RNAi Roundtable:  
Patisiran and ALN-TTRsc in Development for the Treatment of Transthyretin-Mediated Amyloidosis (ATTR) 

July 15, 2014
Agenda

Welcome
- Cynthia Clayton
  Vice President, Investor Relations and Corporate Communications

Introduction
- John Maraganore, Ph.D.
  Chief Executive Officer

Overview of TTR-Mediated Amyloidosis
- Philip N. Hawkins, M.B., B.S., Ph.D., FRCP, Professor of Medicine, National Amyloidosis Centre, University College London Medical School

Q&A Session
  with Professor Hawkins

Patisiran and ALN-TTRsc Programs
- Jared Gollob, M.D., Vice President, Clinical Research

Q&A Session
Reminders

- Event will run until ~2:00 p.m. ET
- Q&A session at end of each presentation
  - Submit questions by clicking “Ask a Question” button
  - Questions may be submitted at any time
- Replay and slides available at www.alnylam.com/capella
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, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, 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
Alnylam 5x15™ Strategy
A Reproducible and Modular Path for Genetic Medicines

1. Liver-expressed target gene
- Involved in disease with high unmet need
- Validated in human genetics
- GalNAc-siRNA enables SC dosing with wide therapeutic index

2. POC achieved in Phase 1
- Blood-based biomarker with strong disease correlation
  - e.g., Serum TTR, thrombin generation, hemolytic activity, LDL-C, HBsAg levels

3. Definable path to approval and market
- Established endpoints
- Focused trial size
- Large treatment effect
- Collaborative approach with physicians, regulators, patient groups, and payers
## Alnylam Development Pipeline

<table>
<thead>
<tr>
<th>Category</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td><strong>TTR-Mediated Amyloidosis</strong></td>
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<td>ALN-AT3</td>
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<td><strong>Complement-Mediated Diseases</strong></td>
<td>ALN-CC5</td>
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<td><strong>Hepatic Porphyrias</strong></td>
<td>ALN-AS1</td>
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<td><strong>Hypercholesterolemia</strong></td>
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<td>ALN-HBV</td>
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<tr>
<td><strong>Beta-Thalassemia and Iron-Overload Disorders</strong></td>
<td>ALN-TMP</td>
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<td><strong>Mixed Hyperlipidemia and Hypertriglyceridemia</strong></td>
<td>ALN-ANG</td>
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<tr>
<td><strong>Additional Genetic Medicine and Other Programs</strong></td>
<td>ALN-AC3</td>
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</table>

**Delivery Technology:**
- LNP
- Standard Template Chemistry (STC)-GalNAc Conjugate
- Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugate
Upcoming RNAi Roundtables

Advances in Delivery of RNAi Therapeutics with Enhanced Stabilization Chemistry (ESC)-GalNAc-siRNA Conjugates
**Tuesday, July 22 @ 11:00 a.m. – 12:00 p.m. ET**
- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development
- Moderator: Laurence Reid, Ph.D., Senior Vice President and Chief Business Officer

ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection
**Tuesday, July 29 @ 9:30 a.m. – 10:30 a.m. ET**
- Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
- Moderator: Laurence Reid, Ph.D., Senior Vice President and Chief Business Officer
- Guest Speaker: Graham Foster, Ph.D., FRCP, Professor of Hepatology at Queen Mary University of London

ALN-AT3 for the treatment of Hemophilia and Rare Bleeding Disorders
**Thursday, August 7 @ 9:30 a.m. – 10:30 a.m. ET**
- Akin Akinc, Ph.D., Director, Research
- Moderator: John Maraganore, Ph.D., Chief Executive Officer
- Guest Speaker: Flora Peyvandi, M.D., Ph.D., Head of the Department of Internal Medicine and Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Maggiore Hospital, University of Milan

ALN-CC5 for the treatment of Complement-Mediated Diseases
**Wednesday, August 13 @ 9:30 a.m. – 10:30 a.m. ET**
- Benny Sorenson, M.D., Ph.D., Medical Director, Clinical Development
- Moderator: Barry Greene, President and Chief Operating Officer
- Guest Speaker: Anita Hill, MBChB (Hons), MRCP, FRCPPath, Ph.D., Consultant Haematologist for Leeds Teaching Hospitals NHS Trust, UK, and Honorary Senior Lecturer at the University of Leeds

More roundtables to be scheduled in the coming weeks; visit www.alnylam.com/capella for updates
- ALN-AS1 for the treatment of hepatic porphyrias
- ALN-PCSsc for the treatment of hypercholesterolemia
- ALN-AAT for the treatment of AAT deficiency-associated liver disease
Select Scientific and Clinical Meetings
Mid to Late ’14

