Please note this is an interactive PDF

Click these bubbles in order to access complete data slides

Click the safety bars in order to access additional safety data
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.
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
Key Features of Alnylam Investigational RNAi Therapeutics
Potential Attributes for Differentiation and Value

- **UNDRUGGABLE TARGETS**
- **MAXIMUM KNOCKDOWN (KD) EFFICACY**
  - Up to 99%
- **CLAMPED PHARMACODYNAMICS (PD)**
- **DURABILITY**
  - As few as 2 doses per year vs. 26 or more doses per year
- **SUBCUTANEOUS (SC) ROUTE**
- **ROOM TEMP**
Extensive Human Safety Experience*
Encouraging Results to Date

<table>
<thead>
<tr>
<th>Number of Programs</th>
<th>Number of Clinical Studies</th>
<th>Total Patients or Volunteers Dosed</th>
<th>Greatest Duration of Exposure</th>
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<td>&gt;10</td>
<td>&gt;20</td>
<td>&gt;1000</td>
<td>~36 months</td>
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</table>

Minimal platform related findings**
- Low incidence (2.2%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Low incidence (15.2%) of generally mild, transient injection site reactions (ISRs)

Revusiran safety events seen in high-risk, end-stage heart failure patients
- Program discontinued in October 2016; ongoing investigation to identify causality
- Revusiran exposure is 12-140 times greater than other pipeline programs

Favorable emerging profile for ESC-GalNAc platform compared with competing oligo platforms†
- No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*As of March 2017 – includes patients dosed in ongoing Phase 3 studies
**All reported data as of December 2016
†Based on reported study data as of March 2017 - not based on direct comparative studies
Alnylam Platform and R&D Strategy
Building a Pipeline of Potentially Transformative Medicines

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access
### Alnylam Clinical Development Pipeline

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

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

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<tr>
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<th><strong>HUMAN POC</strong>*</th>
<th><strong>EARLY STAGE</strong></th>
<th><strong>LATE STAGE</strong></th>
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*Proof of concept defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies.
Hereditary ATTR Amyloidosis

Patisiran
Hereditary ATTR (hATTR) Amyloidosis

**DESCRIPTION**

Orphan multi-system disease caused by mutant transthyretin (TTR) amyloid deposits in nerves, heart, GI tract, and other tissues

**PATIENT POPULATION***

~50,000 worldwide

Significant morbidity and fatal within 2-15 years from symptom onset

*Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012

Image based on Conceicao et al., J Peripher Nerv Syst, 2016;21:5–9
Patisiran for hATTR Amyloidosis
Potential for Disease Modification by Reducing Pathogenic Protein

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Established Endpoint
Neurological Impairment Score

Mutant Transthyretin (TTR) is disease-causing protein

Serum Biomarker

TTR

% Mean Serum TTR KD Relative to BL

Study Day

Placebo
0.01 mg/kg
0.05 mg/kg
0.15 mg/kg
0.30 mg/kg
0.50 mg/kg
Control siRNA 0.4 mg/kg

Motor strength/weakness

Reflexes (20)
Quantitative Sensory Testing (80)
Nerve Conduction Studies (10)

mNIS+7

Patisiran Final Phase 2 OLE Study Results*
Study in hATTR Amyloidosis Patients with Polyneuropathy

Mean max 93% TTR KD clamped thru 24 months

Mean -7.0 point change in mNIS+7 at 24 months

>70% patients show improvement in mNIS+7 scores

TTR KD correlated with improvement in mNIS+7 scores

PLANNED NEXT STEPS
APOLLO Phase 3 top-line in mid-2017
36-month Phase 2 OLE data in late 2017

Evidence for Potential Halting or Improvement of Neuropathy Progression

Safety: Generally well tolerated out to 25 months (N=27)
• 10 non-drug related SAEs in 7 patients
• Majority of AEs mild to moderate, including mild flushing (22.2%) and mild infusion-related reactions (22.2%)
• No significant lab findings; no drug-related discontinuations
• No evidence of thrombocytopenia, renal toxicity, or systemic inflammatory effects

*TTR KD correlated with improvement in mNIS+7 scores

Alnylam US/Can/Western Europe; Sanofi Genzyme ROW
*Final Phase 2 OLE results; Adams et al., AAN, April 2017

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Evidence for Potential Halting or Improvement of Neuropathy Progression

**Safety:** Generally well tolerated out to 25 months (N=27)
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**PLANNED NEXT STEPS**
APOLLO Phase 3 top-line in mid-2017
36-month Phase 2 OLE data in late 2017
Phase 3 Study Design

N=225

Patient Population
- hATTR with polyneuropathy: any TTR mutation, Stages 1 and 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

2:1 RANDOMIZATION

Patisiran IV q3W, 0.3 mg/kg

Placebo IV q3W

Primary Endpoint at 18 months
- mNIS+7

Key Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk

All completers eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE)

