Delivering on RNAi Therapeutics: Patisiran and Beyond

TIDES, May 8, 2018
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 report on Form 10-K 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
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now entering commercial stages
Addressing Delivery Challenge
Alnylam Platforms for Functional siRNA Delivery to Target Tissue

**Lipid Nanoparticles (LNPs)**
- Multi-component lipid formulation (~100 nm in size)
- Encapsulated siRNA
- Highly efficient for targeted delivery to liver
- Administered intravenously (IV)
- Clinically validated

**GalNAc-siRNA Conjugates**
- Single chemical entity
- GalNAc ligand conjugated to extensively modified siRNA
- Targeted delivery to liver
- Administered subcutaneously (SC)
- Clinically validated

Complementary Approaches for Efficient siRNA Delivery to Liver
Alnylam 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):

<table>
<thead>
<tr>
<th>STArS</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Medicines</td>
<td>Cardio-Metabolic Diseases</td>
<td>Hepatic Infectious Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th><strong>HUMAN POC</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
<th><strong>BREAKTHROUGH DESIGNATION</strong></th>
<th><strong>EARLY STAGE</strong> <em>(IND or CTA Filed-Phase 2)</em></th>
<th><strong>LATE STAGE</strong> <em>(Phase 2-Phase 3)</em></th>
<th><strong>REGISTRATION/COMMERCIAL</strong>&lt;sup&gt;2&lt;/sup&gt;</th>
<th><strong>COMMERCIAL RIGHTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patisiran</td>
<td>Hereditary ATTR Amyloidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>Givosiran</td>
<td>Acute Hepatic Porphyrias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>Fitusiran</td>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15-30% Royalties</td>
</tr>
<tr>
<td>Inclisiran</td>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Milestones &amp; up to 20% Royalties</td>
</tr>
<tr>
<td>ALN-TTRsc02</td>
<td>ATTR Amyloidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Primary Hyperoxaluria Type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>Cemdisiran</td>
<td>Complement-Mediated Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global</td>
</tr>
</tbody>
</table>

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

<sup>2</sup>Includes marketing application submissions
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>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>&gt;25</td>
<td>&gt;1200</td>
<td>&gt;48 months</td>
</tr>
</tbody>
</table>

Minimal platform related findings*
- Low incidence (2.9%) of generally mild, asymptomatic, reversible LFT increases >3x ULN
- Injection site reactions (24%) generally mild, transient and rarely led to discontinuation
  - No events of ulceration, necrosis or tissue damage
- One report of anaphylaxis (<0.05%) in patient with prior history of atopy**
  - No anti-drug antibodies (ADA) detected against GalNAc-siRNA

Revusiran program discontinued in October 2016
- Extensive evaluation showed no clear reason for mortality imbalance
- While possible that imbalance was a chance finding, role for revusiran cannot be excluded
- 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

---

*Experience as of December 2017 – Data estimated based on available safety data
** Givosiran OLE study, reported April 2018
† Not based on direct comparative studies
Agenda

• RNAi Therapeutics for hATTR Amyloidosis

• RNAi Therapeutics for Other Rare and Common Diseases

• New Frontiers for RNAi Therapeutics
Hereditary ATTR (hATTR) Amyloidosis
Patisiran and ALN-TTRsc02

Description
Mutations in TTR gene lead to deposition of misfolded protein as amyloid, causing multi-system disease manifestations\(^1\)

**Significant morbidity and fatal within**

**2-15**

years from symptom onset

<table>
<thead>
<tr>
<th>Patient Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>~50,000 worldwide</td>
</tr>
</tbody>
</table>


\(^*\)Ando *et al.*, *Orphanet J Rare Dis*, 2013; Ruberg *et al.*, *Circulation*, 2012
TTR Knockdown for hATTR Amyloidosis

Patisiran Therapeutic Hypothesis

Production of mutant and wild type TTR

Unstable circulating TTR tetramers reduced

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

Neuropathy, cardiomyopathy Stabilization or improvement
**APOLLO Phase 3 Study Design**

Randomized, Double-Blind, Placebo-Controlled Study in hATTR Amyloidosis Patients with Polyneuropathy

**Patient Population**
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neurological impairment score (NIS) of 5-130
- Includes patients with NYHA Class 1 or 2 cardiac disease

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

**Secondary Endpoints**
- Norfolk QOL-DN
- NIS-weakness
- Activities of daily living (R-ODS)
- 10-meter walk
- mBMI
- Autonomic function (COMPASS-31)

**Select Exploratory Endpoints**
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Skin biopsies for nerve fiber density and amyloid

*To reduce likelihood of infusion-related reactions, patients received following premedication or equivalent at least 60 min before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers.