- High Blood Pressure Research (HBPR)*
  » September 9-12, San Francisco, CA

- International Complement Society Workshop (ICSW)*
  » September 14-18, Rio de Janeiro, Brazil

- American Neurological Association (ANA)
  » October 12-14, Baltimore, MD

- Oligonucleotide Therapeutics Society (OTS)*
  » October 12-15, San Diego, CA

- AASLD (The Liver Meeting)*
  » November 7-11, Boston, MA

- American Society of Nephrology (Kidney Week)*
  » November 11-16, Philadelphia, PA

- American Heart Association (AHA)*
  » November 15-19, Chicago, IL

- American Society of Hematology (ASH)*
  » December 6-9, San Francisco, CA

* Pending acceptance of abstracts
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Q&A Session
Amyloid

• Abnormal extracellular protein deposit composed of amyloid fibrils

• Diagnostic Congo red staining in tissue sections

• Different fibril proteins in different types of amyloid but all derived by a similar protein misfolding mechanism and have similar final structure
Amyloid deposits
Amyloidosis

- Disease caused by accumulation of amyloid deposits in various organs: local or systemic
- Systemic amyloidosis usually fatal
- Causes ~1 per 1,000-1,500 deaths; AL type most frequently diagnosed
- Diagnosis usually late
- Treatment very challenging
- Major recent advances in understanding pathogenesis
- Major unmet medical need
Pathogenicity & treatment of amyloidosis

- Amyloid deposits are directly damaging by their physical presence
- No amyloid: no disease
  More amyloid: disease progression & death
  Amyloid regression: clinical benefit, survival
- Early diagnosis, amyloid awareness
- Maintenance of organ function
- Reduce supply of fibril precursor
Hereditary transthyretin (ATTR) amyloidosis
Fibrils derived from mutant TTR

Familial Amyloid Polyneuropathy (FAP)
5-10,000 cases worldwide; 100 different mutations

TTR Met30 most prevalent worldwide
  Younger patients, typically < 40 years of age
  Peripheral & autonomic neuropathy; cardiac involvement rare.
  Death 10-15 years.

TTR Ala60 most prevalent in British Caucasians
  Autonomic neuropathy and cardiac involvement
  Typically present ~60 years of age
  Peripheral neuropathy less prominent. Cardiac deaths in 5-10 yrs.

Familial Amyloid Cardiomyopathy (FAC)
  TTR Ile122 variant in ~4% of black Africans (i.e. ~1.5 million in US)
  Penetrance unknown; likely to be much under-diagnosed
  Cardiac amyloidosis after ~60 years of age. Death in <5 years.
Clinical course of FAP

Progressive impairment of sensation and strength from toes moving upwards.

Stage I  Ambulant
Stage II  Ambulant with assistance
Stage III No longer ambulant

Autonomic symptoms of weight loss, constipation, diarrhoea, difficulty eating meals, difficulty passing urine; low blood pressure and fainting
Stages of FAP

Stage 1: 4-5 yrs
Stage 2: Early 2-3 yrs
Stage 2: Late 1-2 yrs
Stage 3
Clinical course of FAC

Progressive heart failure with diastolic dysfunction followed by systolic dysfunction

Symptoms of left and right heart failure, including: fatigue, shortness of breath, poor exercise tolerance, fluid retention in legs and abdomen, liver enlargement, loss of appetite, nausea

Conduction abnormalities leading to cardiac arrhythmias

Frequent hospitalizations for cardiovascular decompensation in later stages of disease
Cardiac ATTR amyloidosis

Restrictive cardiomyopathy, preserved ejection fraction
Echocardiography

Diffusely thickened heart wall
Therapeutic strategies in amyloidosis

- Immunotherapy
- Destabilise by SAP depletion
- Reduce supply of amyloid precursor protein
- Stabilise precursor proteins
- Inhibit GAG binding
- β sheet breakers
- Reversion to native fold
- Fibril formation

- Immunotherapy
- Destabilise by SAP depletion
### Treatment of amyloidosis

**Reduce supply of fibril precursor protein**

<table>
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<th>Type</th>
<th>Treatment</th>
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<td>AA</td>
<td>control inflammation to reduce SAA protein production by the liver</td>
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<tr>
<td>AL</td>
<td>chemotherapy for plasma cell dyscrasias to reduce monoclonal light chain protein production in the bone marrow</td>
</tr>
<tr>
<td>ATTR</td>
<td>liver transplantation to remove the source of genetically variant amyloid-forming TTR protein</td>
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Regression of AA amyloid
Whole body scintigraphy with $^{123}$I-labelled SAP

in spleen and liver of a patient whose underlying rheumatoid arthritis was well suppressed by anti-inflammatory treatment

1999 2001
Natural turnover & clearance of amyloid deposits

More than 50% of existing AA and AL amyloid deposits can be cleared in one year when amyloid precursor protein supply is cut-off.