Enrollment completed; mid-2017 top-line data readout, supporting 2017 NDA/MAA if positive

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

**Revusiran*/Inotersen**

52 DOISES PER YEAR

**ALN-TTRsc02**

4 DOISES PER YEAR ANTICIPATED

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
Hemophilia and Rare Bleeding Disorders

Fitusiran
Hemophilia and Rare Bleeding Disorders

DESCRIPTION

Genetic deficiency resulting in inability to generate thrombin and stop bleeding

PATIENT POPULATION*

Hemophilia A and B

200,000 worldwide

~4,000 with inhibitors

Highest need is prophylaxis for inhibitor patients and to avoid inhibitor formation in all patients

Global need due to frequent IV infusions, ability to manufacture, and cold chain

Fitusiran for Hemophilia
Potential to Restore Hemostasis in Hemophilia

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Plasma Biomarkers
AT Lowering, Thrombin Generation

Established Endpoint
Annualized Bleeding Rate (ABR)

Photo courtesy of Guy Young, M.D.
Director, Hemostasis & Thrombosis Center at Children's Hospital Los Angeles and Professor of Pediatrics, USC Keck School of Medicine

Fitusiran Phase 1 results: Pasi et al., WFH, July 2016
Fitusiran Phase 1 and Phase 2 OLE Study Results*
Ongoing Study in Hemophilia A & B Patients, Including Inhibitors

**Safety in Phase 1 Part D and Phase 2 OLE:** Generally well tolerated, up to 14 months of dosing (N=32)
- No drug-related SAEs; all AEs mild or moderate in severity
  - Mild ISRs in 11 (34%) patients
- No thromboembolic events; no lab evidence for pathologic clot formation
- ALT increases >3x ULN observed in 6 (19%) patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - Reversible; all patients had medical history of HCV
- No instances of anti-drug antibody formation

**DURABILITY**

*Initial Evidence for Potential Restoration of Hemostasis in Severe Hemophilia A and B*

- Up to **mean 290% increase in thrombin generation**
- Median estimated ABR of **1** in non-inhibitor patients with median 5.7 months treatment
- Median estimated ABR of **0** in inhibitor patients

**PLANNED NEXT STEPS**
Start ATLAS Phase 3 studies in early 2017

*Clinical results as of Oct 6, 2016; Pasi et al., Ragni et al., ASH, December 2016*
**Fitusiran Phase 1 and Phase 2 OLE Study Results**

Ongoing Study in Hemophilia A & B Patients, Including Inhibitors

**DURABILITY**
- Monthly SC fixed dose regimen

**Safety in Phase 1 Part D and Phase 2 OLE:** Generally well tolerated, up to 14 months of dosing (N=32)
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    - Mild ISRs in 11 (34%) patients
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  - No instances of anti-drug antibody formation

**PLANNED NEXT STEPS**

Start ATLAS Phase 3 studies in early 2017

---

*Clinical results as of Oct 6, 2016; Pasi et al., Ragni et al., ASH, December 2016
Preliminary Fitusiran ATLAS Phase 3 Program*
Plan to Initiate in Early 2017

**ATLAS - INH**
- Adults and adolescents with hemophilia A or B with inhibitors
- On-demand
- N~50

2:1

- Fitusiran
- OR
- OD BPA

Endpoints:
- ABR
- Bypassing agent (BPA) consumption
- Quality of life
- Safety

**ATLAS - A/B**
- Adults and adolescents with hemophilia A or B without inhibitors
- On-demand
- N~100

2:1

- Fitusiran
- OR
- OD Factor

Endpoints:
- ABR
- Factor VIII or IX consumption
- Quality of life
- Safety

**ATLAS - PPX**
- Adults and adolescents with hemophilia A or B with or without inhibitors
- Prophylaxis
- N~100

- PPX Factor/BPA

- Fitusiran

Endpoints:
- ABR
- Factor/BPA consumption
- Quality of life
- Safety

All completers will be eligible for fitusiran treatment in Phase 3 OLE study (ATLAS-OLE)

*Preliminary plans subject to further diligence and health authority feedback*
Acute Hepatic Porphyrias

**DESCRIPTION**

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks

**PATIENT POPULATION**

~5,000 Patients with sporadic attacks in U.S./EU

~1,000 Patients with recurrent attacks in U.S./EU

Disease burden includes:
- Acute, Severe Abdominal Pain
- Frequent Hospitalizations
- Peripheral and Autonomic Neuropathy
- Neuropsychiatric Symptoms
- Chronic Pain

Predominantly female, commonly misdiagnosed

*ORPHANET; The Porphyria Consortium*
Givosiran for Acute Hepatic Porphyrias
Potential to Prevent Debilitating Attacks

