Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

Thursday, September 7, 2017
Agenda

Welcome
  • Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
  • Jeff Miller, General Manager, Givosiran

Disease Overview, EXPLORE Natural History Study & Givosiran Ph 1 Data
  • Eliane Sardh, M.D., Ph.D., Porphyria Center Sweden, Karolinska University Hospital

Regulatory Status & Phase 3 Overview
  • Jae Kim, M.D., Vice President, Clinical Development

Program Timelines & Strategy
  • Jeff Miller, General Manager, Givosiran

Q&A Session
Reminders

Event will run for approximately 75 minutes

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

Replay, slides and transcript available at [www.alnylam.com](http://www.alnylam.com)
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This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
RNAi Therapeutics
New Class of Innovative Medicines

Harness natural pathway

Catalytic mechanism

Silence any gene in genome

Upstream of today’s medicines

Clinically proven approach
## Alnylam Clinical Development Pipeline

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

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Condition/Disorder</th>
<th>Human POC*</th>
<th>Early Stage (IND or CTA Filed-Phase 2)</th>
<th>Late Stage (Phase 2-Phase 3)</th>
<th>Registration/Commercial Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patisiran</strong></td>
<td>Hereditary ATTR Amyloidosis</td>
<td>✔</td>
<td></td>
<td></td>
<td>US, Canada, Western Europe</td>
</tr>
<tr>
<td><strong>Fitusiran</strong></td>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td>✔</td>
<td></td>
<td></td>
<td>50% US, Canada, Western Europe</td>
</tr>
<tr>
<td><strong>Inclisiran</strong></td>
<td>Hypercholesterolemia</td>
<td>✔</td>
<td></td>
<td></td>
<td>Milestones &amp; Royalties</td>
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<tr>
<td><strong>Givosiran</strong></td>
<td>Acute Hepatic Porphyrias</td>
<td>✔</td>
<td></td>
<td></td>
<td>Global</td>
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<tr>
<td><strong>ALN-CC5</strong></td>
<td>Complement-Mediated Diseases</td>
<td>✔</td>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td><strong>ALN-GO1</strong></td>
<td>Primary Hyperoxaluria Type 1</td>
<td>✔</td>
<td></td>
<td></td>
<td>Subject to partner option rights</td>
</tr>
<tr>
<td><strong>ALN-TTRsc02</strong></td>
<td>Hereditary ATTR Amyloidosis</td>
<td>✔</td>
<td></td>
<td></td>
<td>Subject to partner option rights</td>
</tr>
<tr>
<td><strong>ALN-HBV</strong></td>
<td>Hepatitis B Virus Infection</td>
<td>✔</td>
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</tr>
</tbody>
</table>

*POC, Proof of concept - defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies

**Currently on hold with intent to resume dosing as soon as possible upon agreement with regulatory authorities on risk mitigation/safety monitoring**
# Alnylam Clinical Development Pipeline

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

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

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<tr>
<th></th>
<th>HUMAN POC*</th>
<th>EARLY STAGE (IND or CTA Filed-Phase 2)</th>
<th>LATE STAGE (Phase 2-Phase 3)</th>
<th>REGISTRATION/COMMERCIAL</th>
<th>COMMERCIAL RIGHTS</th>
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</tr>
</tbody>
</table>

**Givosiran**

*Acute Hepatic Porphyrias*

- Global

**ALN-CC5**

- Complement-Mediated Diseases
- Global

**ALN-GO1**

- Primary Hyperoxaluria Type 1
- Subject to partner option rights

**ALN-TTRsc02**

- Hereditary ATTR Amyloidosis
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**ALN-HBV**

- Hepatitis B Virus Infection
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Q&A Session
Acute Hepatic Porphyrias
Disease Overview

**Acute Hepatic Porphyria Inheritance**

<table>
<thead>
<tr>
<th>Enzyme Name</th>
<th>Related Porphyria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA synthase</td>
<td>X-linked protoporphyria</td>
</tr>
<tr>
<td>ALA dehydratase</td>
<td>ALA dehydratase deficiency porphyria</td>
</tr>
<tr>
<td>Porphobilinogen deaminase</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Uroporphyrinogen synthase</td>
<td>Congenital erythropoietic porphyria</td>
</tr>
<tr>
<td>Uroporphyrinogen decarboxylase</td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Coproporphyrinogen oxidase</td>
<td>Hereditary coproporphyria</td>
</tr>
<tr>
<td>Protoporphyrinogen oxidase</td>
<td>Variegate porphyria</td>
</tr>
<tr>
<td>Protoporphyrin IX</td>
<td></td>
</tr>
<tr>
<td>Ferrochelatase</td>
<td>Protoporphyria</td>
</tr>
</tbody>
</table>

**Clinical Manifestations**

<table>
<thead>
<tr>
<th>Acute Hepatic Porphyria</th>
<th>Inheritance</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>Autosomal Recessive</td>
<td>Acute Neurovisceral Attacks</td>
</tr>
<tr>
<td>AIP</td>
<td>Autosomal Dominant</td>
<td>Acute Neurovisceral Attacks</td>
</tr>
<tr>
<td>HCP</td>
<td>Autosomal Dominant</td>
<td>Acute Neurovisceral Attacks and/or Skin lesions</td>
</tr>
<tr>
<td>VP</td>
<td>Autosomal Dominant</td>
<td>Acute Neurovisceral Attacks and/or Skin lesions</td>
</tr>
</tbody>
</table>

**Disease triggers**

- Delta aminolevulinic acid (ALA)
- Succinyl CoA and glycine
- ALA Synthase 1 (ALAS1)
- Negative feedback

References:
Path to Diagnosis
Female Born 1987

- Sought Emergency Unit due to severe abdominal pain
  - BP 180/112
  - S-sodium 123 mmol/L (ref 137-145)
  - Paresthesia bilateral in face, otherwise no neurological signs

- Patient spends **78 days** in and out of hospital following abdominal pain presentation, without a diagnosis; symptoms persist
- Admitted to five different clinical wards including ICU (hyponatremia) at two different hospitals
- CT scan x 2 with no conclusive diagnosis
- Gastroscopy with no conclusive diagnosis
- Evaluated by several specialists without conclusive diagnosis
- Including psychiatric team, suspicion of depression and anxiety disorder results in SSRI treatment

**Endocrine department consulted due to severe hyponatremia:**
- **Porphyria screening is suggested**

**Diagnosis:**
- Markedly elevated urinary excretion of ALA and PBG
- Mutation analysis identifies AHP
AHPs: Acute Neurovisceral Crisis

**Autonomic neuropathy**
- Abdominal pain, nausea, vomiting, abdominal distension and constipation
- Tachycardia, cardiac arrhythmia, labile hypertension, postural hypotension
- Sweating, hoarse voice

**Acute peripheral neuropathy**
- Diffuse muscle weakness
- Pain in back and limbs
- Neuropathic sensory loss
- Cranial neuropathy (mainly III, VI, IX and X)
- Respiratory paresis due to diaphragm paresis

**CNS manifestations**
- Mental symptoms; anxiety, insomnia, depression, confusion, agitation, hallucinations
- Acute encephalopathy; headache, somnolence, altered consciousness and behaviour, seizures

**Metabolic manifestations**
- Hyponatremia
- Mild LFT elevation
Treatment of Acute Attacks

• **Identify and eliminate if possible precipitating factors**

• **Symptomatic and supportive treatment**

• **Carbohydrate Loading - can ameliorate/abort mild attack**
  - Oral intake
  - Intravenous administration **CAVE** hyponatremia

• **Human hemin (Normosang®, Panhematin®)**
  - 3-4 mg/kg body weight, 4 consecutive days
  - Dissolved in 100 mL human albumin (4-20%)
Porphyria Attack Experience
Patient Perspective

Female born 1987: first visit at porphyria out-patient clinic

• Recurrent acute attacks
• Developed chronic manifestations
  • Chronic Neuropathic Pain and Progressive Neuropathy
  • Fatigue, nausea, insomnia
  • Impaired QoL
• Had to give up career as professional dancer
Recurrent Acute Attacks – Treatments

1. **GnRH agonist**
   - Benefits must be carefully weighed against effects of estrogen suppression
   - Case reports - *proven clinical efficacy is lacking in literature*

2. **Prophylactic hemin therapy**
   - Increasingly used – although *proven clinical efficacy is lacking in literature*
   - Not approved by Regulators
   - **UK/NAPS: 22 patients** – concludes to offer significant short- to medium –term benefits*
   - **USA: 23 AIP patients** “most effective treatment for prevention”**

*Side effects/complications:*
- **Adverse Reactions** (headache, fever, phlebitis..)
- **Loss of Venous access**
- **Need of Port a catheter** (risk of infections and thrombosis)
- **Iron accumulation – Risk of Liver fibrosis?**#

3. **Liver transplantation**
Late Complications

• Chronic kidney disease
• Chronic Neuropathic Pain and Progressive Neuropathy
• Primary Liver Cancer
• Impaired Quality of Life

Specific treatment not available
Unmet Need/Areas for Improvement

• **Need better knowledge of pathophysiology and natural history of acute porphyrias**
  - International collaborations

• **Need better biomarkers of clinical condition**
  - Who will become symptomatic?
  - To better monitor and assess severity of acute attack
  - Who will become recurrent?
  - Who are at risk to develop late complications?

• **Need new treatments – in acute attack and prophylaxis for recurrent acute attacks but also to prevent late complications**
EXPLORE:
Natural History Study of Patients with AHP
## EXPLORE Natural History Study
Demographic and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age, years</strong></td>
<td>39.3</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>Female</td>
<td>100 (89%)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (11%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>95 (85%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Not Answered</td>
<td>11 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHP etiology: AHP type</strong></td>
<td></td>
</tr>
<tr>
<td>AIP</td>
<td>104 (93%)</td>
</tr>
<tr>
<td>VP</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>HCP</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>Genotypes represented</strong></td>
<td>n</td>
</tr>
<tr>
<td>AIP†</td>
<td>56</td>
</tr>
<tr>
<td>VP / HCP</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Common Associated Medical Conditions</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal/Vascular Disorders</td>
<td>43 (38%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (23%)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>35 (31%)</td>
</tr>
<tr>
<td>Headaches/Migraine</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Neuropathy/Nerve Pain</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Psychiatric/Sleep Disorders</td>
<td>33 (30%)</td>
</tr>
<tr>
<td>Depression</td>
<td>19 (17%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>25 (22%)</td>
</tr>
<tr>
<td>GERD</td>
<td>9 (8%)</td>
</tr>
</tbody>
</table>

Data as of 11 April 2017
†p.R173W and p.W283X were most common (n=4 each).
### EXPLORE Natural History Study

**Attacks During Study**

96 patients experienced 481 attacks*

<table>
<thead>
<tr>
<th>Attack characteristics (N=94)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) attack duration, days</td>
<td>7.05 (1.3–33.2)</td>
</tr>
</tbody>
</table>

**Attack rate per person-year**

<table>
<thead>
<tr>
<th>Overall</th>
<th>4.9</th>
</tr>
</thead>
</table>

**Chronic symptoms**

- Yes (n=52) | 5.1 |
- No (n=57) | 4.8 |

**Current hemin prophylaxis**

- Yes (n=52) | 4.0 |
- No/unknown (n=60) | 5.5 |

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*In patients completing 12 months of follow up.*

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Data as of 11 April 2017
EXPLORE Natural History Study
Attack Treatment Location

>2/3 of attacks in US and EU treated at healthcare facility

Data as of 11 April 2017
EXPLOR E Natural History Study
Quality of Life: EQ-5D-5L at 12 Months (Non-Attack)

<table>
<thead>
<tr>
<th>Category</th>
<th>Problems</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility/Walking</td>
<td>No problems</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>Slight problems</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Moderate problems</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Severe problems</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Unable to walk</td>
<td>16%</td>
</tr>
</tbody>
</table>

| Self-Care              | No problems                       | 52%          |
|                        | Slight problems                   | 28%          |
|                        | Moderate problems                 | 4%           |
|                        | Severe problems                   | 0%           |
|                        | Unable to wash or dress myself    | 4%           |

| Usual Activities       | No problems                       | 56%          |
|                        | Slight problems                   | 28%          |
|                        | Moderate problems                 | 4%           |
|                        | Severe problems                   | 0%           |
|                        | Unable to do my usual activities  | 30%          |

| Pain/Discomfort        | No pain                           | 56%          |
|                        | Slight pain                       | 28%          |
|                        | Moderate pain                     | 4%           |
|                        | Severe pain                       | 0%           |
|                        | Extreme pain                      | 43%          |

| Anxiety/Depression     | Not anxious or depressed          | 56%          |
|                        | Slightly anxious or depressed     | 28%          |
|                        | Moderately anxious or depressed   | 4%           |
|                        | Severely anxious or depressed     | 0%           |
|                        | Extremely anxious or depressed    | 28%          |

N=74

Moderate or Greater Problems Reported

Data as of 11 April 2017
EXPLORE Natural History Study
Screening Questionnaire: Patient-Reported Chronic Symptoms

- 65% of patients with chronic symptoms - most commonly pain, tiredness, anxiety, and nausea
- 46% of patients having daily symptoms

Data as of 11 April 2017
Interim Data from a Randomized, Placebo Controlled, Phase 1 Study of Givosiran (ALN-AS1)
Givosiran: Investigational RNAi Therapeutic Therapeutic Hypothesis

Reduction of Liver ALAS1 Protein to Lower ALA/PBG

ALAS1 protein

Givosiran (ALN-AS1) results in knockdown of ALAS1 and lowers ALA/PBG production to prevent attacks and disease symptoms

ALA/PBG induce porphyria symptoms

Givosiran

ALAS1 siRNA

Liver targeting ligand

GalNAc
Givosiran Phase 1 (Part C and OLE) Study
Study Design and Objectives

<table>
<thead>
<tr>
<th>Run-in Period</th>
<th>Treatment Period</th>
<th>OLE Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-month observation</td>
<td>6 months</td>
<td>OLE (42 months)</td>
</tr>
<tr>
<td>Run-in</td>
<td>Cohort 1, 2.5 mg/kg q3M x 2, N=4</td>
<td>5.0 mg/kg q3M, N=4</td>
</tr>
<tr>
<td>Run-in</td>
<td>Cohort 2, 2.5 mg/kg qM x 4, N=4</td>
<td>2.5 mg/kg qM, N=4</td>
</tr>
<tr>
<td>Run-in</td>
<td>Cohort 3, 5 mg/kg qM x 4, N=4</td>
<td>5.0 mg/kg qM, N=3</td>
</tr>
<tr>
<td>Run-in</td>
<td>Cohort 4/5, 5 mg/kg q3M x 2, N=5</td>
<td>2.5 mg/kg qM, N=5</td>
</tr>
</tbody>
</table>

Study Design
• Placebo-controlled, double-blind, randomized 3:1, MD in patients with AIP recurrent attacks
• Key Inclusion:
  ◦ Genetic confirmation of AIP
  ◦ ≥ 2 attacks in past 6 months if on-demand treatment or willing to stop hemin prophylaxis during study. One attack in run-in required for randomization

Objectives
• Safety and tolerability
• Characterize PK and PD

Exploratory Objectives
• Clinical activity on attack frequency and treatment
• Characterize circulating ALAS1 mRNA from liver in urine and serum
## Baseline and Run-In Disease Severity by Cohort
### Part C Cohorts 1-3

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>Cohort 1 (N=4)</th>
<th>Cohort 2 (N=4)</th>
<th>Cohort 3 (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Reported Attacks in last 12 mos, mean (range)</strong></td>
<td>22.3 (5-50)</td>
<td>13.5 (0-36)</td>
<td>8.5 (4-12)</td>
</tr>
<tr>
<td><strong>Hemin Prophylaxis Use Prior to Study, n (%)</strong></td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Baseline PBG, mmol/mol Cr mean, (range)</strong>*</td>
<td>51.8 (12.3 - 90.3)</td>
<td>50.8 (44.1 – 51.8)</td>
<td>41.4 (37.1 – 45.7)</td>
</tr>
<tr>
<td><strong>Baseline ALA, mmol/mol Cr mean, (range)</strong>*</td>
<td>22.5 (2.6 – 36.7)</td>
<td>24.5 (17.6 – 31.5)</td>
<td>19.7 (14.6 – 25.6)</td>
</tr>
</tbody>
</table>

**Run-in Period**

<table>
<thead>
<tr>
<th>Annualized Attack Rate mean (SEM)</th>
<th>Cohort 1 (N=4)</th>
<th>Cohort 2 (N=4)</th>
<th>Cohort 3 (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualized Attack Rate mean (SEM)</strong></td>
<td>38.4 (6.4)</td>
<td>16.6 (4.2)</td>
<td>12.8 (3.4)</td>
</tr>
</tbody>
</table>

* ULN: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Pharmacodynamics, Urine ALA and PBG

**Mean ALA* (mmol/mol Cr)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=3)</th>
<th>Cohort 1: 2.5 mg/kg q3M (n=3)</th>
<th>Cohort 2: 2.5 mg/kg qM (n=3) (n=3)</th>
<th>Cohort 3: 5 mg/kg qM (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in (SD)</td>
<td>22.6 (6)</td>
<td>20.6 (11)</td>
<td>28.6 (2)</td>
<td>20.4 (4)</td>
</tr>
<tr>
<td>Treatment (SD)</td>
<td>20.8 (5)</td>
<td>11.8 (4)</td>
<td>6.7 (0.1)</td>
<td>4.3 (3)</td>
</tr>
<tr>
<td>% change</td>
<td>-7.6</td>
<td>-42.5</td>
<td>-76.7</td>
<td>-78.9</td>
</tr>
</tbody>
</table>

**Mean PBG* (mmol/mol Cr)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=3)</th>
<th>Cohort 1: 2.5 mg/kg q3M (n=3)</th>
<th>Cohort 2: 2.5 mg/kg qM (n=3) (n=3)</th>
<th>Cohort 3: 5 mg/kg qM (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in (SD)</td>
<td>42.8 (7)</td>
<td>55.5 (29)</td>
<td>51.1 (3)</td>
<td>34.2 (4)</td>
</tr>
<tr>
<td>Treatment (SD)</td>
<td>41.1 (6)</td>
<td>39.5 (21)</td>
<td>12.5 (1)</td>
<td>7.9 (6)</td>
</tr>
<tr>
<td>% change</td>
<td>-3.9</td>
<td>-28.8</td>
<td>-75.5</td>
<td>-76.9</td>
</tr>
</tbody>
</table>

* ULN: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results Clinical Activity, Annualized Attack Rates

**Decreased Annualized Attack Rates**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=3)</th>
<th>Cohort 1 (N=3)</th>
<th>Cohort 2 (N=3)</th>
<th>Cohort 3 (N=3)</th>
<th>Mean Cohorts 1-3 (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease in Annualized Attack Rate</td>
<td>9</td>
<td>73</td>
<td>58</td>
<td>46</td>
<td>63</td>
</tr>
</tbody>
</table>

**63% Mean Decrease in Annualized Attack Rate Treatment Compared to Run-in**

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N=3)</th>
<th>Cohort 2 (N=3)</th>
<th>Cohort 3 (N=3)</th>
<th>Mean Cohort 1-3 (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease in Annualized Attack Rate</td>
<td>52</td>
<td>86</td>
<td>81</td>
<td>73</td>
</tr>
</tbody>
</table>

**73% Mean Decrease in Annualized Attack Rate Givosiran Compared to Placebo**

*All attacks, regardless of treatment type or treatment location*

*Attacks requiring hospitalization, urgent health care visit or hemin*
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Clinical Activity, Annualized Hemin Doses

73% Mean Decrease in Annualized Hemin Doses

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=3)</th>
<th>Cohort 1 (N=3)</th>
<th>Cohort 2 (N=3)</th>
<th>Cohort 3 (N=3)</th>
<th>Mean Cohorts 1-3 (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease</td>
<td>17</td>
<td>76</td>
<td>83</td>
<td>57</td>
<td>73</td>
</tr>
</tbody>
</table>

Hemin doses in run-in vs treatment for each individual

Data cut date of 21 Apr 2017
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Clinical Activity, Annualized Attack Rates by ALA Lowering Quartiles

### ALA % Lowering Quartile

<table>
<thead>
<tr>
<th>ALA % Lowering Quartile</th>
<th>≤0%</th>
<th>&gt;0-25%</th>
<th>&gt;25-50%</th>
<th>&gt;50-75%</th>
<th>&gt;75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SEM) Annualized Attack Rate</td>
<td>17.6 (3.5)</td>
<td>19.6 (6.2)</td>
<td>11.9 (4.2)</td>
<td>5.5 (2.3)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>Number of Attacks</td>
<td>25</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Patient-years</td>
<td>1.4</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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

Data transfer date of 14 Feb 2017
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Clinical Activity, Annualized Attack Rates by PBG Lowering Quartiles

<table>
<thead>
<tr>
<th>PBG % Lowering Quartile</th>
<th>≤0%</th>
<th>&gt;0-25%</th>
<th>&gt;25-50%</th>
<th>&gt;50-75%</th>
<th>&gt;75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SEM) Annualized Attack Rate</td>
<td>19.0 (3.5)</td>
<td>14.4 (5.5)</td>
<td>8.7 (3.1)</td>
<td>7.5 (3.1)</td>
<td>3.4 (1.3)</td>
</tr>
<tr>
<td>Number of Attacks</td>
<td>29</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Patient-years</td>
<td>1.5</td>
<td>0.5</td>
<td>0.9</td>
<td>0.8</td>
<td>2.1</td>
</tr>
</tbody>
</table>

PBG increase from baseline
More PBG lowering from patient's baseline

Data transfer date of 14 Feb 2017
Givosiran activity maintained potential for further reductions in attack rate with extended dosing.

Mean Annualized Attack Rate
Cohorts 1 and 2

Run-In: 27
Treatment: 9
OLE: 5

Mean Annualized Hemin Doses
Cohorts 1 and 2

Run-In: 41
Treatment: 10
OLE: 4

Data cut date of 21 Apr 2017
Interim Givosiran Phase 1 (Part C, Cohort 1-2 OLE) Study Results Clinical Activity, Placebo

### Mean Annualized Attack Rate Placebo

<table>
<thead>
<tr>
<th></th>
<th>Run-In</th>
<th>Placebo Treatment</th>
<th>OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=2</strong></td>
<td>29</td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Mean Days on Study

<table>
<thead>
<tr>
<th></th>
<th>Run-In</th>
<th>Treatment</th>
<th>OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Days on Study</strong></td>
<td>77</td>
<td>169</td>
<td>31</td>
</tr>
</tbody>
</table>

Data cut date of 21 Apr 2017
Interim Givosiran Phase 1 (Part C and OLE) Study Results
Safety and Tolerability

Part C (Cohorts 1-3)
- 3 patients had 4 SAEs (excluding porphyria attacks), none assessed as related to study drug
  - 1 patient in Cohort 3 had fatal SAE of hemorrhagic pancreatitis, complicated by pulmonary embolism, as previously reported; assessed unlikely related due to presence of gallbladder sludge
- All randomized patients reported AEs
  - Majority of AEs were mild to moderate; 25% patients had severe AEs, assessed as unrelated to study drug
  - AEs in ≥3 patients: Abdominal pain, headache, nasopharyngitis, nausea, vomiting
  - 4 patients had related AEs:
    - Injection site reactions (mild and self-limiting), hypersensitivity, myalgia, headache, moderate renal impairment (in patient with history of moderate renal impairment) and erythema
- No other discontinuations due to AEs or other clinically significant changes in EKG, clinical laboratory or physical examination

OLE (Cohorts 1-2)
- Overall safety experience in OLE consistent with Phase 1 Study
- No SAEs (excluding porphyria attacks) or discontinuations due to AEs
- 4 patients reported AEs; most assessed as mild or moderate in severity
  - 2 patients experienced mild or moderate AEs that were considered related or possibly related to study drug (epistaxis, hypertension and renal impairment, in same patient with history of moderate renal impairment as noted above)
- No clinically significant changes in EKG, clinical laboratory, or physical examination reported
Agenda

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• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
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• Eliane Sardh, M.D., Ph.D., Porphyria Center Sweden, Karolinska University Hospital

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Program Timelines & Strategy
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Q&A Session
Progress in Regulatory Authority Interactions

**European Medicines Agency**

- Reached alignment on overall Phase 3 Study design with EMA and FDA

**U.S. Food and Drug Administration**

- Achieved additional alignment with FDA on Phase 3 interim analysis:
  - Interim endpoint: reduction of urinary levels of ALA at 3 months of treatment as biomarker reasonably likely to predict clinical benefit
Interim Endpoint Provides Path to Potential Initial Approval
Phase 3 Clinical Results Provide Path to Confirmatory Data

Genetically validated, liver-expressed target gene

ALA biomarker for initial US approval*

Path to confirmatory data and access

Clinical Benefit:
- Reduce porphyria attacks
- Reduce IV hemin doses
- Improve Symptoms and QoL

Genetically validated, liver-expressed target gene

ALA biomarker for initial US approval*

Path to confirmatory data and access

Clinical Benefit:
- Reduce porphyria attacks
- Reduce IV hemin doses
- Improve Symptoms and QoL

*pending FDA review of the program at the time of the interim analysis and assuming positive results
Lowering ALA is Reasonably Likely to Predict Clinical Benefit

- ALA is late in biological pathway; causal factor of disease manifestations*
- Lowering of ALA with other interventions (hemin, liver transplant) has been shown to predict reduction in porphyria attacks
- Continuous relationship between ALA lowering and attack reduction

### OBSERVATIONAL DATA**
Urinary ALA Levels

<table>
<thead>
<tr>
<th>ALA % Lowering Category</th>
<th>Mean (SEM) Annualized Attack Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0%</td>
<td>17.6 (3.6)</td>
</tr>
<tr>
<td>&gt;0-25%</td>
<td>19.6 (6.3)</td>
</tr>
<tr>
<td>&gt;25-50%</td>
<td>11.9 (4.0)</td>
</tr>
<tr>
<td>&gt;50-75%</td>
<td>5.5 (2.2)</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>3.8 (1.3)</td>
</tr>
</tbody>
</table>

*Temple R, JAMA, 1999
Givosiran Potently Reduces ALA Levels
Interim Givosiran Phase 1 ALA Results; 2.5 mg/kg Monthly

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Day 0 Baseline</th>
<th>Day 84 Post-treatment</th>
<th>Day 84 % change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4</td>
<td>14.6 ± 3.0</td>
<td>18.2 ± 10.1</td>
<td>+37.6 ± 91.3</td>
</tr>
<tr>
<td>Givosiran 2.5 mg/kg/mo</td>
<td>3</td>
<td>21.8 ± 3.6</td>
<td>1.5 ± 1.4</td>
<td>-92.9 ± 7.0</td>
</tr>
</tbody>
</table>

* ULN: ALA <3.9 or 3.8 mmol/mol Cr, depending on site
Givosiran Phase 3 Study Design; plan to initiate in late 2017
Randomized, Double-Blind, Placebo-Controlled Study, Followed by Open-Label Extension

N ~ 74

**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
6 months

OR

Placebo SC QM
6 months

**Primary Endpoint:**
- Attacks requiring hospitalization, urgent care visit, home IV hemin

**Key Secondary Endpoints:**
- ALA and PBG
- Hemin doses
- Symptoms
- QoL

Interim analysis when 30 patients complete 3 months treatment - mid-2018 interim readout, supporting potential NDA at or around YE 2018 (if positive); potential FDA approval early-to-mid 2019

**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 in 30 patients using endpoint of reduction in urinary ALA level at 3 months
  - No plan to stop early for efficacy or futility

**Global Footprint**
Plan to conduct Phase 3 in ~22 countries

*Preliminary plans subject to further diligence and health authority feedback*
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Q&A Session
Key Targeted Milestones for Givosiran

- **Start Ph 3 – Late 2017**
- **Interim Analysis – Mid-2018**
- **NDA Filed – End 2018***
- **US Approval – Early/Mid-2019***

*pending FDA review of the program at the time of the IA and assuming positive results; discussions ongoing with EMA*
Givosiran
Key Commercial Elements

**Map Patient Journey**
- Further clarify epidemiology
- Partner with porphyria physician network
- Identify treating specialists and referral networks

**Education**
- Partner with Patient Advocacy Groups
- Better define disease/red flag symptoms
- Improve timing and rates of diagnosis

**Ensure Rapid Access**
- Work with payor and provider networks
- Define economic burden of disease
- Characterize disease chronicity

**Launch and Expand**
- Leverage existing US/EU infrastructure
- Expand to ROW
- Expand patient eligibility
Epidemiology Overview

Current Global Assumption: Range of 1,000-1,500 patients

- As with many rare diseases, epidemiology data are limited
- Consensus estimate: 2-5 patients per 100,000 for AIP*
  - Ratio between AHP types (AIP:VP:HCP) is ~6:3:1**
  - ~5% of AIP to be recurrent (lower VP/HCP)
- Porphyria is rare and difficult to diagnose – intermittent, highly variable, and non-specific: leads to lengthy delays in diagnosis, up to 15 years
- Ongoing research, database analyses, and discussions with KOLs suggest many patients are either misdiagnosed or undiagnosed

* Anderson KE, Metabolic & Molecular Bases of Inherited Disease, 2001
** Elder, J Inherit Metabol Dis, 2013
Porphyria Management
Long Journey, Many Specialties, Testing Options Not Well Understood

**Diagnostic Churn**

1. Porphyria symptoms drive follow-up; patients admitted or referred to specialists
2. Negative imaging and labs; patients discharged with no dx; process may be repeated many times
3. Opportunistic finding, worsening, luck or patient-driven research often needed to suspect porphyria

**Diagnostic Workup**

4. Suspicion of porphyria often opportunistic; gastroenterology, neurology, hematology most aware of the disease. Confusion about diagnostics and lack of point-of-care test may create further delay

**Management**

5. Limited number of centers of excellence have porphyria specialists
5. Awareness of expert centers is low; many patients treated in local settings

Diagnostic delay: Time from symptoms to dx often >5 years
Low Awareness of AHP
Educational Needs are Extensive

Current Knowledge

- HEMs are most familiar and knowledgeable about AIP; fairly consistent in diagnosis and most experienced managing AIP patients
- GASTROs and NEUROs are somewhat knowledgeable about disease and have seen AIP patients, but limited management experience
- ERs and IMs are somewhat knowledgeable about disease and have seen patients with AIP, but few IMs have experience managing patients
- OB/GYNs are least familiar with AIP; unlikely to have ever seen a case
Patient Experience with Porphyria
Debilitating, Unpredictable, and Life Altering

- Search for diagnosis is usually triggered by episode of abdominal or chest pain, accompanied by nausea
- Patients get range of misdiagnoses on long journey to identifying porphyria
  - Guillain-Barre, endometriosis, IBS, cancer, abdominal migraine may be considered
  - Patients often thought to have psychiatric disorders or labeled as drug-seekers
- Disease progression not linear; characterized by variable disease activity
  - Frequent hospitalizations limit employability and reduce quality of life
  - Chronic symptoms of pain, fatigue, nausea and weakness may linger between attacks

Illustrative Patient Experience with Porphyria
Significant Economic Burden of AHP
Ranges from approximately $400,000 to $650,000*

EXPLORE Natural History Study – Healthcare Utilization and Cost Analysis

<table>
<thead>
<tr>
<th>Total with Hospital Costs, mean (95% CI)</th>
<th>$398,463 ($328,303 - $475,477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with Hospital Charges, mean (95% CI)</td>
<td>$655,418 ($482,278 - $847,448)</td>
</tr>
</tbody>
</table>

- $141,738 Hemin Acute Attacks
- $148,145 Hemin Prophylaxis
- $148,145 Hemin Prophylaxis
- $100,078 Hospitalizations (Costs)
- $356,853 Hospitalizations (Charges)

- Both hospitalization charges (amount billed) and costs (amount paid) were reported
- ICD-9 code is not specific to porphyrias; thus hospitalization costs may be under-represented due to disease severity
Timeline Assumptions*
Start with US, Europe, and progressively add countries over time

2019 → 2020 → 2021+

*assuming positive interim analysis results
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Q&A Session
Givosiran
Conclusions

**AHPs are a group of ultra-rare orphan diseases with devastating manifestations and high unmet needs**

**EXPLORE Natural History study shows most attacks require hospitalization/ER and many patients suffer from a dramatically reduced QoL**

**Targeting ALAS1 upstream of genetic defects and enzyme responsible for toxic heme intermediates that mediate porphyria attacks has shown to reduce attacks**

**Givosiran Phase 1/OLE data demonstrate that once-monthly, subcutaneous delivery could be transformative for patients**

**Alnylam has reached alignment on Phase 3 Study design with EMA and FDA; also reached additional alignment with FDA on Phase 3 interim analysis endpoint**

**Phase 3 expected to start in late ‘17, with target IA filing date at-or-around end ‘18, assuming data are positive, with potential initial US approval in early/mid ‘19**

**Medical Affairs and Commercial planning & build up have commenced**
Thank you

Rose
Living with Porphyria