Rate of clearance varies from patient to patient.

Without treatment, clearance of amyloid is almost always slower than the on-going rate of new amyloid deposition.

Any degree of reduction in the supply of the respective precursor protein will slow down disease progression.

A 50% reduction can completely halt disease progression.
Management of FAP

- Symptom relief for neuralgic pain, gastrointestinal symptoms associated with autonomic disease, cardiac failure

- Liver transplantation to remove source of genetically variant amyloid forming TTR protein variants
  - Improved survival and stabilization of disease in early stage V30M patients
  - Progressive amyloid deposition occurs in heart and other sites due to normal TTR continuing to build up on the pre-existing template of variant TTR amyloid, especially in patients with later stage disease and non-V30M mutations
  - Only 6 liver transplants in UK for FAP past 5 yr.

- TTR tetramer stabilizers tafamidis and diflunisal show modest effect on neuropathy progression
  - Tafamidis: Approved in EU only for early stage FAP; not approved in US
  - Diflunisal: Positive Phase 3 study results in trial conducted by academic centre
Management of FAC

- Symptom relief for congestive heart failure, chiefly just with diuretics and fluid balance management.

- Liver transplantation has no role.

- Cardiac transplantation in highly selected cases; most patients too old.
Case History
FAP associated with TTR Met30

36 yr old Greek Cypriot woman
2 yr history of painful peripheral neuropathy
Loss of bladder control and self-catheterization
No cardiac amyloidosis

2 year wait for liver transplantation, associated with progression of peripheral neuropathy and weight loss

Stabilization during 5 yr follow-up, weight gain, slight recovery of bladder control
59 yr old Afro-Carribean man presented with congestive heart failure in 2003
Thick walled heart on echo with well preserved ejection fraction
Suspicion of amyloid supported by genetic testing – homozygous for TTR Ile122 variant
Amyloidosis confirmed by cardiac biopsy

Marked deterioration over following year; accepted for cardiac transplant 2004
Remains well; no cardiac amyloid on DPD scan.
Prospects for treatment of ATTR amyloidosis

Serious disease with substantial unmet need

Liver transplantation for FAP patients with early symptoms associated with TTR Met30. Amyloidogenic property of wild-type TTR limits this approach in patients with cardiac involvement

TTR stabilization shows some promise, though limited clinical efficacy demonstrated to date in FAP

Management of FAC largely limited to supportive care

Robust rationale for reducing the supply of TTR in the plasma to treat FAP and FAC, a strategy that has proved to be highly effective in other types of amyloidosis
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Q&A Session
Transthyretin-Mediated Amyloidosis (ATTR) Program
Unmet Need and Product Opportunity

RNAi to treat genetic disease

- ATTR is significant orphan disease
  - ~50,000 Patients worldwide
- Clinical pathology
  - Onset ~40 to >60 yr; fatal within 5-15 years
  - Two predominant forms
    - Familial amyloidotic polyneuropathy (FAP)
    - Familial amyloidotic cardiomyopathy (FAC)
- Halting disease progression remains unmet need
  - Liver transplantation required early
  - TTR stabilizers provide modest benefit

Mutant transthyretin (TTR) is genetic cause

- Autosomal dominant with >100 defined mutations
- Misfolds and forms amyloid deposits in nerves, heart, other tissues

RNAi opportunity as transformative therapy

- Aim to halt progression, possibly achieve regression
- Value proposition supported by pharmacoeconomics and cost of disease burden
- Concentrated provider base and active patient community
ALN-TTR Therapeutic Hypothesis

Production of mutant and wild type TTR

Unstable circulating TTR tetramers

Organ deposition of monomers, amyloid (β-pleated) fibril

Neuropathy, cardiomyopathy
ALN-TTR Therapeutic Hypothesis

Production of mutant and wild type TTR

ALN-TTR acts to knock down both mutant and wild type TTR production

Unstable circulating TTR tetramers reduced

Organ deposition of monomers, amyloid (β-pleated) fibril prevented, clearance promoted