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Potential Endpoints
- Annualized attack rate
- ALA and PBG levels

ALAS1 upstream of genetic defect

Up-regulation of ALAS1

Accumulation of toxic intermediates ALA and PBG

 Serum and Urinary Biomarkers ALA and PBG

Givosiran Interim Phase 1 results: Sardh et al., ASH, December 2016
DURABILITY

MONTHLY and possibly quarterly SC dose regimen

Initial Evidence for Clinical Activity in Recurrent Attack Porphyria Patients

Safety: Generally well tolerated (N=8)
• No discontinuations due to AEs
• Majority of AEs mild-moderate in severity
• No clinically significant changes in vital signs, EKG, clinical laboratory parameters or physical examination
• After data transfer date, one patient in blinded cohort experienced SAE of acute pancreatitis complicated by pulmonary embolism resulting in death, considered unlikely related to givosiran or placebo

PLANNED NEXT STEPS

Additional data from Phase 1 in mid-2017
Start Phase 3 in late 2017

Givosiran Interim Phase 1 Study Results*
Ongoing Randomized, Double-Blind, Placebo-Controlled Study in Recurrent Attack Porphyria Patients

Up to 86% lowering of ALA, 95% lowering of PBG in ASHE subjects
Mean Decrease in Annualized Attack Rate 74%
Mean Decrease in Annualized Hemin Use 75%
Maximum Attack Free Interval 10.5x Relative to Run-In
Givosiran Interim Phase 1 Study Results*
Ongoing Randomized, Double-Blind, Placebo-Controlled Study in Recurrent Attack Porphyria Patients

**Safety:** Generally well tolerated (N=8)
- No discontinuations due to AEs
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**DURABILITY**
- Monthly and possibly quarterly SC dose regimen

**EMA PRIME Designation**

**Initial Evidence for Clinical Activity in Recurrent Attack Porphyria Patients**

**Cohort 1:**
- Decrease in Annualized Attack Rate

- Givosiran treated

- % Decrease in Annualized Attack Rate
  - PBO
  - Pt 1: 23%
  - Pt 2: 63%
  - Pt 3: 69%
  - Mean: 74%

**Run-in**

**Treatment**

**PLANNED NEXT STEPS**
- Additional data from Phase 1 in mid-2017
- Start Phase 3 in late 2017

*Interim Phase 1 study results as of Nov 7, 2016; Sardh et al., ASH, December 2016
Potential Phase 3 Study Design for Givosiran*
Initial Focus on Prophylaxis for Recurrent Attack Acute Intermittent Porphyria (AIP) Patients

Patient Population
- Biochemical and genetic diagnosis of AIP
- ≥ 4 attacks per yr if not on hemin prophylaxis
- If on hemin prophylaxis, willing to stop for study duration
- N = 50-100

Endpoints
- Change in annualized attack rate compared to baseline
- ALA, PBG and ALAS1 levels
- Hemin usage
- Hospitalization
- EQ-5D-5L QoL
- Safety and tolerability

All completers will be eligible for givosiran treatment in Phase 3 OLE study

*Preliminary plans subject to further diligence and health authority feedback
Other Programs to Watch
Other Programs to Watch

**Inclisiran** for Hypercholesterolemia*

- **53%** mean LDL-C lowering at Day 180 after two quarterly doses

**ALN-CC5** for Complement-Mediated Diseases

- **67%** reduction in eculizumab dose in PNH patients

**ALN-GO1** for Primary Hyperoxaluria 1 (PH1)

- **Up to 8-fold** increase in plasma glycolate in healthy volunteers

**ALN-HBV** for Hepatitis B Virus (HBV) Infection

- **Pre-clinical results:** up to **3.6 log\(_{10}\)** HBsAg reduction

---

*The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful

1. Safety (N=501):
   - No drug-related SAEs, no discontinuations due to AEs
   - Two patient deaths due to MI and stroke, both unrelated to study drug
   - No LFT elevations related to study drug
   - Majority of AEs mild or moderate in severity

2. Safety (N=6):
   - No SAEs, no discontinuations due to AEs
   - 1 AE of hemolysis in setting of URI; moderate in severity and considered unrelated to study drug
   - 1 AE of asymptomatic, transient grade 3 elevation of LFTs; considered possibly related

3. Safety (N=501):
   - No drug-related SAEs, no discontinuations due to AEs
   - Two patient deaths due to MI and stroke, both unrelated to study drug
   - No LFT elevations related to study drug
   - Majority of AEs mild or moderate in severity

4. Safety (N=32):
   - No SAEs, no discontinuations due to AEs
   - All AEs mild or moderate, with exception of one subject with transient, asymptomatic CPK elevation considered unrelated to study drug

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**PLANNED NEXT STEPS FOR INCLISIRAN:**