99% of patients who completed APOLLO study enrolled in Global OLE study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261
Adams D, et al. BMC Neurology 2017
Phase 3 Study Results

Serum TTR Knockdown

87.8% mean max serum TTR knockdown from baseline for patisiran over 18 months

<table>
<thead>
<tr>
<th>TTR Change</th>
<th>Change from Baseline at 9 Months</th>
<th>Change from Baseline at 18 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>1.5% (4.47)</td>
<td>82.6% (1.36)</td>
</tr>
</tbody>
</table>

SEM, standard error of the mean
Phase 3 Study Results

Patisiran Met Primary and all Secondary Endpoints

At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*

At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

All secondary endpoints encompassing QOL, walk speed, activities of daily living and autonomic dysfunction met

Adams et al., EU-ATTR Meeting, Nov 2017

*Improvement defined as patients with <0 point increase from baseline to 18 months
**APOLLO Phase 3 Study Results**

Patisiran Met Key Exploratory Endpoints in Cardiac Subpopulation*

**Biomarker**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Placebo</th>
<th>Patisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ΔNT-proBNP from baseline at 18 mos (ng/L)</td>
<td><strong>p=7.74 x 10^{-8}</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Echocardiographic**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Patisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Wall Thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ΔLV wall thickness from baseline at 18 mos (cm)</td>
<td><strong>p=0.0173</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Patisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal Strain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ΔLongitudinal strain from baseline at 18 mos (%)</td>
<td><strong>p=0.0154</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Functional**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Patisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>10MWT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Δ10-MWT gait speed from baseline at 18 mos (m/sec)</td>
<td><strong>p=7.42 x 10^{-9}</strong></td>
<td></td>
</tr>
</tbody>
</table>

Adams et al., EU-ATTR Meeting, Nov 2017

*Cardiac subpopulation: patients with pre-existing cardiac amyloid involvement without confounding medical conditions (i.e., patients with baseline LV wall thickness ≥1.3 cm and no aortic valve disease or hypertension in medical history)

**p-values are nominal
APOLLO Phase 3 Study Results
Recurrent Hospitalization and Death Events by Treatment Arm (Post-Hoc Analysis)*

Mean Cumulative Function: average number of events per patient by a certain time

Composite Rate of All-Cause Hospitalization and Mortality

- Approximately 50% reduction in event rate**

Composite Rate of Cardiac Hospitalization and All-Cause Mortality

- Approximately 45% reduction in event rate†

Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization.

Adams et al., AAN Meeting, Apr 2018
*mITT population
**For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]
†For cardiac hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.54 [0.25, 1.16]; Anderson-Gill hazard ratio HR) 0.54 [0.28, 1.01]
AE, adverse event; CRF, case report forms; SAEs, serious adverse events; SOC, system organ class
Phase 3 Study Results

Encouraging Safety & Tolerability Profile

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug

- Lower percent deaths in patisiran vs. placebo treatment groups
- Causes (e.g., cardiovascular, infection) consistent with NH

Majority of AEs mild or moderate in severity

- Most common AEs more frequently observed in patisiran arm vs. placebo included peripheral edema (29.7% vs. 22.1%) and infusion-related reactions (18.9% vs. 9.1%)
  - Both AEs decreased over time; IRRs led to discontinuation in only 1 patient (0.7%); peripheral edema led to no discontinuations

Additional notable safety findings

- Encouraging safety & tolerability in cardiac subpopulation
  - Lower percent deaths in patisiran (5.6%) vs. placebo (11.1%) treatment groups
- No safety signals related to steroid pre-medication regimen or TTR KD
- No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

<table>
<thead>
<tr>
<th>Type of Adverse Event, Number of patients (%)</th>
<th>Placebo (N=77)</th>
<th>Patisiran (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>75 (97.4)</td>
<td>143 (96.6)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>28 (36.4)</td>
<td>42 (28.4)</td>
</tr>
<tr>
<td>Serious AE (SAE)</td>
<td>31 (40.3)</td>
<td>54 (36.5)</td>
</tr>
<tr>
<td>AE w/ discontinuation</td>
<td>11 (14.3)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>AE w/ withdrawal</td>
<td>9 (11.7)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (7.8)</td>
<td>7 (4.7)</td>
</tr>
</tbody>
</table>
hATTR Amyloidosis and APOLLO Assessments