Neuropathy, cardiomyopathy Stabilization and recovery
TTR Knockdown and Rationale for Clinical Outcomes

TTR knockdown is validated endpoint

- ~50% Knockdown in other systemic amyloidoses
  » Disease improvement or stabilization
- Elimination of mutant TTR following liver transplantation
  » Disease improvement or stabilization
- Stabilization of TTR by tafamidis and diflunisal
  » Disease stabilization using NIS-LL and NIS+7 endpoints
  » Includes Stages I and II disease
- V30M transgenic mouse model data
  » Complete amyloid regression with TTR knockdown

~50% Lowering in AL Amyloidosis

~50% Lowering in AA Amyloidosis

Gillmore et al., Lancet; 358:24-9 (2001)
Relationship of TTR KD with TTR Tissue Deposits
Increased Regression of TTR Deposits with Greater TTR KD in hV30M Mouse Model

Zimmerman et al., Int'l Symp of Amyloidosis, Apr. 2014;
Collaboration with Maria Saraiva Lab, Institute for Molecular and Cellular Biology, Portugal
Comparison of RNAi with Tafamidis
Superior Regression of TTR Tissue Deposits with RNAi in hV30M Mouse Model

Zimmerman et al., Int’l Symp of Amyloidosis, Apr. 2014;
Collaboration with Maria Saraiva Lab, Institute for Molecular and Cellular Biology, Portugal
Patisiran (ALN-TTR02)
Familial Amyloidotic Polyneuropathy (FAP)

Patisiran in clinical development
- International Nonproprietary Name designation for ALN-TTR02 = Patisiran (Pa-TEE-sa-ran)
- Orphan drug status in US/EU
- Fast track designation by FDA
- Positive Phase 1 results in human volunteers
  - Data published in *New England Journal of Medicine*
- Positive multi-dose Phase 2 results in FAP patients
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Includes clinical endpoints measured every 6 months
  - Positive initial data reported at ISA, April 2014
- APOLLO Phase 3 trial ongoing
Robust knockdown of both wild-type and mutant TTR in ATTR patients

- Open label, multi-center, multi-dose, dose escalation study
- Results (n=29) show up to 96% TTR knockdown; 84% and 87% mean TTR knockdown after 1\textsuperscript{st} and 2\textsuperscript{nd} doses in 0.30 mg/kg q3w cohort (p<0.001 vs. 0.01 mg/kg)
- 1:1 knockdown of wild-type and mutant TTR; similar knockdown in patients with TTR stabilizers

**Dose Response and Duration of TTR Knockdown**

**Knockdown in Wild Type vs. Mutant**

\[ R^2 = 0.89 \quad p < 0.0001 \]

*Excludes post-day 28 data from one patient that experienced drug extravasation during second infusion*
Patisiran Open-Label Extension (OLE) Study

FAP patients dosed in Phase 2 trial eligible for Phase 2 OLE study

- Clinical endpoints evaluated every 6 months for up to 2 years
  - Clinical endpoints same as APOLLO Phase 3 study
  - Dosing at 0.30 mg/kg every 3 weeks
- Study objectives
  - Primary: Safety and tolerability of long-term dosing with patisiran
  - Secondary: Effects on neurologic impairment (mNIS+7), quality of life, mBMI, disability, mobility, nerve fiber density in skin biopsies, and serum TTR levels

Status
- Ongoing; enrollment completed (N=27)
- Initial data reported at ISA, April 2014
- Additional data in late ’14, to include 6 mo mNIS+7 data from ~20 patients
  - Presentation at ANA, October 12-14, 2014 (Baltimore)
- Report data at least once annually
# Patisiran Phase 2 OLE Preliminary Study Results

## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>N=23</td>
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<tr>
<td>Median age</td>
<td>65.5 years (range 30-77)</td>
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<tr>
<td>Gender</td>
<td>16 males, 7 females</td>
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<tr>
<td>TTR genotype</td>
<td>• Val30Met (V30M) = 16</td>
</tr>
<tr>
<td></td>
<td>• Ser77Tyr (S77Y) = 2</td>
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<tr>
<td></td>
<td>• Ser77Phe (S77F) = 2</td>
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<tr>
<td></td>
<td>• Tyr116Ser (Y116S) = 1</td>
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<tr>
<td></td>
<td>• Phe64Leu (F64L) = 1</td>
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<tr>
<td></td>
<td>• Arg54Thr (R54T) = 1</td>
</tr>
<tr>
<td>FAP stage/PND score</td>
<td>• Stage 1: 20</td>
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<tr>
<td></td>
<td>• Stage 2: 3</td>
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<tr>
<td></td>
<td>• I: 12</td>
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<td></td>
<td>• II: 8</td>
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<td></td>
<td>• IIIa: 2</td>
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<tr>
<td></td>
<td>• IIIb: 1</td>
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<tr>
<td>Concurrent tetrramer stabilizer</td>
<td>10 tafamidis, 7 diflunisal, 6 none</td>
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<tr>
<td>Total doses administered to date</td>
<td>81</td>
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<tr>
<td>Median doses/patient to date</td>
<td>4 (range 1-8 doses)</td>
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## Patisiran Phase 2 OLE Preliminary Study Results

### Baseline Characteristics

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<tr>
<td>Serum TTR (µg/mL)</td>
<td>241.4 (179.2 – 313.7)</td>
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<td>NIS (max impairment: 244 points)</td>
<td>35.4 (4.0 - 93.4)</td>
</tr>
<tr>
<td>mNIS+7 (max impairment: 304 points)</td>
<td>55.0 (3.0 – 122.5)</td>
</tr>
<tr>
<td>mBMI</td>
<td>1030.3 (747.8 – 1410.9)</td>
</tr>
<tr>
<td>EQ-5D-5L (max impairment: 0)</td>
<td>0.8 (0.3-1.0)</td>
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<tr>
<td>10-Meter walk test (sec)</td>
<td>10.7 (5.3-22.0)</td>
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### Cardiac subgroup: n = 9

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<td>NT-proBNP (ng/L)</td>
<td>911.6 (105.0-2070.0)</td>
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<tr>
<td>Troponin I (ng/mL)</td>
<td>0.16 (0.0–0.7)</td>
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<tr>
<td>LV wall thickness (cm)</td>
<td>1.5 (1.3-1.7)</td>
</tr>
<tr>
<td>V30M/non-V30M (N)</td>
<td>6/3</td>
</tr>
</tbody>
</table>

Patisiran OLE Preliminary Study Results
Sustained TTR Knockdown at 80% Target Level

Sustained knockdown of TTR in ATTR patients
- Initial OLE study results presented at ISA 2014
- Results (n=23) showed sustained TTR knockdown at the 80% target level for ~6 months and >8 doses
  » Blood samples obtained pre-dose
Patisiran Phase 2 OLE Preliminary Study Results
Reduction in IRR Rate with 70-minute Microdosing Regimen

**Patisiran**

0.30 mg/kg

\[ \text{Infusion Time} \]

<table>
<thead>
<tr>
<th>% Doses Associated with IRR</th>
<th>60 min</th>
<th>70 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3/20</td>
<td>2/99</td>
</tr>
</tbody>
</table>

\[ {\text{*p = 0.03}} \]

\[ \text{Fisher’s Exact Test} \]

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>60 min (# of patients)</th>
<th>70 min (# of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Phase 2 OLE</td>
<td>--</td>
<td>23</td>
</tr>
</tbody>
</table>

Patisiran Safety and Tolerability
Results from Phase 1, Phase 2, and OLE Studies

Generally well tolerated in human volunteers (n=17) with single dose in Phase 1

- No SAEs, no discontinuations due to study drug
- All AEs associated with drug administration mild or moderate in severity
  » Moderate infusion reaction in one subject at 0.50 mg/kg
- No laboratory abnormalities

Generally well tolerated in ATTR patients (n=29) with multi-dose in Phase 2

- No significant AEs associated with drug up through 0.30 mg/kg
- Favorable safety profile with 0.30 mg/kg administered either q3w or q4w
  » Two SAEs reported
  - Self-limiting cellulitis of arm due to drug extravasation
  - Severe nausea/vomiting in patient with autonomic disease; patient discontinued therapy
  » Mild to moderate infusion-related reactions seen in 3 patients; all completed dosing
  » No laboratory abnormalities

Generally well tolerated in ATTR patients (n=23) with up to 8 doses in Phase 2 OLE

- No SAEs, no discontinuations due to study drug
- All AEs associated with drug administration mild or moderate in severity
  » Mild infusion reactions in one subject
- Use of proprietary micro-dosing regimen associated with significantly reduced infusion reactions (2% vs. 15%, p=0.03)
- No laboratory abnormalities

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1 Coelho et al., N Eng J Med;369:819-29 (2013); 2 ISFAP, November, 2013, Updated at ISA, April 2014; 3 ISA, Apr. 2014
Phase 3 Trial of Patisiran in FAP

Randomized, double-blind, placebo-controlled, global study

- Sample size and randomization
  » N=200
  » 2:1, Patisiran vs. placebo

- Key eligibility criteria
  » V30M and non-V30M FAP
  » Baseline NIS 10-100 (FAP stages 1 and 2)

- Treatment regimen
  » Patisiran 0.30 mg/kg vs. placebo IV q3w for 18 months
  » All completers eligible for patisiran treatment on Phase 3 OLE study

Primary Endpoint

- mNIS+7 at 18 months

Secondary Endpoints

- Norfolk QOL-DN, NIS-weakness, mBMI, timed 10-meter walk, COMPASS-31 autonomic symptom score

Statistical Considerations

- Placebo mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 FAP patients
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
- Blinded interim analysis of variability planned for potential sample size re-estimation
mNIS+7 Components

**mNIS+7** (304 points)

- **Postural Blood Pressure (PBP, 2 points)** –
  Measures autonomic function to address risk of orthostasis (low BP shortly after standing, leading to dizziness)

- **Quantitative Sensory Testing (QST)** –
  Measures heat pain and touch pressure at multiple sites over entire body

- **Nerve Conduction Studies (NCS)**
  Measures motor and sensory nerve function with focus on number of nerve fibers (action potentials)

- **Motor strength/weakness** (192)

- **Reflexes** (20)

- **QST** (80)

- **NCS** (10)

**Neurological Impairment Score (NIS)**

Neurologic exam of lower limbs, upper limbs, and cranial nerves
Correlation of NIS with Genotype and Disease

**All Study Countries**

- **Early Onset V30M**
- **Late Onset V30M**
- **Non-V30M**

- **Genotype Class**
- **NIS**
  - *** p < 0.001 (ANOVA)
  - *** p < 0.001
  - * p < 0.05

**France and Italy**

- **PND Score**
- **NIS**
  - p < 0.000 (ANOVA)

**France, Portugal, Italy**

- **FAP Stage**
- **NIS**
  - p < 0.0001 (ANOVA)

**France**

- **Right Manual Grip (KPa)**
  - 30.8
  - 23.5
  - 13
  - 9.8
  - 6

- **PND Score**
  - p < 0.0001 (ANOVA)

Adams, Int'l Symp Amyloidosis, Apr. 2014
Currently 21 sites recruiting

- United States
  - California
  - Colorado
  - Illinois
  - Missouri
  - New York
  - Oregon
- France
- Germany
- Italy
- S. Korea
- Portugal
- Spain
- Sweden
- Taiwan
ALN-TTRsc in clinical development

- Subcutaneous delivery
- Completed GLP tox studies confirming wide therapeutic index
- Positive Phase 1 study results
  » Normal healthy volunteer study in UK
- Pilot Phase 2 study ongoing
- Phase 3 start planned for 2014
GalNAc-siRNA Conjugates
Targeted Delivery to Hepatocytes and SC Dosing

**ASGPR**
- Clears serum glycoproteins via clathrin-mediated endocytosis
- Highly expressed in hepatocytes
  - 0.5-1 million copies/cell
- High rate of uptake
- Recycling time ~15 minutes
- Conserved across species

**GalNAc-siRNA**
- GalNAc ligand conjugated to chemically modified siRNA to mediate targeted delivery
- Trivalent GalNAc carbohydrate cluster has nM affinity for ASGPR
- Administered subcutaneously (SC)

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**Diagram:**
- GalNAc-siRNA conjugate
- Clathrin-coated pit
- Clathrin-coated vesicle
- Endosome
- Recycling
- ASGPR
- mRNA
- Nucleus
- Target protein
- RISC
- Adapted from *Essentials of Glycobiology* (2009)
ALN-TTRsc Phase 1 Study Results

Randomized, double-blind, placebo-controlled SAD and MAD study in healthy volunteers

- Rapid, dose-dependent, consistent, and durable knockdown of serum TTR
  - Significant knockdown of serum TTR (p<0.01) up to 94% TTR knockdown; Mean knockdown up to 92.4%
- Generally well tolerated
  - Only AEs associated with drug were generally mild ISRs, resolving within ~2 hours of onset
- Excellent correlation of human to non-human primate TTR knockdown on mg/kg basis
  - Confirmation of human translation of GalNAc-siRNA conjugate platform
  - Extended durability in human vs. NHP due to attenuated nuclease environment

Zimmermann, HFSA, Sep. 2013; Manoharan, TIDES, May 2014
ALN-TTRsc Phase 2 Study

Study Design

- Open-label, multi-dose study in TTR cardiac amyloidosis
  - Includes patients with FAC and senile systemic amyloidosis (SSA)
- 25 Patients
- 5 mg/kg dose (qd x5 load, qw x5 maintenance)

Primary Objective

- Assess safety and tolerability

Secondary Objective

- Obtain preliminary evidence for clinical activity
  - Serum TTR knockdown of wild-type and mutant protein
  - Additional exploratory clinical endpoints: Cardiac imaging (echo and MRI), cardiac biomarkers (BNP, troponins), 6 minute walk, NYHC, and QOL

Status

- Ongoing; expanded target enrollment to 25
- Initial data late ’14
- Initiate open-label extension (OLE) in mid ’14
Alnylam FAC/SSA natural history study
- Retrospective study of ~400 FAC and SSA patients
- Data on multiple endpoints including death, hospitalization, NYHA class, 6-minute walk distance, cardiac biomarkers
- Analysis to be presented at future meeting

Phase 3 study design considerations
- Patient population
  » FAC alone or FAC plus SSA
  » Mild to moderate heart failure
- Study size
  » N=200-400
- Treatment regimen
  » Fixed dose administered SC weekly x 18-24 months
- Potential endpoints
  » Mortality
  » Hospitalization
  » 6-Minute Walk Distance
  » Composite of above
- Status
  » Ongoing regulatory discussions
  » On track to initiate study by end of year
Patisiran and ALN-TTRsc Programs
Summary

Patisiran (ALN-TTR02) for FAP
- Robust and durable TTR knockdown demonstrated in patients with multi-dose regimen in Phase 2
- Phase 2 OLE study ongoing with enrollment now completed
  » Safety profile encouraging to date with significant reduction in IRR rate using 70-minute microdosing infusion regimen
  » Sustained TTR knockdown of approximately 80% based on pre-dose samples with data available out to 168 days
  » Interim 6-month data on approximately 20 patients, including mNIS+7 and other clinical activity endpoints, to be presented at ANA meeting in October 2014
- APOLLO Phase 3 study in FAP ongoing

ALN-TTRsc for FAC
- Positive data from Phase 1 trial in healthy volunteers
  » Human POC for GalNAc-siRNA delivery approach
- Pilot Phase 2 trial in FAC and SSA patients ongoing
  » Phase 2 OLE to start in mid 2014
- Phase 3 trial expected to start in late 2014
Welcome
- Cynthia Clayton
  Vice President, Investor Relations and Corporate Communications

Introduction
- John Maraganore, Ph.D.
  Chief Executive Officer

Overview of TTR-Mediated Amyloidosis
- Philip N. Hawkins, M.B., B.S., Ph.D., FRCP, Professor of Medicine, National Amyloidosis Centre, University College London Medical School

Q&A Session
- with Professor Hawkins

Patisiran and ALN-TTRsc Programs
- Jared Gollob, M.D., Vice President, Clinical Research

Q&A Session
Upcoming RNAi Roundtables

Advances in Delivery of RNAi Therapeutics with Enhanced Stabilization Chemistry (ESC)-GalNAc-siRNA Conjugates

*Tuesday, July 22 @ 11:00 a.m. – 12:00 p.m. ET*
- Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development
- Moderator: Laurence Reid, Ph.D., Senior Vice President and Chief Business Officer

ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection

*Tuesday, July 29 @ 9:30 a.m. – 10:30 a.m. ET*
- Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
- Moderator: Laurence Reid, Ph.D., Senior Vice President and Chief Business Officer
- Guest Speaker: Graham Foster, Ph.D., FRCP, Professor of Hepatology at Queen Mary University of London

ALN-AT3 for the treatment of Hemophilia and Rare Bleeding Disorders

*Thursday, August 7 @ 9:30 a.m. – 10:30 a.m. ET*
- Akin Akinc, Ph.D., Director, Research
- Moderator: John Maraganore, Ph.D., Chief Executive Officer
- Guest Speaker: Flora Peyvandi, M.D., Ph.D., Head of the Department of Internal Medicine and Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Maggiore Hospital, University of Milan

ALN-CC5 for the treatment of Complement-Mediated Diseases

*Wednesday, August 13 @ 9:30 a.m. – 10:30 a.m. ET*
- Benny Sorenson, M.D., Ph.D., Medical Director, Clinical Development
- Moderator: Barry Greene, President and Chief Operating Officer
- Guest Speaker: Anita Hill, MBChB (Hons), MRCP, FRCPPath, Ph.D., Consultant Haematologist for Leeds Teaching Hospitals NHS Trust, UK, and Honorary Senior Lecturer at the University of Leeds