Start Phase 3 study in mid-2017

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1. ORION-1 Phase 2 Study; Ray *et al.*, ACC, Mar 2017
2. Phase 1/2 Study; Hill *et al.*, ASH, Dec 2016
3. Phase 1/2 Study; Milliner *et al.*, IPNA, Sep 2016
4. Mouse model; Sepp-Lorenzino *et al.*, Liver Meeting, Nov 2015
Guidance and Goals
3 STArs
3 Marketed Products
10 Clinical Programs
4 Late Stage Programs
Transition to Potential Commercialization
Planned Rapid Launch Succession

- **Givosiran** ~2020
- **Fitusiran** ~2019
- **Patisiran** ~2018

**Manufacturing build-out to ensure consistent drug supply underway**
- Alewife facility fully operational and ready for patisiran launch
- Norton drug substance facility expected to be commercially operational in 2020

**Building commercial capabilities to prepare for upcoming product launches**
- Patisiran in US, Canada, and Western Europe
- Fitusiran co-develop/co-commercialize in US, Canada, and Western Europe
- Givosiran globally
## Alnylam 2017 Pipeline Goals

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

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<th>Early</th>
<th>Mid</th>
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<td>ADDITIONAL CLINICAL PROGRAMS</td>
<td>Continue to advance early/mid-stage pipeline; Present clinical data</td>
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**Based on The Medicines Company guidance as of January 2017**

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**33**
Financial Summary and Guidance

2017 Q1 Financial Results

• Cash $962.2M
  ◦ Includes $150.0M in restricted investments
• GAAP Revenues $19.0M
• Total GAAP Operating Expenses $125.5M
  ◦ Research and Development Expense $87.0M
  ◦ General and Administrative Expense $38.5M
• GAAP Net Loss of $107.3M
• Shares Outstanding 86.1M

2017 Guidance

• Year-end cash >$700M
  ◦ Includes $150.0M of restricted investments
Thank You
## ALT Elevations in Clinical Programs

**Data Transfer as of November 2016**

<table>
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<th>LNP-siRNA Study</th>
<th>Study Population</th>
<th>Subjects Treated</th>
<th>Max Duration Treatment</th>
<th>ALT &gt;3x ULN</th>
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<tr>
<td>Patisiran Phase 1</td>
<td>NHV</td>
<td>22</td>
<td>Single dose</td>
<td>0</td>
</tr>
<tr>
<td>Patisiran Phase 2</td>
<td>hATTR polyneuropathy</td>
<td>29</td>
<td>Up to 4 wks</td>
<td>0</td>
</tr>
<tr>
<td>Patisiran Phase 2 OLE</td>
<td>hATTR polyneuropathy</td>
<td>27^</td>
<td>Up to 25mos</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GalNAc-siRNA Study</th>
<th>Study Population</th>
<th>Subjects Treated</th>
<th>Max Duration Treatment</th>
<th>ALT &gt;3x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revisiran Phase 1</td>
<td>NHV</td>
<td>66</td>
<td>6 wks</td>
<td>1</td>
</tr>
<tr>
<td>Revisiran Phase 2</td>
<td>ATTR cardiomyopathy</td>
<td>26</td>
<td>6 wks</td>
<td>1</td>
</tr>
<tr>
<td>Revisiran Phase 2 OLE</td>
<td>ATTR cardiomyopathy</td>
<td>25^</td>
<td>Up to 18 mos</td>
<td>0</td>
</tr>
<tr>
<td>Fitusiran Phase 1, Part A</td>
<td>NHV</td>
<td>3</td>
<td>Single dose</td>
<td>0</td>
</tr>
<tr>
<td>Fitusiran Phase 1, Parts B &amp; C</td>
<td>Severe and moderate HA and HB w/o inhibitor</td>
<td>25</td>
<td>Up to 3 mos</td>
<td>1</td>
</tr>
<tr>
<td>Fitusiran Phase 1 D</td>
<td>HA and HB w/ inhibitor</td>
<td>16</td>
<td>Up to 3 mos</td>
<td>3</td>
</tr>
<tr>
<td>Fitusiran Phase 2 (OLE)</td>
<td>HA and HB w/ and w/o inhibitor</td>
<td>23^</td>
<td>Up to 14 mos</td>
<td>3</td>
</tr>
<tr>
<td>ALN-CC5 Phase 1, Parts A &amp; B</td>
<td>NHV</td>
<td>33</td>
<td>Up to 3 wks</td>
<td>0</td>
</tr>
<tr>
<td>ALN-CC5 Phase 1, Part C</td>
<td>PNH</td>
<td>6</td>
<td>Up to 6 mos</td>
<td>1</td>
</tr>
<tr>
<td>Inclisiran Phase 1</td>
<td>NHV w/ elevated LDL-C</td>
<td>51</td>
<td>Up to 2 mos</td>
<td>1</td>
</tr>
<tr>
<td>Inclisiran Phase 2</td>
<td>High Risk CVD; elevated LDL</td>
<td>370</td>
<td>Single dose</td>
<td>1</td>
</tr>
<tr>
<td>Givosiran Phase 1, Parts A &amp; B</td>
<td>ASHE</td>
<td>23</td>
<td>Up to 2 mos</td>
<td>1</td>
</tr>
<tr>
<td>Givosiran Phase 1, Part C</td>
<td>AIP</td>
<td>11</td>
<td>Up to 6 mos</td>
<td>1</td>
</tr>
<tr>
<td>ALN-AAT Phase 1/2, Parts A &amp; B</td>
<td>NHV</td>
<td>19</td>
<td>Up to 4 mos</td>
<td>1</td>
</tr>
<tr>
<td>ALN-GO1 Part A</td>
<td>NHV</td>
<td>24</td>
<td>Single dose</td>
<td>0</td>
</tr>
</tbody>
</table>

ALT=alanine aminotransferase; ULN=upper limit of normal

^Subjects treated with drug in previous study
ISRs in GalNAc Conjugate Clinical Programs
Data Transfer as of November 2016

Most ISRs Reported as Mild and Transient

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects Treated</th>
<th>Max Duration Treatment</th>
<th>ISR N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revusiran Phase 1</td>
<td>66</td>
<td>6 wks</td>
<td>32 (48.5%)</td>
</tr>
<tr>
<td>Revusiran Phase 2</td>
<td>26</td>
<td>6 wks</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Revusiran Phase 2 OLE</td>
<td>25</td>
<td>Up to 18 mos</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Fitusiran Phase 1, Part A</td>
<td>3</td>
<td>Single dose</td>
<td>0</td>
</tr>
<tr>
<td>Fitusiran Phase 1, Parts B, C &amp; D</td>
<td>41</td>
<td>Up to 3 mos</td>
<td>14 (34%)</td>
</tr>
<tr>
<td>Fitusiran Phase 2 (OLE)</td>
<td>23</td>
<td>Up to 14 mos</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>ALN-CC5 Phase 1, Parts A &amp; B</td>
<td>33</td>
<td>Up to 3 wks</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>ALN-CC5 Phase 1, Part C</td>
<td>6</td>
<td>Up to 6 mos</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Inclisiran Phase 1</td>
<td>51</td>
<td>Up to 2 mos</td>
<td>4 (7.8%)</td>
</tr>
<tr>
<td>Inclisiran Phase 2</td>
<td>370</td>
<td>Single dose</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td>Givosiran Phase 1, Parts A &amp; B</td>
<td>23</td>
<td>Up to 2 mos</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Givosiran Phase 1, Part C</td>
<td>11</td>
<td>Up to 6 mos</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>ALN-AAT Phase 1/2, Parts A &amp; B</td>
<td>19</td>
<td>Up to 4 mos</td>
<td>0</td>
</tr>
<tr>
<td>ALN-G01 Part A</td>
<td>24</td>
<td>Single dose</td>
<td>4 (19%)</td>
</tr>
</tbody>
</table>

ISR = injection site reaction, IS = injection site, d/c = discontinuation

^Subjects treated with drug in previous study
Exposure Levels with Revusiran Significantly Higher than other GalNAc Conjugate Programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revusiran 500mg qW</td>
<td>1</td>
</tr>
<tr>
<td>Patisiran 0.3mg/kg q3W</td>
<td>70</td>
</tr>
<tr>
<td>Fitusiran 80mg qM</td>
<td>30</td>
</tr>
<tr>
<td>Givosiran 5.0mg/kg q3M</td>
<td>18</td>
</tr>
<tr>
<td>Givosiran 2.5mg/kg qM</td>
<td>12</td>
</tr>
<tr>
<td>Inclisiran 300mg q6M</td>
<td>48</td>
</tr>
<tr>
<td>Inclisiran 300mg q3M</td>
<td>24</td>
</tr>
<tr>
<td>ALN-CC5 600mg q3M</td>
<td>12</td>
</tr>
<tr>
<td>ALN-TTRsc02 50mg q3M</td>
<td>140</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
Serum TTR Knockdown

- Mean serum TTR knockdown: 82%
- Mean maximal serum TTR knockdown: 93%
- Maximal individual patient post-dose knockdown: 97%
- Similar TTR knockdown in patients on patisiran alone or on patisiran + TTR tetramer stabilizers

SEM: Standard Error of the Mean
Adams et al., AAN, April 2017
Patisiran Phase 2 OLE Final Study Results
Change in mNIS+7 Over 24 Months

<table>
<thead>
<tr>
<th>mNIS+7 component</th>
<th>Change from Baseline to Month 24 (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>Total+</td>
<td>-7.0 (2.0)</td>
</tr>
<tr>
<td>NIS-weakness</td>
<td>1.2 (1.4)</td>
</tr>
<tr>
<td>NIS-reflexes</td>
<td>-0.5 (0.5)</td>
</tr>
<tr>
<td>QST</td>
<td>-7.4 (2.0)</td>
</tr>
<tr>
<td>NCS Σ5</td>
<td>-0.2 (0.2)</td>
</tr>
<tr>
<td>Postural BP</td>
<td>-0.1 (0.1)</td>
</tr>
</tbody>
</table>

SEM: Standard Error of the Mean
+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., AAN, April 2017
Patisiran Phase 2 OLE Final Study Results
Change 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

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

- 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 et al., AAN, April 2017; SEM: Standard Error of the Mean; *One patient discontinued prior to the Month 24 assessment and is included in the denominator.
Patisiran Phase 2 OLE Preliminary Study Results*
Correlation of TTR Knockdown with ΔmNIS+7

Note: three patients had missing D17 TTR: one was replaced by D7 and two replaced by D84.

† Percent (%) TTR knockdown from baseline at Day 17 post-first dose of patisiran

*Coelho et al., ISA, July 2016; Data as of 12May2016
ALN-TTRsc02 Phase 1 Preliminary Study Results*
SAD Safety and Tolerability

**TTRsc02 appears generally well tolerated in healthy volunteers (N=48)**

- No SAEs and no discontinuations due to AEs
- All AEs mild or moderate in severity
- 9 AEs in 5 subjects considered possibly related to treatment; all mild
  - Events included injection site erythema, injection site pain, pruritus, cough, nausea, fatigue and abdominal pain
- ISRs reported in 2 subjects – symptoms mild and transient
- No clinically significant changes in physical exams or clinical laboratory parameters (e.g., LFTs)

*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

Potent, Dose-Dependent, Highly Durable TTR Knockdown

Max TTR knockdown of 98.4% with mean max of 97.1 ± 0.5%
Most potent Alnylam investigational RNAi therapeutic to date

*Data cut-off 26Oct2016; reported at Alnylam R&D Day in December 2016
Interim Fitusiran Phase 1 & Phase 2 OLE Study Results* Safety/Tolerability† in Patients with and without Inhibitors

Up to 14 months continuous administration of fitusiran at 50-80 mg qM

- No discontinuations due to AEs or drug-related SAEs
- No thromboembolic events
- All AEs mild or moderate in severity
  - Injection site reactions (ISRs) reported in 11/32 patients (34%)
  - ISRs all mild; mostly pain and/or erythema at injection site
- ALT increases >3x ULN observed in 6 patients
  - 3 patients with inhibitors, 3 without inhibitors
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - All patients had medical history of HCV
- Non-clinically significant D-dimer increases observed in some patients with inhibitors; none associated with laboratory signs of pathological clot formation (changes in platelets, fibrinogen, and/or PT/INR)
- No clinically significant changes in other laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- All bleed events successfully managed with replacement factor or bypassing agents (rFVIIa, aPCC)
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part C

AT lowering after monthly dosing in patients with hemophilia A and B

*Data transfer: 30Jun2016
Pasi et al., WFH, July 2016
Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles

- Mean thrombin generation increase of 289% relative to baseline at AT lowering >75% (p<0.001†)

*Data transfer 30Jun2016; Pasi et al., WFH, July 2016
†%Change in Peak TG: p<0.001 by Mann-Whitney test, when compared with AT3 lowering than <25% group
Interim Fitusiran Phase 1 Study Results*
AT Lowering, Parts A, B & C

Dose-dependent AT lowering
- Mean maximal AT lowering of $87 \pm 1\%$ at 80 mg fixed dose
Interim Fitusiran Phase 2 OLE Study Results*
Summary of Median ABRs in Patients without Inhibitors

- Median ABR, Observation period = 1
  - Patients reporting no bleeds: 8/16 (50%)
  - Patients reporting no spontaneous bleeds (AsBR = 0): 11/16 (69%)
- Median duration in observation period = 170 days (5.7 months)

*Data transfer 30Jun2016; Pasi et al., WFH, July 2016
†%Change in Peak TG: p<0.001 by Mann-Whitney test, when compared with AT3 lowering than <25% group
Interim Fitusiran Phase 1 (Part D) and OLE Study Results*

Summary of Median ABRs

All Inhibitor Patients

<table>
<thead>
<tr>
<th></th>
<th>Pre-Study</th>
<th>Onset</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>31</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Observation Period, 50 mg vs 80 mg

<table>
<thead>
<tr>
<th></th>
<th>50 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>AsBR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Median ABR, Pre-study period: 31
- Median ABR, Observation period: 0
  - Patients reporting no bleeds: 9/16 (56%)
  - Patients report no spontaneous bleeds (AsBR = 0): 11/16 (69%)
- 50 mg: Median ABR = 8, median AsBR = 5
  - Patients reporting no bleeds: 7/10 (70%)
  - Patients report no spontaneous bleeds (AsBR = 0): 9/10 (90%)
- 80 mg: Median ABR = 0, median AsBR = 0
  - Patients reporting no bleeds: 7/10 (70%)
  - Patients report no spontaneous bleeds (AsBR = 0): 9/10 (90%)

*Data cut-off 06Oct2016; Pasi et al., ASH, December 2016
OLE, open-label extension; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleed rate
Updated Givosiran Phase 1 (Parts A,B) Study Results*

**Parts A and B Study Summary**

**Study Status**
- Dosing is complete (n=23†), patients in follow up to monitor ALA/PBG recovery

**Results**
- Givosiran was generally well tolerated
  - No discontinuations or serious adverse events related to study drug
  - No clinically significant changes in physical examination or laboratory tests
    - 2 mild and transient injection site reactions
- Givosiran led to rapid, dose-dependent, and prolonged urinary PBG and ALA lowering after single (SAD) or multiple doses (MAD) (data not shown)

*S*Data transfer 07Nov2016; Sardh *et al.*, ASH, December 2016

SAD, Single-Ascending Dose; †5 subjects had >1 treatment assignment: 2 subjects repeated Part A; 3 subjects enrolled in Parts A and B
Interim Givosiran Phase 1 (Part C) Study Results*
Safety and Tolerability in AIP Patients with Recurrent Attacks

No drug-related SAEs in Cohorts 1-4

Cohorts 1 and 2
- No discontinuations due to AEs
- During treatment period, all randomized patients (8/8) reported at least 1 non-porphyria attack AE
  - Majority of AEs mild or moderate in severity
  - AEs reported in ≥3 patients were abdominal pain, nausea, vomiting, nasopharyngitis, and headache (3 patients each)
  - Possibly or definitely related AEs reported in ≥ 2 cases were injection site reaction and myalgia; all mild
  - No clinically significant changes in vital signs, EKG, clinical laboratory parameters or physical examination

Cohort 3
- After data transfer date, one patient experienced an SAE of acute pancreatitis complicated by pulmonary embolism resulting in death
  - Event assessed as unlikely related to givosiran or placebo by investigator due to presence of gallbladder sludge
  - Safety Review Committee in agreement with assessment

*Data transfer 07Nov2016; Sardh et al., ASH, December 2016
Updated Givosiran Phase 1 (Parts A,B) Study Results*

Parts A and B Study Summary

Study Status
- Dosing is complete (n=23†), patients in follow up to monitor ALA/PBG recovery

Results
- Givosiran was generally well tolerated
  - No discontinuations or serious adverse events related to study drug
  - No clinically significant changes in physical examination or laboratory tests
    - 2 mild and transient injection site reactions
- Givosiran led to rapid, dose-dependent, and prolonged urinary PBG and ALA lowering after single (SAD) or multiple doses (MAD) (data not shown)

*SData transfer 07Nov2016; Sardh et al., ASH, December 2016
SAD, Single-Ascending Dose; †5 subjects had >1 treatment assignment: 2 subjects repeated Part A; 3 subjects enrolled in Parts A and B
Interim Givosiran Phase 1 (Part C) Study Results*
Summary of Clinical Activity Data Cohorts 1 and 2 in AIP Patients

Givosiran Treated Period Relative to Run-in

- Cohort 1 is through D168, Cohort 2 through D84 of the treatment phase
- Cohort 2 data is aggregated (including placebo) to protect blind
ORION-1 Phase 2 Study of Inclisiran*

Safety Summary

Generally safe and well tolerated (N=501)

- Overall incidence of treatment emergent adverse events (TEAE) 76% both in patients randomized to placebo and in patients randomized to inclisiran
  - No significant differences in TEAEs between inclisiran doses
- Two deaths on study, both unrelated to study drug
  - One fatal MI in patient w/ prior MI and unstable angina >3 months after single inclisiran dose
  - One death in patient w/ complications of aortic aneurysm surgery including sepsis and stroke
- No elevations of liver enzymes related to study drug
  - One SAE of elevated ALT and AST attributed to increased dose of statin therapy which resolved upon lowering to original dose
- No thrombocytopenia, neuropathy, or changes in renal function
- Injection site reactions (ISRs) infrequent and transient
  - Observed in 5.1% of patients
  - Mild or moderate

*Phase 2 study results; Ray et al., ACC, March 2017

Inclisiran also known as “ALN-PCSsc” and “PCSK9si”

The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful.
Robust and Sustained LDL-C Reductions with Inclisiran*
Results to Day 270 Following Two Doses

*Phase 2 study results; Ray et al., ACC, March 2017
Inclisiran also known as “ALN-PCSsc” and “PCSK9si”
The Medicines Company is leading and funding development of inclisiran from Phase 2 onward and will commercialize the program, if successful.
Interim ALN-CC5 Phase 1/2 (Part C) Study Results*
Updated Safety and Tolerability Summary

ALN-CC5 generally well tolerated in patients with PNH after multiple doses
• No SAEs or discontinuations due to AEs
• All 6 patients reported at least one AE
  ◦ Majority of AEs mild to moderate in severity
  ◦ 1 AE reported as hemolysis in setting of upper respiratory tract infection; moderate in severity and considered unrelated to study drug
  ◦ 1 possibly related reported severe AE reported as hepatotoxicity (previously reported1)
    – Asymptomatic, transient grade 3 elevation of ALT and AST without increase in total bilirubin
    – Under ongoing ALN-CC5 PD effects, liver enzyme levels returned to baseline on D182 until end of study (D280)
  ◦ AEs reported in ≥ 2 patients: Fatigue, oropharyngeal pain (N=2 each)
  ◦ 1 additional patient reported at least one possibly or definitely related AE
    – All AEs were mild injection site reactions (ISRs)
      » Discomfort; erythema and pain (N=1)
• No other clinically significant changes in vital signs, EKG, physical exams or clinical laboratories (hematology, biochemistry, coagulation and urinalysis)

*Data transfer 13 October 2016; Hill et al., ASH, December 2016
SAE, serious adverse event; AE, adverse event
Effective Control of Intravascular Hemolysis with Spared Ecu

During ALN-CC5-mediated knockdown of serum C5, investigators administered Ecu at a spared dose and frequency and monitored patients clinically

- Ecu naïve patients: LDH < 1.5 x ULN achieved and maintained with 600 mg Ecu q4W‡
- Background Ecu patients: LDH < 1.5 x ULN maintained with 900 mg Ecu q4W
  - In patient with prior inadequate Ecu response, LDH normalization generally maintained with 900 mg q4W
- Dosing every 4 weeks (q4W) of 600 or 900 mg Ecu represents 33% or 50% of maintenance dose, respectively

*Data as of 13 October 2016; Hill et al., ASH, December 2016
‡1.5x ULN values for LDH: 321-338 IU/L
*Patient 0081 experienced hemolysis on D98 due to viral URI, received 600 mg Ecu on D102 and q4W dosing resumed on D112
ALN-GO1 Phase 1/2 Interim Study Results*
Safety: Part A (Healthy Volunteers)

ALN-GO1 was generally well-tolerated in healthy volunteers

No drug-related SAEs or discontinuations due to AEs

Total of 61 AEs reported in 5 placebo and 21 ALN-GO1 treated healthy volunteers

- AEs occurring in greater than 10% of ALN-GO1 treated subjects included nasopharyngitis (N=6), headache (N=5), and transient injection site pain (N=4).
  - All AEs were mild to moderate with the exception of one healthy volunteer in the lowest dose cohort who had transient, asymptomatic CPK elevation which was unrelated to study drug.

No clinically significant changes in vital signs or EKG

*Data transfer 17 August 2016; Milliner et al., IPNA, September 2016
ALN-GO1 Phase 1/2 Interim Study Results*
Plasma Glycolate: Part A (Healthy Volunteers)

- A dose-dependent increase in plasma glycolate levels is observed, with earliest onset of activity at higher doses evident by Day 29 post dose and sustained until Day 85
- The lowest dose with appreciable glycolate increase is 1 mg/kg

*Treatment Group:
- Placebo (N=8)
- ALN-GO1 0.3 mg/kg (N=6)
- ALN-GO1 1.0 mg/kg (N=6)
- ALN-GO1 3.0 mg/kg (N=6)
- ALN-GO1 6.0 mg/kg (N=6)

Mean [± SEM] Plasma Glycolate (nmol/mL)

Days from single dose

Normal range: <14 nmol/mL
ALN-HBV Development Candidate (DC)
Potent ESC-GalNAc Conjugate for SC Administration

**Potent, multi-log HBsAg knockdown in murine model**
- Mouse model with AAV-HBV vector
- ALN-HBV DC achieves potent and highly durable knockdown of HBsAg
  - Up to $3.6 \log_{10}$ HBsAg reduction
  - Single SC dose achieves $>2 \log_{10}$ HBsAg reduction lasting $>30$ days
  - Multiple SC doses achieve $>2 \log_{10}$ HBsAg reduction lasting $>90$ days

---

**Single SC Dose**

**Multiple SC Doses**

*Pre-dose HBsAg titer range ~10-500 ng/mL*