Clinical Manifestations
- Loss of sensation
- Muscle weakness
- Impaired ambulation

APOLLO Assessments
- mNIS+7
  - NIS-W subdomain
  - QST subdomain
  - Reflexes subdomain
  - Norfolk-QOL
  - R-ODS disability
  - 10-MWT
  - Grip strength
  - AE profile

Sensorimotor Nerves
- Orthostatic hypotension
- Syncope/falls
- Constipation/diarrhea
- Urinary retention/UTIs

Autonomic Nerves
- mNIS+7
  - Postural BP subdomain
  - Norfolk-QOL
  - Autonomic subdomain
  - mBMI
  - COMPASS-31
  - Orthostatic hypotension
  - GI & bladder subdomains
  - AE profile

Heart
- Heart failure
- Arrhythmias/syncope
- Impaired exercise tolerance

Misfolded mutant & wild-type TTR amyloid fibrils in circulation deposit in nerves and tissues of many organs

Mutant & wild-type TTR in liver

Patisiran
Advancing Continued Innovation for Patients with ATTR Amyloidosis

**ALN-TTRsc02 Opportunity**

**Mean max TTR KD of 97.1%; ~80% TTR KD at nearly 1 year after single 50 mg dose**

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

**Phase 1 Study – Healthy Volunteers**

- **Inotersen**
  - 52 DOSES PER YEAR

- **ALN-TTRsc02**
  - 4 DOSES PER YEAR ANTICIPATED

*As of data cutoff on 31 May 2017*
Agenda

• RNAi Therapeutics for hATTR Amyloidosis

• RNAi Therapeutics for Other Rare and Common Diseases

• New Frontiers for RNAi Therapeutics
Acute Hepatic Porphyrias
Givosiran

Description
Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks, leading to frequent hospitalizations and chronic pain.

<table>
<thead>
<tr>
<th>Predominantly</th>
<th>female, commonly misdiagnosed</th>
</tr>
</thead>
</table>

Patient Population*

<table>
<thead>
<tr>
<th>~5,000</th>
<th>~1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with sporadic attacks in U.S./EU</td>
<td>Patients with recurrent attacks in U.S./EU</td>
</tr>
</tbody>
</table>

Severe, burning pain in abdomen, chest, back
Weakness, numbness, respiratory failure
Confusion, anxiety, seizures, hallucinations
Lesions on sun-exposed skin; chronic/blistering

*ORPHANET; The Porphyria Consortium
**Givosiran: Investigational RNAi Therapeutic**

**Therapeutic Hypothesis**

**Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG**

- **ALAS1 protein**
- **Givosiran (ALN-AS1)**
- **ALAS1 siRNA**
- **Liver targeting ligand**

**Diagram:**
- ALAS1 protein upregulated
- ALA/PBG production
- ALA/PBG induce porphyria symptoms
- Givosiran (ALN-AS1) knockdown of ALAS1 reduces ALA/PBG production and prevents attacks
Givosiran Interim Phase 1 and OLE Study Results†

Decreased Annualized Attack Rates (AAR)* Observed with up to 22 Months of Total Treatment in Phase 1 and OLE

73% Mean Decrease in AAR
Givosiran Compared to Placebo

93% Decrease in AAR
Givosiran Compared to Phase 1 Run-In

Phase 1 and OLE Safety:
In OLE study (N=16):
- Two patients with SAEs, including one with anaphylactic reaction, assessed as definitely related to study drug. Patient had past history of asthma, oral allergy syndrome, and prior allergic reactions to acne cream and possibly latex gloves; patient discontinued from study
- Most common AEs: abdominal pain, nausea, injection site erythema, headache, injection site pruritis, fatigue, nasopharyngitis

In Phase 1 (N=40):
- Six patients with SAEs, including one who developed acute pancreatitis complicated by pulmonary embolism resulting in death, considered unlikely related to study drug
- Majority of AEs mild-moderate in severity