More roundtables to be scheduled in the coming weeks; visit www.alnylam.com/capella for updates
- ALN-AS1 for the treatment of hepatic porphyrias
- ALN-PCSsc for the treatment of hypercholesterolemia
- ALN-AAT for the treatment of AAT deficiency-associated liver disease
Speaker Biographies

John Maraganore, Ph.D.,
Chief Executive Officer, Alnylam Pharmaceuticals, Inc.
Since 2002, John Maraganore has served as the CEO and a Director of Alnylam. Prior to Alnylam he served as an officer and a member of the management team for Millennium Pharmaceuticals, Inc. As Senior Vice President, Strategic Product Development for Millennium, he was responsible for the company’s product franchises in oncology, cardiovascular, inflammatory, and metabolic diseases. He was previously Vice President, Strategic Planning and M&A and prior to that he was General Manager of Millennium BioTherapeutics, Inc., a former subsidiary of Millennium. Before Millennium he served as Director of Molecular Biology and Director of Market and Business Development at Biogen, Inc. At Biogen, Dr. Maraganore invented and led the discovery and development of Angiomax™ (bivalirudin for injection, formerly Hirulog™) currently marketed by The Medicines Company. Prior to Biogen, Dr. Maraganore was a scientist at ZymoGenetics, Inc., and the Upjohn Company. Dr. Maraganore received his M.S. and Ph.D. in biochemistry and molecular biology at the University of Chicago. Dr. Maraganore is a Director for Agios Pharmaceuticals and bluebird bio. He also serves as a Venture Partner with Third Rock Ventures. Dr. Maraganore is a member of the Biotechnology Industry Organization (BIO) Board and the BIO Executive Committee, and serves as the chair of the Emerging Company Section and as co-chair of the Regulatory Environment Committee.

Philip Hawkins, M.D., B.S., Ph.D., FRCP
Professor of Medicine, National Amyloidosis Centre, University College London Medical School, Royal Free Hospital
Philip Hawkins studied medicine at St. George’s Hospital Medical School, London where he qualified with double distinction in 1982. After training in general internal medicine at St. George’s, he undertook specialist training in rheumatology at the Royal Postgraduate Medical School, Hammersmith Hospital where he subsequently obtained his Ph.D. for studies on the pathogenesis, diagnosis and treatment of amyloidosis during a Medical Research Council Training Fellowship under the supervision of Professor Mark Pepys. He was appointed Senior Lecturer at the Royal Postgraduate Medical School in 1990, and was promoted to Reader in 1994. He has co-held a Medical Research Council Programme Grant with Mark Pepys since 1994, and received a Wellcome Trust University Award in 1997 for his work on amyloidosis. In 1999, he was appointed Professor of Medicine at University College London, and Clinical Director of the NHS National Amyloidosis Centre at the Royal Free Hospital, which was newly commissioned by the UK Department of Health to provide diagnostic and management services for the national amyloidosis caseload. He was awarded the Goulstonian Lectureship of the Royal College of Physicians in 1994 and was elected Fellow of the Academy of Medical Sciences in 2004. His clinical research program is focused on diagnosis, pathogenesis, monitoring and treatment of amyloidosis and inherited autoinflammatory diseases with an emphasis on translational, early phase and otherwise novel approaches. The cohort of amyloid patients referred to the National Amyloidosis Centre is now by far the largest and most diverse in the world.

Jared A. Gollob, M.D.,
Vice President, Clinical Research, Alnylam Pharmaceuticals, Inc.
Dr. Gollob joined Alnylam in 2007 and has been responsible for management of the clinical development organization, in addition to serving in a program leadership role for the company’s ALN-TTR programs. Prior to Alnylam, he was an Associate Professor of Medicine and Director of the Biologic Therapy Program at Duke University Medical Center, with a secondary appointment as Associate Professor of Immunology. He was also concurrently Head of Hematology/Oncology at the Duke VA Medical Center. Jared received his A.B. and M.D. from Columbia University, and then completed his clinical training at Massachusetts General Hospital, Harvard Medical School, and the Dana-Farber Cancer Institute. Jared is a board certified Medical Oncologist with interests in tumor biology and development of new treatments for renal cell carcinoma and melanoma. Previously, he has advised Chiron, Schering-Plough, Bayer, and Novartis on their oncology programs.
Thank You

www.alnylam.com