ALN-AS1, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

September 24, 2015
Agenda

Welcome
• Joshua Brodsky
  Senior Manager, Investor Relations and Corporate Communications

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

Overview of Hepatic Porphyrias
• Robert J. Desnick, M.D., Ph.D., Dean for Genetics and Genomic Medicine, Professor and Chair Emeritus, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

Patient Advocacy: Porphyria Patient Perspective
• Desiree Lyon Howe, Co-Founder and Executive Director, American Porphyria Foundation

Q&A Session
• With Dr. Desnick and Desiree Lyon Howe

ALN-AS1 Program
• Bill Querbes, Ph.D., Associate Director, Research

Q&A Session
Reminders

• Event will run for approximately 90 minutes
• Q&A Session at end of each presentation
  ◦ Submit questions at top of webcast screen
  ◦ Questions may be submitted at any time
• Replay, slides and audio available at www.alnylam.com
This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of our drug candidates, obtain, maintain and protect intellectual property, enforce our patents and defend our patent portfolio, obtain regulatory approval for products, establish and maintain business alliances; our dependence on third parties for access to intellectual property; and the outcome of litigation, as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
Alnylam RNAi Therapeutics Strategy
A Reproducible and Modular Path for Innovative Medicines

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

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

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

## Genetic Medicines

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Discovery</th>
<th>Development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
<td></td>
<td>ALN-AT3</td>
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<td>Patisiran</td>
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<tr>
<td>Hemophilia and Rare Bleeding Disorders</td>
<td></td>
<td>ALN-CC5</td>
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<td>Revusiran</td>
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<td>Complement-Mediated Diseases</td>
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<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
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<td>ALN-G01</td>
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<tr>
<td>Primary Hyperoxaluria Type 1</td>
<td>ALN-TTRsc02</td>
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<tr>
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<td>ALN-TMP</td>
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<tr>
<td>Additional Genetic Medicine Programs</td>
<td>ALN-PCsSc</td>
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## Cardio-Metabolic Diseases

<table>
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<tr>
<th>Condition</th>
<th>Discovery</th>
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<tr>
<td>Hypertriglyceridemia</td>
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<td>ALN-ANG</td>
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<td>ALN-HDV</td>
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<td>Chronic Liver Infection</td>
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Q&A Session
CLINICAL OVERVIEW OF THE ACUTE HEPATIC PORPHYRIAS

Robert J. Desnick, Ph.D., M.D.
Dean for Genetic & Genomic Medicine
Professor & Chair Emeritus
Department of Genetics & Genomic Sciences
Icahn School of Medicine at Mount Sinai, New York, NY
• Heme Biosynthesis & Regulation

• The Acute Hepatic Porphyrias:
  • Incidence and Prevalence
  • Clinical Manifestations of Acute Attacks
  • Pathogenesis of Acute Attacks

• Current and Emerging Therapies
  • Heme Replacement
  • Orthotopic Liver Transplantation
  • Gene Replacement Therapy
  • RNAi Therapy
THE PORPHYRIAS: INBORN ERRORS OF HEME BIOSYNTHESIS

ALAS1 (ALA-Synthase)

ALA-Dehydratase Deficiency Porphyria (ADP)

Acute Intermittent Porphyria (AIP)

Hereditary Coproporphyria (HCP)

Variegate Porphyria (VP)

Succinyl CoA — Glycine

δ-Aminolevulinic Acid (ALA)

ALA-Dehydratase

Porphobilinogen (PBG)

Hydroxymethylbilane Synthase

Hydroxymethylbilane

Uroporphyrinogen III Synthase

Uroporphyrinogen III

Uroporphyrinogen Decarboxylase

Coproprophyrinogen III

Coproprophyrinogen Oxidase

Protoporphyrinogen IX

Protoporphyrinogen Oxidase

Protoporphyrin IX

Ferrochelatase

HEME

Negative Feedback
ACUTE HEPATIC PORPHYRIAS

<table>
<thead>
<tr>
<th>Porphyria</th>
<th>Deficient Enzyme Activity (% of Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant:</strong></td>
<td></td>
</tr>
<tr>
<td>– Acute Intermittent Porphyria (AIP)</td>
<td>HMB-Synthase 50%</td>
</tr>
<tr>
<td>– Hereditary Coproporphyria (HCP)</td>
<td>COPRO-Synthase 50%</td>
</tr>
<tr>
<td>– Variegate Porphyria (VP)</td>
<td>PROTO-Synthase 50%</td>
</tr>
<tr>
<td><strong>Autosomal Recessive:</strong></td>
<td></td>
</tr>
<tr>
<td>– ALA-Dehydratase Deficient</td>
<td>ALA-Dehydratase &lt;5%</td>
</tr>
<tr>
<td>Porphyria (ADP)</td>
<td></td>
</tr>
<tr>
<td><strong>Major Clinical Manifestations:</strong></td>
<td></td>
</tr>
<tr>
<td>– Acute Neurological Attacks</td>
<td></td>
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<tr>
<td>– Neuropathic Pain &amp; Progressive Neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemical &amp; Molecular Diagnoses:</strong></td>
<td></td>
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<tr>
<td>– During an Acute Attack:</td>
<td></td>
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<tr>
<td>– Increased Liver ALAS1 Levels</td>
<td></td>
</tr>
<tr>
<td>– Markedly Elevated Urinary/Plasma ALA/ PBG</td>
<td></td>
</tr>
<tr>
<td>– Gene Mutation Analysis Identifies All Patients</td>
<td></td>
</tr>
</tbody>
</table>
# ESTIMATED PREVALENCE OF AIP

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>8 -10*</td>
</tr>
<tr>
<td>Finland</td>
<td>2 - 3*</td>
</tr>
<tr>
<td>UK &amp; Western Europe</td>
<td>2 - 5*</td>
</tr>
<tr>
<td>United States</td>
<td>2 – 5**</td>
</tr>
</tbody>
</table>

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**American Porphyria Foundation Patient Registry**

8700 Registered, ~3000 Acute Hepatic Patients, of these there is Biochemical/Mutation Confirmed for:

- **AIP:** 1284
- **HCP:** 361
- **VP:** 161
- **Total:** 1806

*Andersson C., AIP in Northern Sweden, PhD Thesis, 1997; Elder et al., *J. Inherit Metab Dis* Epub Nov 1, 2012, **Estimated*
MOUNT SINAI PORPHYRIA DIAGNOSTIC & TREATMENT CENTER

- Acute Hepatic Porphyria Patients Annual Number Diagnosed and Mutations Confirmed; 1/1/2010 to 9/1/2015

<table>
<thead>
<tr>
<th>Year</th>
<th>AIP</th>
<th>VP</th>
<th>HCP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>29</td>
<td>18</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>2011</td>
<td>59</td>
<td>8</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>2012</td>
<td>56</td>
<td>3</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>2013</td>
<td>76</td>
<td>11</td>
<td>9</td>
<td>96</td>
</tr>
<tr>
<td>2014</td>
<td>61</td>
<td>26</td>
<td>17</td>
<td>104</td>
</tr>
<tr>
<td>2015 (8 Mon)</td>
<td>39</td>
<td>2</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td>68</td>
<td>44</td>
<td>432</td>
</tr>
</tbody>
</table>

- Initial Misdiagnosis is Common in Many Patients
  - Mean Time from First Symptoms to Diagnosis is ~10 Years
PATHOGENESIS OF ACUTE ATTACKS IN AIP

Normal

Hepatic Heme-Mediated Feedback Repression

Glycine + Succinyl CoA

ALAS1 → ALA → ALAD → PBG → HMB → HEME

50% HMB-Synthase

Decreased Hepatic Heme-Mediated Feedback Repression

Clinically Manifest

PATHOGENESIS OF ACUTE ATTACKS IN AIP

Normal

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Clinically Manifest
ACUTE INTERMITTENT PORPHYRIA (AIP)
Most Common Acute Hepatic Porphyria

• Frequency of Acute Neurologic Attacks:
  – **Recurrent Attacks:** >3-4 Attacks/yr; Men & Women
    • As Frequent as Weekly or Monthly
    • Women with Monthly Attacks during Luteal Phase of Menstrual Cycle
  – **Sporadic Attacks:** <3 Attacks/yr; Men & Women
  – **Asymptomatic High ALA/PBG Excreters:** Asymptomatic Men & Women
    • Previous Attack in Most Cases, with Persistently Elevated ALA and PBG
## ACUTE NEUROLOGIC ATTACKS: INCIDENCE OF SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>95</td>
</tr>
<tr>
<td>Vomiting</td>
<td>72</td>
</tr>
<tr>
<td>Constipation</td>
<td>70</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>68</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>62</td>
</tr>
<tr>
<td>Mental Symptoms</td>
<td>48</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
</tr>
<tr>
<td>Convulsions</td>
<td>15</td>
</tr>
<tr>
<td>Paralysis</td>
<td>10</td>
</tr>
</tbody>
</table>
CASE STUDY - RECURRENT ATTACKS IN A 30 Y/O FEMALE WITH AIP

2012: 20 Attacks; 32 Days of IV Hematin Prophy Heme with Still Breakthrough Attacks

HMBS Mutation: L30P
MANAGEMENT OF THE ACUTE PORPHYRIC ATTACK

• Admit to Hospital or Outpatient Clinic
• Withdraw All Common Precipitants
  – (Drugs, Alcohol, Fasting, Infection...)
• Use Opiates and Chlorpromazine as Needed
• Start IV Glucose in D\textsubscript{10}W Immediately
  – (300-400g/Day)
• Order Hematin and Begin Infusions
INTRAVENOUS HEMIN TREATMENT

- Start as Soon as Possible
- Recommended Dose of Hemin (Panhematin®): 3-4 Mg/Kg Daily for 4 Days
  - Continue Treatment if Symptoms Persist
- Hemin (Panhematin®) Suppresses Hepatic $ALAS1$ Through the Negative Feedback Loop
- Intravenous Glucose Alone is Appropriate Only for Mild Attacks or Until Hemin is Available
SAFETY OF HEMIN

- **Hematin (Panhematin®) – 1ST Orphan Drug in 1982**
  - Approved Based on Small Open Label Studies, but in Clinical Use for >30 Years
  - Adverse Reactions or Side Effects\(^1\text{-}^4\): Phlebitis, Coagulopathy\(^1\), Fever, Aching, Malaise, Migraine, Hemolysis, One Case of Circulatory Collapse\(^2\), One Case of Transient Renal Failure After Excessive Dose\(^3\)
  - Tachyphylaxis Reported in Patients with Long Term Use\(^5\)
  - Chronic Patients May Require a Port with Infection Risk
  - Chronic Use Has Been Associated with Iron Overload
  - FDA Has Not Approved Prophylactic Use

LIVER TRANSPLANTATION IN ACUTE HEPATIC PORPHYRIA

Soonawalla et al., Lancet 363: 705-706, 2004

A 19 Year Old Woman with Recurrent Acute Neurologic Attacks Had an Orthotopic Liver Transplant.

- Transplant Demonstrated Importance of Liver in Disease Pathogenesis
- Domino Transplant Patients Had ↑↑ ALA & PBG and Attacks
- Challenges:
  - High Frequency of Arterial Vessel Thromboses
  - Limited Availability of Organs
  - High Morbidity & Mortality

Pre-Tx: 37 Attacks over 29 Months
Post-Tx: None for > 8 Years

Urinary Excretion of ALA & PBG after Liver Transplant

- ALA/Creatinine
- PBG/Creatinine

μmol/mmol Creatinine

Hr after Liver Transplant

-12 -1 0 24 72 128 176
• Based on the Experience with Gene Therapy in AIP Mouse Model, UniQure has Completed an rAAV-2/5-PBGD Clinical Phase I Single Ascending Dose Study for AIP Patients

• Latest Data Indicate no ALA/PBG Lowering in any of the 8 Patients with Recurrent Attacks*
  • All Developed Antibody Response to Vector

• Gene Therapy is Disease-Specific for AIP; Not for ADP, HCP, VP

• Safety Concerns:
  - Patients Screened for Pre-Existing Anti-Capsid Abys
  - Immune Response to AAV5 Capsid; Neutralizing Abys
  - Cannot Re-Administer in Patients Who Develop Abys

*Gonzalez-Aseguinolaza et al. International Congress on Porphyrins and Porphyrias 20-15
IDEAL NEXT GENERATION THERAPY

• Excellent Safety Profile

• Convenient Administration:
  – Ideally Subcutaneous Route
  – Potential for at Home Use

• Faster/Longer Lasting Effects for Acute Treatment:
  – Minimize Multi-Day Hospitalizations

• Effective for Prophylaxis in Recurrent Attack Patients
CONCLUSIONS

• AHPs are a Worldwide Problem/Panethnic

• Attacks Can Be Either Spontaneous or Recurrent:
  – Life-Threatening Symptoms
  – Poor Quality of Life, Long Hospital Stays
  – Chronic & Progressive Neuropathic Pain

• ALAS1 Targeting in Liver Has Been Validated
  – Liver Transplant and Heme MOA

• Unmet Need for New Therapeutic Options
  – Better Safety Profile and Faster Onset
  – Effective for Prophylaxis
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Q&A Session
Protect the Future (PTF) Doctors
Research Team at Work
APF Praise from the FDA, NIH and others
Experts Consult Around the World
Experts Assist with Diagnosis
Fundraising Efforts

The Shadow Race

WCEC INDOOR ARENA
301 WILBARGER
VERNON, TEXAS

$1800 added money
with other prizes

BENEFIT BARREL RACE
(PORPHYRIA AWARENESS)
All proceeds from the race goes to:
American Porphyria Foundation in
Houston, Tx.

NOVEMBER 14
EXHIBITIONS: 11 AM
OPEN: 2 PM
T-SHIRTS
$12

PSALM 121:5-6
NBHA RULES
AND PAYOFFS

# PORPHYRIA
PIE CHALLENGE
I NOMINATE
TERRI WITTER &
GEORGE TAKDIBONO

The Shadow Ride
American Porphyria Foundation

Together we’ll go far
Henry Wells
Awareness Efforts

National Porphyria Awareness Week
April 20-26

RAISE AWARENESS

ANXIETY, SEIZURES, MENTAL DISTURBANCES, DEPRESSION, NEEDLESS SURGERIES, MISDIAGNOSES.

Porphyria Awareness Week | April 11 - 18, 2015

IT'S A BEAUTIFUL DAY FOR PAIN

ACUTE INTERMITTENT PORPHYRIA CRUSADE

Porphyria, A Lyon's Share of Trouble

PORPHYRIA IS CALLED THE INVISIBLE DISEASE. Approximately 1 in 25,000 people in the United States have been diagnosed with Porphyria but it has an estimated 90% latency which has led to cases being misdiagnosed for years. Pain is severe and often requires multiple types of medication to reduce it to tolerable levels. Because Porphyria is a rare disease, hospital labs do not have the expertise, technology, or staff to perform testing for a positive diagnose. False negatives often occur in samples when a patient is not having an acute attack which then leads to mistreatment by physicians. Porphyria is a life-long disease.
Educational Materials
Congressional Efforts

One of Many Rare Disease Heroes

Hemin & Desiree Lyon

Hemin was the first orphan designated drug to receive marketing approval in 1983. It is used to relieve recurrent attacks of acute intermittent porphyria (AIP). In AIP, an important part of the body's metabolism is not working properly, causing varying symptoms, including severe abdominal pain. Desiree Lyon was 17 years old when she had her first attack, and she was undiagnosed for a decade. In 1983, she was given experimental hemin at the National Institutes of Health, which significantly improved her quality of life. At the time, Desiree served on the board of the American Porphyria Foundation and spoke in support of the enactment of the Orphan Drug Act. She continues to be an advocate for the rare disease community today.
Psalm 139:14: I praise You, because I am fearfully and wonderfully made.
Agenda

Welcome
• Joshua Brodsky
  Senior Manager, Investor Relations and Corporate Communications

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

Overview of Hepatic Porphyrias
• Robert J. Desnick, M.D., Ph.D., Dean for Genetics and Genomic Medicine, Professor and Chair Emeritus, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

Patient Advocacy: Porphyria Patient Perspective
• Desiree Lyon Howe, Co-Founder and Executive Director, American Porphyria Foundation

Q&A Session
• With Dr. Desnick and Desiree Lyon Howe

ALN-AS1 Program
• Bill Querbes, Ph.D., Associate Director, Research

Q&A Session
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Q&A Session
Acute Intermittent Porphyria (AIP) Program
Unmet Need, Product Opportunity, and Program Status

AIP is autosomal dominant disorder
• Ultra-rare orphan disease
  ◦ ~5,000 Patients with annual attacks U.S./EU
  ◦ ~500 Patients with recurrent attacks U.S./EU

High unmet need and cost
• Patients present with acute or recurrent attacks
• Limited treatment options
  ◦ Blood-derived hemin given IV via central line
  ◦ No prophylactic treatment to prevent attacks

Opportunity to treat and prevent porphyria attacks
• Orphan disease with substantial morbidity
• Value supported by significant burden of disease
• Explore study ongoing in patients
  ◦ Prospective observational study to monitor attacks

RNAi therapeutics – potential to halt disease symptoms
• Targets ALAS-1, upstream of genetic defect
• Blocks toxic intermediates (ALA/PBG)
• ALN-AS1 in development to treat and/or prevent attacks

ALN-AS1 in clinical development
• Proof of concept and efficacy in animal models
• Positive initial Phase 1 data at ICPP, Sept. 13-16, 2015
• Additional data expected in 2016
ALN-AS1: RNAi Therapeutic Hypothesis
Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG

ALN-AS1 knockdown of ALAS1 reduces ALA/PBG production and prevents attacks.

ALA/PBG induce porphyria symptoms.
ALN-AS1 Multidose Prophylaxis in Rat AIP Model

**ALAS1 mRNA**

<table>
<thead>
<tr>
<th>siRNA</th>
<th>PBS</th>
<th>3mg/kg</th>
<th>1mg/kg</th>
<th>0.3mg/kg</th>
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<tr>
<td>PB</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PBGD LNP</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
</tbody>
</table>

**URINARY ALA OR PBG (mmol/mol creatinine)**

<table>
<thead>
<tr>
<th>ALN AS1</th>
<th>PBS</th>
<th>3 mg/kg</th>
<th>1 mg/kg</th>
<th>0.3 mg/kg</th>
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<tbody>
<tr>
<td>PB</td>
<td>-</td>
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</table>

**ALAS-GalNAc 3, 1, 0.3mg/kg (QWx4)**

**Phenobarb**
ALN-AS1 Phase 1 Study: Design and Doses


- 0.035 mg/kg* x 1 SC, N=4
- 0.10 mg/kg x 1 SC, N=4
- 0.35 mg/kg x 1 SC, N=4
- 1.0 mg/kg x 1 SC, N=4

(All completed except 1.0 mg/kg x 1 SC, N=4 as ongoing)

Part B: Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled in ASHE

- 0.35 mg/kg, qMx2 SC, N=4
- Cohort 2, qMx2 SC, N=4

(Both cohorts ongoing)

Part C: Multiple-Dose (MD) | AIP patients with recurrent attacks

- Run-in Observation (4 to 24 weeks)
  - Cohort 1 x 12 weeks SC, N=4-6
  - Cohort 2 x 12 weeks SC, N=4-6

*The 0.035 mg/kg SAD cohort was dosed after the 0.10 and 0.35 mg/kg cohorts

Up to 4 additional cohorts for Part A and B
ALN-AS1 Phase 1 Study Initial Results
Safety and Tolerability

ALN-AS1 generally well tolerated

- No SAEs related to study drug and no discontinuations to date
  - One patient (0.10 mg/kg dose) required hospitalization for abdominal pain considered unlikely related to ALN-AS1

- Other AEs reported; all mild-moderate in severity
  - 9 AEs occurred in 4 placebo patients and 19 AEs occurred in 12 ALN-AS1-treated patients
  - No dose-related trend observed
  - No event occurred in more than one treated subject
  - One patient (1mg/kg dose) experienced a mild, transient injection site reaction (erythema)

- No clinically significant laboratory abnormalities related to study drug
  - One patient (0.35 mg/kg dose) had increased AST, ALT, CPK and myoglobin
    - Attributed to starting intensive weight lifting program that resolved with cessation of exercise

Data in database as of 02 September 2015
Circulating Extracellular RNA Detection (cERD) Method for Circulating ALAS1 mRNA Detection

Monitoring RNAi Activity in Liver
- mRNA or 5’RACE product in tissue
- Circulating secreted protein

Detection of Circulating ALAS1 mRNA
- Exosomes are shed into bodily fluids from many different cell types and contain mRNA and miRNA derived from tissue of origin
- Exosomes can be used to monitor ALAS1 mRNA levels after ALN-AS1 dosing in serum/urine without need for biopsy

![Graph showing ALAS1 mRNA Transcript in NHP](image-url)

**ALAS1 mRNA Transcript in NHP**

- by cERD
- by liver biopsy

**ALAS-GalNAc (mg/kg)**

QDx5, EOD, d15 (not DC)
ALN-AS1 Phase 1 Study Initial Results
Pharmacodynamic Data: Liver ALAS1 mRNA from Serum

ALAS1 mRNA increased approximately 3-fold in ASHE compared to normal healthy volunteers
Rapid, dose-dependent, and durable ALAS1 mRNA reduction after single dose
• 44 ± 8% mean (SEM) maximal reduction in 0.35 mg/kg group; p < 0.01 vs. Placebo^*  
• Up to 59% reduction in 0.35 mg/kg group  
• Essentially identical ALAS1 mRNA changes detected in urine

Data in database as of 02 September 2015
* Pairwise comparison vs. Placebo under baseline-adjusted ANCOVA model

^1 mg/kg ALAS1 mRNA data not available
ALN-AS1 Phase 1 Study Initial Results
Pharmacodynamic Data: Urinary ALA and PBG

Rapid, dose-dependent, and durable ALA and PBG lowering after single dose
- Mean (SEM) maximal reduction in 0.35 mg/kg group: 77 ± 7% (ALA) and 73 ± 6% (PBG); p = 0.03 and 0.06 vs. Placebo, respectively
- 1.0 mg/kg group (ongoing): Up to 82% (ALA) and 93% (PBG) reduction

N = 1 in 1 mg/kg group at Days 21, 28
Biorad assay performed at Porphyria Center Sweden

Data in database as of 02 September 2015
* Pairwise comparison vs. Placebo under baseline-adjusted ANCOVA model
ALN-AS1 Phase 1 Study Initial Results
Changes in ALAS1 mRNA and Urinary ALA/PBG Highly Correlated

Data in database as of 02 September 2015
ALN-AS1 Phase 1 Study Initial Results

Summary

ALN-AS1 generally well tolerated to date
- No significant AEs or laboratory abnormalities associated with ALN-AS1

Non-invasive method to quantify liver ALAS1 mRNA expression demonstrated:
- ASHE patients have 3-fold induced ALAS1 mRNA compared to normal subjects
- Rapid, dose-dependent, and durable ALAS1 mRNA lowering up to 59%; correlated with changes in ALA and PBG

Rapid, dose-dependent, and durable lowering of urinary ALA and PBG of up to 82% and 93%, respectively, with single 1 mg/kg dose
- Mean maximal reduction of 77% (ALA) and 73% (PBG) at 0.35 mg/kg dose

Next Steps for Phase 1 Study
- Part B, MAD portion ongoing in Sweden and UK
- Part C, MD portion in recurrent attack patients planned in Sweden, UK and US
Study Design Overview

**Design**
- Observational, multinational, prospective natural history study in up to 100 patients

**Key Eligibility Criteria**
- Males or Females ≥ 18 years old
- Diagnosis of acute hepatic porphyria (AHP) by specialist, including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP)
- Recurrent attacks
  - 3+ attacks* within 12 months of screening
  - Using heme or GnRH analogs prophylactically

**Key Objectives**
Characterize natural history and current AHP management
- Medical history and medication usage
- Porphyria signs and symptoms
- Biomarkers
- Quality of life

**Study Schedule**
- **Clinic Visit**
  - Questionnaires
  - Blood/urine samples
- **Clinic Visit**
  - 2 phone calls
  - Mail urine samples
  - If having attack:
    - Notify clinic
    - Blood/urine sample

*3+ attacks within 12 months of screening
Patient-reported Attack Symptoms
Screening Questionnaire

In addition, some attack symptoms present chronically in 49% of patients
- Most common chronic symptoms: pain, tiredness, N/V, constipation, and anxiety

Data as of 14 AUG 2015
101 attacks total with mean duration of 7.9 days
41/68 (60%) patients reported 1+ attack during study

<table>
<thead>
<tr>
<th>Attack Number</th>
<th>Heme Prophylaxis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No (60%, n=41)</td>
</tr>
<tr>
<td>Mean (SD) Days on Study</td>
<td>137.7 (102.9)</td>
</tr>
<tr>
<td># of Attacks* , total= 101</td>
<td>63</td>
</tr>
<tr>
<td>Annualized Attack Rate</td>
<td>4 attacks/per person</td>
</tr>
</tbody>
</table>

Attacks defined as patients reporting symptoms of porphyria attack (such as but not limited to: severe abdominal pain, back pain, constipation, tachycardia, or peripheral neuropathy).
Urinary ALA and PBG and ALAS1 mRNA

- Mean ALAS1 mRNA is increased >4-fold in asymptomatic AIP patient compared to normal healthy volunteers (NHV)
- ALAS1 mRNA further increased in AIP patients during acute attack

- Curated list of 16 patients with ≥ 1 asymptomatic measure and ≥1 attack measure
- Graph in Ln scale; arrows show mean and (median) fold change in actual scale
- BIORAD assay results; similar trends seen with LC-MS assay
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Speaker Biographies

**John Maraganore, Ph.D.**  
*Chief Executive Officer, Alnylam*

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

**Robert J. Desnick, M.D., Ph.D.**  
*Dean for Genetics and Genomic Medicine, Professor and Chair Emeritus, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai*

Dr. Desnick’s Porphyria research is focused on the clinical, biochemical and molecular genetic characterization of all eight porphyria’s. His laboratory was the first to purify several of the human heme biosynthetic enzymes, and to isolate their genes. They identified gene defects in all of the porphyrias and are currently working with mouse models of Acute Intermittent Porphyria (AIP) and Congenital Erythropoietic Porphyria (CEP) to characterize their pathogenesis and to investigate various therapeutic approaches, including cell and gene therapies. In addition to his Porphyria research, Dr. Desnick is the Director of the Mount Sinai Porphyrias Diagnostic and Treatment Center, and directs Mount Sinai’s DNA testing laboratory for the porphyrias. He is Principal Investigator of the NIH-sponsored Rare Diseases Clinical Research Consortium established to accelerate development of rare disease diagnosis and treatment. Dr. Desnick has served on the American Porphyria Foundation’s Scientific Advisory Board since its inception in 1982. He has published over 700 peer-reviewed research articles and chapters, and nine edited books. He is an elected Senior Fellow of the American Academy for the Advancement of Science and an elected member of the Academy of Medicine of the National Academy of Sciences.
Speaker Biographies

Desiree Lyon Howe

*Co-Founder and Executive Director, American Porphyria Foundation*

Desiree Lyon Howe is the Founder and Executive Director of the American Porphyria Foundation (APF), an international educational agency for the porphyrias, a group of rare, genetic diseases. The APF, which now hosts a membership of 8,000 patients, maintains a comprehensive educational program for patients and physicians. Desiree was just 17 years old when she had her first porphyria attack and suffered many years undiagnosed. Since that time, Desiree’s diagnosis of acute intermittent porphyria has motivated her to actively advocate for the development and approval of safe and effective treatment options for porphyria. Her activities over the past thirty years have centered on patient education, patient advocacy efforts and as an award winning writer. In these capacities, Desiree has authored health related books and articles, lectured on a variety of health related subjects, including patient support programs, the unique difficulties of rare and genetic diseases and cancer. Her book, *Porphyria: A Lyon’s Share of Trouble*, deals with the unique emotional and physical struggles of a patient with a genetic disorder. Desiree presently serves on the boards of M. D. Anderson Cancer Center and The University of Texas Medical Branch. In the past, she has served as a board member of the National Organization of Rare Disorders (NORD), the National Prostate Cancer Coalition, Alliance of Genetic Support Groups and Council of Regional Genetics.

Bill Querbes, Ph.D.

*Associate Director, Research, Alnylam*

As Associate Director of Research, Dr. Querbes is responsible for project leadership related to Alnylam’s discovery and early clinical stage programs, with a current focus on ALN-AS1, Alnylam’s investigational RNAi therapeutic for acute hepatic porphyrias. Bill joined Alnylam as a scientist in 2006 and since that time has played key roles in the advancement of RNAi delivery technologies and preclinical programs in the Genetic Medicine and Cardio-Metabolic Disease STArts. He received his Ph.D. in Medical Science from Brown University and his BS in Biology from SUNY Genesee.
Thank You

www.alnylam.com