†Phase 1 and interim OLE study results as of Feb 26, 2018; Sardh et al., EASL, April 2018
*Includes attacks treated in healthcare facility or with hemin
**Aggregated across all dose groups
Mean time in Phase 1 run-in and treatment of 103 days and 165 days, respectively; mean time in OLE of 322 days
**ENVISION Phase 3 Study Design**
Randomized, Double-Blind, Placebo-Controlled Study in Acute Hepatic Porphyria Patients

**N ~ 75 Patient Population**
- Age ≥ 12 years
- Diagnosis of AHP
- ≥ 2 attacks within prior 6 months
- Willing to discontinue and/or not initiate hemin prophylaxis

**1:1 RANDOMIZATION**

- **Givosiran SC qM 2.5 mg/kg**
- **Placebo SC qM**

**Primary Endpoint**
- Attacks requiring hospitalization, urgent care visit, home IV hemin at 6 months

**Key Secondary Endpoints**
- ALA and PBG
- Hemin doses
- Symptoms
- QOL

**Interim analysis planned in mid-2018**

**Statistical Considerations:**
- 70 patients will have at least 90% power to detect 45% reduction in annualized attack rate at 2-sided alpha of 0.05
- Unblinded interim analysis of urinary ALA levels in 30 patients at 3 months
  - Includes blinded assessment to adjust sample size for primary endpoint

**Open-Label Extension**

**FDA Breakthrough and EMA PRIME Designations**
Alignment with FDA that reduction of urinary ALA is reasonably likely to predict clinical benefit

- Interim analysis with ~30 patients after 3 mo dosing; expect topline data in mid-2018
- Expect NDA submission in late 2018 and potential FDA approval in mid-2019

**Relationship of ALA Lowering with Annualized Attack Rate in Recurrent Attack Patients**

- 2.5 mg/kg/mo (N=3)
- Placebo (N=4)

**ALA Lowering in Recurrent Attack Patients at 2.5 mg/kg qM**

- 0-25%
- >25-50%
- >50-75%
- >75%

- ALA increased from baseline
- More ALA lowering from patient's baseline

*Sardh et al., EASL, April 2018; Includes attacks treated in healthcare facility or with hemin

**Sardh et al., ICPP, June 2017
PCSK9

Inclisiran
PCSK9 Therapeutic Hypothesis
RNAi vs. Mabs

**PCSK9 Synthesis Inhibitors**
Durably block PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

**Anti-PCSK9 Mabs**
Transiently block PCSK9 binding to LDL receptor (LDLR)
ORION-1 Phase 2 Clinical Study

501 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy

**Primary objectives**
- LDL-C levels at day 180

**Secondary objectives**
- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

**Randomized 3:1, Double blind, Placebo controlled**

<table>
<thead>
<tr>
<th>Placebo x 1 SC</th>
<th>N~60</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg x 1 SC</td>
<td>N~60</td>
</tr>
<tr>
<td>300 mg x 1 SC</td>
<td>N~60</td>
</tr>
<tr>
<td>500 mg x 1 SC</td>
<td>N~60</td>
</tr>
</tbody>
</table>

Open label extension

<table>
<thead>
<tr>
<th>Placebo qQ x 2 SC</th>
<th>N~60</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg qQ x 2 SC</td>
<td>N~60</td>
</tr>
<tr>
<td>200 mg qQ x 2 SC</td>
<td>N~60</td>
</tr>
<tr>
<td>300 mg qQ x 2 SC</td>
<td>N~60</td>
</tr>
</tbody>
</table>

Open label extension

= dose
Robust and Sustained LDL-C Reductions with Inclisiran*
Results to Day 360 Following One Dose

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.

*Phase 2 study results; Ray et al., ESC, Aug 2017
Free from CVD for 100 Years?
Hypothesis on Inclisiran Primary Prevention by E. Braunwald, ACC 2018

Image of a graph showing the relationship between cumulative LDL-C burden and age, with a note for Inclisiran and an average line. The graph is modified from Horton JD et al., J. Lipid Res. 2009;50:S172-S177.
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
ORION Phase 3 Program

- 3,660 patients (1:1 inclisiran or placebo) dosed across ORION-9, ORION-10 and ORION-11
  - Baseline data and demographics consistent with ASCVD and ASCVD Risk Equivalents including HeFH

- Encouraging safety results to date with >1000 patient years exposure
  - Including, ORION-3, ORION-2 and ORION-7 open label studies

- ORION-4 CVOT study in ~15,000 patients with ASCVD and Risk Equivalents to start in mid-2018
Agenda

• RNAi Therapeutics for hATTR Amyloidosis

• RNAi Therapeutics for Other Rare and Common Diseases

• New Frontiers for RNAi Therapeutics
UK Biobank Consortium

World-leading effort to connect genotype to full medical records for phenome-wide association studies

- Goal to generate 500K exome sequences linked to medical records by end-2019
  - 50K exomes sequenced to date
- Consortium members receive broad, ongoing access to UK Biobank data linked to exome sequences
  - Exclusive for 1 year after generation

Substantial value to Alnylam R&D efforts

- Modern drug discovery must incorporate human genetics
- Provides additional genetic validation for existing programs
- Identify/de-risk new programs
- *In silico* natural history data for new and existing programs
- Patient finding efforts
Nonalcoholic Steatohepatitis (NASH)

HSD17B13 Target

Description
Progressive disease characterized by hepatic fat buildup and inflammation, potentially leading to cirrhosis

HSD17B13 as a novel target

- Hepatocyte expressed intracellular target amenable to RNAi therapeutic approach
- Loss-of-function variant (TA) associated with reduced risk of chronic liver disease, including NASH

PATIENT POPULATION
>9 million adults in U.S.
RNAi Therapeutics for CNS Diseases
No Current Therapies to Prevent or Reverse Neurodegenerative Disease

• Dominantly inherited neurodegenerative diseases include
  – Alzheimer’s disease
  – Parkinson’s disease
  – Frontotemporal dementia
  – Huntington’s disease
  – Amyotrophic lateral sclerosis (ALS)
  – Spinocerebellar ataxia
  – Prion disease
  – Many other orphan genetic diseases with CNS component

• Many genetically validated targets known but no current disease modifying therapies for these devastating, life threatening disorders

• RNAi therapeutics directed to disease-causing, CNS-expressed genes represent next great frontier

• Expect superior potency, duration and systemic safety profile vs. ASOs
Alnylam Advancements in Conjugate-Based Delivery

- **siRNA design/chemistry**
- **Linker**
- **Ligand**

**Potency/duration/specificity**
**Stability, optimal ligand orientation**
**Efficient delivery to target cells**

**Evolution of conjugate potency**
*mouse, SD ED$_{50}$*

Graph showing the evolution of conjugate potency from 2004 to 2018 with different modifications:
- **Partially modified**
- **STC**
- **ESC**
- **Advanced ESC**
- **ESC+**
Intrathecal Delivery of Novel siRNA Conjugates
Single Dose Time Course in Rat

Two targets tested to demonstrate sequence specificity
siRNA conjugate dose of 0.9 mg

Day 0 2 4 7 14 28

Tissue collection

Tissues: Spinal cord: lumbar, thoracic and cervical
Brain: prefrontal cortex, cerebellum and remaining brain
Fluids: CSF and plasma

Assays: mRNA, tissue siRNA levels, RISC loaded siRNA

Histology
Robust, Durable CNS Silencing by Novel siRNA Conjugates
Single Intrathecal Dose in Rats

Sequence specific target knockdown across the brain and spinal cord for both targets

- Confirmed siRNA uptake in several different cell types
- Widespread distribution and knockdown in all key anatomical regions of brain and spinal cord tissue
Alnylam CNS Pipeline Strategy
Expanding a Pipeline of Potentially Transformative Medicines

Genetically validated, CNS-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access

Alnylam CNS Objectives
• 1st DC in 2018
• 1st IND in late ’19/early ’20
• 1-2 INDs/yr starting in ’20
Summary

• RNAi therapeutics are in advanced stages of clinical development and at cusp of commercialization
  – Patisiran poised to emerge as industry’s 1st RNAi therapeutic to reach market
  – RNAi therapeutics emerge as high impact, transformational medicines
• Many RNAi therapeutic opportunities advancing for rare and common diseases
  – E.g., Givosiran for acute hepatic porphyrias
  – E.g., Inclisiran for hypercholesterolemia
  – Many significant opportunities for breakthrough medicines and high patient impact
• New frontiers for future expansion of RNAi therapeutics opportunity
  – Convergence of RNAi and genetic data to advance highly innovative medicines across many diseases (e.g., NASH)
  – Delivery of RNAi therapeutics to CNS achieved!
    ◦ Novel siRNA conjugate approach
    ◦ Opens advancement of MANY new opportunities for high impact medicines
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED