autonomic neuropathy

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Stage I, independent ambulation; Stage 2, assistance required when walking; Stage 3, wheel-chair or bed bound

Assessment of Everyday Functioning: Rasch-built Overall Disability Scale (R-ODS)

24-item patient-reported outcome instrument

- Has been used to measure activity and social participation limitations in patients with Guillain–Barré syndrome, CIDP, and gammopathy-related polyneuropathy\(^1\)
- No limitations: 48

Patients with hATTR amyloidosis reported difficulty performing everyday activities\(^2\) including:

- Washing dishes
- Fastening buttons
- Turning key in a lock
- Moving a chair
- Walking ~0.5 miles

CIPD, chronic inflammatory demyelinating polyradiculoneuropathy

Patisiran Phase 2 OLE Study Design

hATTR amyloidosis patients previously dosed on Phase 2 trial eligible to roll over onto Phase 2 OLE study

- **Up to 2 years of dosing**, 0.30 mg/kg every 3 weeks, with clinical endpoints evaluated every 6 months
- **Primary objectives**: Safety and tolerability of long-term dosing with patisiran
- **Secondary objectives**: Effects on neurologic impairment (mNIS+7 and NIS), quality of life, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac involvement (in cardiac subgroup), serum TTR levels

Timelines are not to scale
Patisiran Phase 2 OLE Final Study Results
Summary of Safety and Tolerability

Adverse Events (AE) reported in ≥10% of patients

<table>
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<th>AE by Preferred Term</th>
<th>Patisiran (N=27)</th>
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<td>7 (25.9%)</td>
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<tr>
<td>Diarrhea</td>
<td>6 (22.2%)</td>
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<td>Infusion related reaction</td>
<td>6 (22.2%)</td>
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<tr>
<td>Nasopharyngitis</td>
<td>6 (22.2%)</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Vomiting</td>
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<td>Wound</td>
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<td>Nausea</td>
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<td>3 (11.1%)</td>
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<tr>
<td>Cataract</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Infusion site extravasation</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

- 7 patients (25.9%) with 10 reports of serious adverse events (SAE); not related to study drug
  - One discontinuation for gastroesophageal cancer at ~20 months; patient subsequently died
  - One death due to myocardial infarction after patient completed 24 months of treatment
  - One patient with 3 reports (distal femur fracture/proximal tibia fracture/osteonecrosis/ligament rupture, dehydration/acute prerenal failure/urinary tract infection and thermal burn)
  - One patient with 2 reports (ankle fracture/foot fracture/osteonecrosis and ankle arthrodesis)
  - One patient with venous thrombosis of the lower limb
  - One patient with foot abscess and osteomyelitis
  - One patient with pacemaker implantation due to amyloid cardiomyopathy

- Majority of AEs were mild or moderate
  - 5 patients (18.5%) had severe AEs not related to study drug
  - Related AEs reported in ≥4 patients were infusion related reaction (22.2%) and flushing (22.2%), all of which were mild

- No clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets
Patisiran Phase 2 OLE Final Study Results
Change in mNIS+7 at 24 Months

Mean 7.0-point decrease in mNIS+7 at 24 months
20 out of 27* patients (74%) with no change or an improvement in mNIS+7 at month 24 compared to baseline

Individual ΔmNIS+7 at Month 24 (n=26)

Mean (SEM) ΔmNIS+7 from baseline at 24 mos

Natural History (nonlinear; N=283) ~
Placebo (N=66)
Diflunisal (N=64)

Patisiran
Ph 2 OLE* (N=26)

Mean ΔmNIS+7 Across hATTR Amyloidosis Studies at 24 mos

SEM: Standard Error of the Mean; *One patient discontinued prior to the Month 24 assessment and is included in the denominator
- Assessments drawn from studies in patients with similar baseline neurologic impairment and not based on head-to-head studies
#Predicted progression of median NIS value from Gompertz curve fit (Adams D et al. Neurology. 2015;85:675-682)
+Linear interpolation from 2-year NIS progression measurement in longitudinal analysis set (Berk JL et al. JAMA. 2013;310:2658-67)
^Patisiran results similar in patients with/without concurrent TTR stabilizer therapy; mNIS+7 using full mNIS+7 set; partial imputation was used to recover mNIS+7 data points where components were missing at one or more replicate measurements (per patient/visit)
Adams et al. Neurology 2017; 88:16 Supplement S27.004
Patisiran Phase 2 OLE Final Study Results
TTR Amyloid Burden in Skin: Lower Limb

- Amyloid detected in ~80% of skin biopsies at baseline
- Dermal amyloid burden in distal thigh and distal leg decreased over time relative to baseline
  - Statistically significant decrease in absolute change for distal thigh at 6, 18 and 24 months and at all time points for distal leg

![Graph showing mean absolute change from baseline in dermal amyloid burden](image)

### Median Relative Change from Baseline in Dermal Amyloid Burden

<table>
<thead>
<tr>
<th></th>
<th>Distal Thigh</th>
<th>N</th>
<th>Median Relative Percent Change (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>22</td>
<td>-52.5 (-75.7, 0)</td>
<td></td>
</tr>
<tr>
<td>12 months†</td>
<td>19</td>
<td>-61.8 (-87.5, 0)</td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>20</td>
<td>-78.2 (-89.7, -8.3)</td>
<td></td>
</tr>
<tr>
<td>24 months†</td>
<td>19</td>
<td>-23.8 (-78.3, 0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Distal Leg</th>
<th>N</th>
<th>Median Relative Percent Change (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>22</td>
<td>-48.5 (-74.3, 0)</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>18</td>
<td>-64.6 (-85.8, 0)</td>
<td></td>
</tr>
<tr>
<td>18 months†</td>
<td>18</td>
<td>-67.5 (-91.3, -10)</td>
<td></td>
</tr>
<tr>
<td>24 months†</td>
<td>18</td>
<td>-40.4 (-78.3, -21.6)</td>
<td></td>
</tr>
</tbody>
</table>

*IQR, Interquartile Range; †1 patient excluded due to baseline value of 0 and a non-zero post-baseline value*
**Patisiran Phase 2 OLE Final Study Results**

**Nerve Fiber Density: Lower Limb**

**Sweat gland nerve fiber density (SGNFD):**
- Statistically significant increase in distal thigh at 6, 12, 18, and 24 months and in distal leg at 24 months

**Intraepidermal nerve fiber density (IENFD):**
- Stable throughout the 2-year treatment period; mean change from baseline consistent from 6 through 24 months

### Sweat Gland Nerve Fiber Density (SGNFD): Change from Baseline

<table>
<thead>
<tr>
<th>Location</th>
<th>SGNFD (meters/mm²)</th>
<th>Baseline</th>
<th>Δ Baseline to Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thigh</td>
<td>1.8 (0.6)</td>
<td>N=22, P=0.0323*</td>
<td>N=20, P=0.0008*</td>
</tr>
<tr>
<td>Leg</td>
<td>0.1 (0.4)</td>
<td>N=21, P=0.0072*</td>
<td>N=19, P=0.0025*</td>
</tr>
</tbody>
</table>

### IENFD (fibers/mm)

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline</th>
<th>Δ Baseline to Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thigh</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>10.2 (2.0)</td>
<td>24</td>
</tr>
<tr>
<td>Leg</td>
<td>3.5 (1.3)</td>
<td>24</td>
</tr>
</tbody>
</table>

*Intraepidermal nerve fiber density; SGNFD, sweat gland nerve fiber density; SEM: Standard Error of the Mean

*2-sided p-values from paired t-test comparing post-baseline vs baseline

Phase 3 Study (APOLLO) of Patisiran
Phase 3 and OLE* Ongoing

**APOLLO**
(n=225)

**Patient population**
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neuropathy Impairment Score (NIS) of 5–130
- Prior TTR tetramer stabilizer use

**Primary endpoint**
- Change in mNIS+7 from baseline at 18 months

**Secondary endpoints**
- Norfolk QoL-DN
- NIS-weakness
- Rasch-built Overall Disability Scale (R-ODS)
- 10-meter walk test
- mBMI
- COMPASS-31

**Exploratory endpoints**
- EQ-5D QoL
- Grip strength
- Cardiac assessments
- Serum TTR levels
- Dermal amyloid burden and nerve fiber density in skin

*Patients who complete the study may be eligible for patisiran treatment in Phase 3 OLE study (APOLLO-OLE; NCT01960348)*

**Statistical Considerations**
- Placebo-estimated mNIS+7 progression rate of 17.8 points/year derived from natural history study of 283 hATTR patients with polyneuropathy
- 90% Power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
  - Based on original target enrollment of 200 patients
Ionis Reported NEURO-TTR Phase 3 Topline Results

Statistically significant benefit observed for inotersen-treated patients as compared to placebo in both mNIS+7 and Norfolk QOL-DN endpoints at 15 months

- p<0.0001 and p=0.0006, respectively
- Statistically significant differences also observed for both endpoints at eight months
- Benefit in disease progression achieved regardless of TTR mutation and in both Stage 1 and Stage 2 patients

Key safety findings included thrombocytopenia and renal SAEs

- Three patients had SAEs of thrombocytopenia
  - Two patients recovered, and one patient died due to intracranial hemorrhage
  - One additional patient discontinued inotersen treatment due to lower grade thrombocytopenia
- Four patients discontinued inotersen treatment due to renal observations
  - Two patients met a predefined renal stopping rule, and two experienced renal SAEs, one of whom experienced chronic renal insufficiency
  - One placebo-treated patient also met a predefined renal stopping rule
- Enhanced monitoring implemented during study to support management of these issues; Ionis anticipates that regulators will require safety monitoring in inotersen prescribing information if approved
- Treatment-emergent AEs considered related to treatment were seen more commonly with inotersen than placebo
- Detailed review of safety data ongoing

ALN-TTRsc02 Opportunity
Potential for Best-in-Class Profile

Ongoing Study in Normal Healthy Volunteers
Mean max TTR KD of 97.1 ± 0.5%; >80% TTR KD at Day 90 after single 50 mg dose**

Safety: Generally well tolerated in healthy volunteers (N=48)
- No SAEs or discontinuations due to AEs; all AEs mild or moderate
- 9 AEs in 5 subjects considered possibly related to treatment; all mild
- ISRs reported in 2 subjects – symptoms mild and transient
- No clinically significant changes in physical exams or lab parameters (e.g., LFTs)

*Alnylam discontinued development of revusiran in October 2016
**Data cut-off 26Oct2016; reported at Alnylam R&D Day in December 2016
ALN-TTRsc02 Phase 1 Preliminary Study Results
Single Ascending Dose Study in Healthy Volunteers

- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity
  - 14 AEs in 8 subjects considered possibly related to treatment; majority mild
  - Events included injection site erythema, injection site pain, injection site bruising, rhinorrhea, pruritus, cough, nausea, fatigue, genital rash and abdominal pain
  - No clinically significant changes in lab parameters, EKG or physical exam

As of data cutoff on 31 May 2017
Summary

• hATTR amyloidosis is a **multisystemic disease** with multiple different clinical manifestations of polyneuropathy, often accompanied by cardiac involvement, which could lead to **progressive disability, diminished quality of life, and death**

• **Composite neuropathy impairment scores** such as mNIS+7, along with additional clinical and biomarker endpoints, have the potential to **demonstrate the clinical benefit** of novel therapeutics in this disease

• The **patisiran** Phase 2 OLE study results suggest that TTR lowering has the potential to have a disease-modifying **effect on the polyneuropathy in hATTR amyloidosis**, as shown by the effects on mNIS+7, dermal amyloid burden, and sweat gland nerve fiber density

• The emerging results of **randomized Phase 3 trials** with patisiran and inotersen will further **elucidate the utility of these and other endpoints** in assessing the magnitude and clinical meaningfulness of the response to treatment

• ALN-TTRsc02 offers the potential of a **best-in-class profile** of quarterly, low-volume dosing with **clamped knockdown** of TTR
Agenda

Welcome
• Joshua Brodsky, Associate Director, Investor Relations and Corporate Communications

Introduction
• Eric Green, Vice President, General Manager, TTR Program

Path to Diagnosis
• Dr. Michael Polydefkis, M.D., Director, Cutaneous Nerve Lab, Professor of Neurology, Johns Hopkins University School of Medicine

Overview of Disease and Patisiran Data
• Jared Gollob, M.D., Vice President, Clinical Research

Commercial Opportunity and Preparation
• Eric Green, Vice President, General Manager, TTR Program

Q&A Session
Key Targeted Milestones for Patisiran

- APOLLO Data – Mid’17
- NDA / MAA Filed – Late’17
- US / EU Launch – 2018
Alnylam to Commercialize in US / Canada / W.Europe
Collaboration with Sanofi Genzyme in Rest of World

Patisiran to be commercialized by Alnylam in its territories
hATTR Amyloidosis Market Landscape

Limited available therapies; no approved drugs that halt disease progression and improve patient quality of life

- **US**: No approved drugs; limited use of diflunisal off-label
- **EU**: Tafamidis approved for Stage 1 polyneuropathy patients only; limited access (e.g., not reimbursed in UK)
  - Multiple studies that document disease progression during tafamidis treatment

- **Orthotopic liver transplantation (OLT) use declining worldwide**
  - Generally limited to younger patients with V30M mutation
  - Involves significant risks and may still result in disease progression
  - Contraindicated for patients with cardiomyopathy

- **Few investigational therapies in clinical development**

<table>
<thead>
<tr>
<th>Cortese et al.¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
</tr>
<tr>
<td>61</td>
</tr>
<tr>
<td><strong>Baseline NIS-LL</strong></td>
</tr>
<tr>
<td>28 ± 5</td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
</tr>
<tr>
<td>+4.5 (62% of patients)</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
</tr>
<tr>
<td>+5.9 (65% of patients)</td>
</tr>
<tr>
<td><strong>Month 18</strong></td>
</tr>
<tr>
<td>+8.0 (65% of patients)</td>
</tr>
</tbody>
</table>

Randomized controlled trial in 61 patients with hATTR Amyloidosis
NIS-LL = neuropathy impairment score-lower limb

hATTR Amyloidosis Market Opportunity

~50,000 patients WW
- ~10,000 with predominant polyneuropathy plus
  ~20%-30% of remainder with mixed phenotype
- Some mutations endemic to certain regions

- Often misdiagnosed due to heterogeneity of disease
  - Variable age of onset, disease penetrance, symptoms at presentation, and comorbidities
  - Efforts underway to improve diagnosis rates and enable earlier intervention

Patisiran has potential to address unmet medical needs
- Evidence for potential halting or improvement of neuropathy in Phase 2 OLE study
- APOLLO Phase 3 study will evaluate mNIS+7 and multiple secondary endpoints

Med Res Opin. 2013;29:63 - 76
Succeeding in Rare Disease Requires a Specific Road Map

RNAi Therapeutics Success

- Diagnose
- Educate
- Access
- Engagement and Advocacy
- Retain
- Support and Solutions
- Best or First-in-Class Product Profiles
Digital Educational Initiatives

Recently launched two websites for disease education

Health care professionals

Patients and their families

https://hATTRamyloidosis.com/

https://hATTRbridge.com/
Scientific Leadership and Education

- >20 primary abstracts and publications since 2013
  - Including manuscripts in New England Journal of Medicine, Neurology and Orphanet Journal of Rare Diseases

- Attendance at >55 international, regional and local congresses and ~4,000 peer engagements

- Symposia and facilitation of dialogue among specialists to increase awareness of disease burden
Alnylam Act™
No-charge third-party genetic testing and counseling program*

Individuals with a suspected diagnosis or a confirmed family history of hATTR amyloidosis are eligible to take part in the AlnylamAct™

Genetic Screening performed by CLIA-certified clinical diagnostic laboratory
• Three testing options now available via saliva or blood
  ◦ Neuropathy Panel
  ◦ Cardiomyopathy Panel
  ◦ Single TTR Gene Testing

Genetic counseling offered by a genetics services provider
• Counseling available before, during or after genetic testing

Exploring a supported diagnostic program in the EU

*Available in the United States Only
**Since program inception and as of July 22, 2017.
CLIA - Clinical Laboratory Improvement Amendments
At no time does Alnylam receive patient-identifiable information.
Patient Advocacy

Mutual goals of increasing awareness, enabling earlier diagnosis, advancing the development of potential new therapies, and designing initiatives that support the unique needs of patient communities

2017 activities:

• Patient education: three educational webinars supported
• Initiatives that support the unique needs of patient communities: three Care Days hosted, in conjunction ThinkGenetic, across the US
• Advancing the development of potential new therapies: >25 Advocacy Support Meetings attended
• Collaboration with and support of a variety of patient support groups
hATTR Amyloidosis: A Multisystemic Disease

CNS Manifestations
- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Stroke-like episodes

GI Manifestations
- Nausea and vomiting
- Changes in GI motility (i.e., diarrhea, constipation, gastroparesis, early satiety)
- Unintentional weight loss

Nephropathy
- Proteinuria
- Renal failure

Carpal tunnel syndrome

Autonomic Neuropathy
- Orthostatic hypotension
- Recurrent urinary tract infection (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities

Peripheral Sensory-Motor Neuropathy
- Neuropathic pain
- Altered sensation (i.e., change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired weakness
- Difficulty walking

Cardiac Manifestations
- Conduction block
- Cardiomyopathy
- Palpitations and arrhythmia
- Mild regurgitation
- Shortness of breath
- Edema

Ocular Manifestations
- Vitreous opacification
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

Heart Failure Specialists / Cardiologists
- Edema

Neuromuscular specialists / neurologists

Gastroenterologists

Pathologists

US Go-to-Market Strategy
US Expected to be Alnylam’s First Launch

Patisiran expected to enter a competitive US market in a disease state with significant unmet need and low physician and patient awareness

Our stakeholder-facing teams will interact with a wide variety of external stakeholders:

- Health Care Professionals and Office Staff
- Patients and Caregivers
- Advocacy Organizations
- Payers

Patisiran will be supported by a number of stakeholder-facing roles with an overall footprint similar to current orphan disease products:

- High coordination across the field-based teams and HQ-based Patient Services
Actively Building EU Teams and Infrastructure
Focusing on EU5, Plus Endemic Countries: Sweden and Portugal

Head of EU in place

Regional Support
- Market Access
- G&A
- Supply Chain

Country organizations being built
- Country Manager
- Medical Affairs
- Sales and Marketing
- Local Market Access
Patisiran
Conclusions

hATTR amyloidosis is similar to other ultra-rare diseases:
• Difficult to find patients, who are often hidden among more common diseases → increase disease awareness and patient diagnosis
• Difficult to know true market opportunity until treatment options available and concerted efforts to educate and treat patients are in place

Given Phase 2 OLE experience and recent inotersen efficacy data, we are encouraged by the potential for positive APOLLO results in mid-2017

Alnylam is preparing for commercialization in our territories beginning in 2018, assuming approvals by health authorities

Working closely with Sanofi Genzyme to enable the delivery of patisiran to patients around the world

<table>
<thead>
<tr>
<th>2017*</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
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<tr>
<td>Phase 2 OLE data</td>
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<tr>
<td>APOLLO Phase 3 top-line</td>
<td></td>
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<td>APOLLO Phase 3 results</td>
<td></td>
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<tr>
<td>NDA/MAA filing</td>
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</tbody>
</table>

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

PATISIRAN
(hATTR Amyloidosis)
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Q&A Session
Upcoming RNAi Roundtables

Revusiran investigation results
• Wednesday, August 9, 12:30 pm ET

Platform advances in RNAi therapeutics
• Wednesday, August 23, 3:30 pm ET

Givosiran, in development for the treatment of acute hepatic porphyrias
• Thursday, September 7, 10:30 am ET

Fitusiran, in development for the treatment of hemophilia and rare bleeding disorders
• Tuesday, September 12, 10:30 am ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella.