CLINICAL OVERVIEW OF THE ACUTE HEPATIC PORPHYRIAS

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OUTLINE: PORPHYRIA / ALN-AS1
Dr. Desnick (KOL)

• Heme Biosynthesis & Regulation

• The Acute Hepatic Porphyrias/(AHPS):
  – 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

• Key Take-Home Messages
  - AHPs are life threatening diseases that seriously affect QoL
  - Their Prevalence is likely Higher than Appreciated
  - Current Therapies Are Limited; Need New & Effective Therapies
  - Hepatic ALAS1 Is Clearly the Therapeutic Target for All AHPs
### ACUTE HEPATIC PORPHYRIAS

<table>
<thead>
<tr>
<th>Porphyria</th>
<th>Deficient Enzyme Activity (% of Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Autosomal Dominant:</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>• Autosomal Recessive:</td>
<td></td>
</tr>
<tr>
<td>– ALA-Dehydratase Deficient Porphyria (ADP)</td>
<td>ALA-Dehydratase &lt;5%</td>
</tr>
<tr>
<td>• Major Clinical Manifestations:</td>
<td></td>
</tr>
<tr>
<td>– Acute Neurological Attacks</td>
<td></td>
</tr>
<tr>
<td>– Neuropathic Pain &amp; Progressive Neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Biochemical &amp; Molecular Diagnoses:</td>
<td></td>
</tr>
<tr>
<td>– During an Acute Attack:</td>
<td></td>
</tr>
<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>4 - 5*</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>

### American Porphyria Foundation Patient Registry

9200 Registered Members, ~3000 Acute Hepatic Patients, of these the following Are Biochemically/Mutation Confirmed:

- **AIP**: 1771
- **HCP**: 420
- **VP**: 352
- Total = 2543

*Andersson C., AIP in Northern Sweden, PhD Thesis, 1997; Elder et al., *J. Inherit Metab Dis* Epub Nov 1, 2012, **Estimated
ACUTE NEUROVISCERAL ATTACKS

• Manifestations:
  – Prodrome: “Brain Fog”, Insomnia, Fatigue
  – Autonomic Neuropathy: Abdominal Pain, Vomiting, Hypertension
  – Peripheral Neuropathy: Weakness, Paralysis
  – Mental Involvement: Psychosis, Seizure, Etc.
  – Progressive Neuropathy and Neuropathic Pain

• Precipitating Factors:
  – Drugs (P450 Inducers), Alcohol
  – Dieting, Low Caloric Intake
  – Hormonal Changes (Menstruation), Etc.

• Diagnosis:
  – Increased Plasma/Urinary 5’-Aminolevulinic Acid (ALA) & Porphobilinogen (PBG)
PATHOGENESIS OF THE ACUTE ATTACKS IN AIP

Normal

Hepatic Heme-Mediated Feedback Repression

Glycine + Succinyl CoA

ALAS1 → ALA → ALA

ALAD → PBG → 50% HMB-Synthase HEME

Decreased Hepatic Heme-Mediated Feedback Repression

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

- Frequency of Acute Neurologic Attacks:
  - **Recurrent Attacks**: >3 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 (ASHE)**: 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>
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$_{10}$W Immediately
  - (300-400g/Day)
- Order Hematin and Begin Infusions
INTRAVENOUS HEMATIN 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 \textit{ALAS1} Through the Negative Feedback Loop

• Intravenous Glucose Alone is Appropriate Only for Mild Attacks or Until Hemin is Available
SAFETY OF HEMATIN

- Hematin (Panhematin®) – 1ST Orphan Drug, 1982
  - Approved Based on Small Open Label Studies, but in Clinical Use for >30 Years
  - Adverse Reactions or Side Effects\(^1\)\(^-\)\(^4\): 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

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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
- ~10 Additional Patients Transplanted in Europe
- Domino Transplant Patients Had ↑↑ ALA & PBG and Attacks
- Challenges:
  - High Frequency of Arterial Vessel Thromboses
  - Limited Availability of Organs
  - High Morbidity & Mortality
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
RATIONALE FOR TARGETING HEPATIC ALAS1 IN LIVER

- ALAS1 mRNA Strongly Upregulated During Attacks
- Hematin Down Modulates ALAS1
- Addition of Heme to Liver Cells in Culture Leads to Reduced ALAS1 mRNA
- Liver Transplant Is Curative
- Domino Transplant Recipients Have Increased ALA/PBG & Have AIP Symptoms
- Liver Derived Metabolites Drive Attacks
CONCLUSIONS

• Acute Hepatic Porphyrias 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 Mechanism of Action

• Unmet Need for New Therapeutic Options:
  – Better Safety Profile and Faster Onset
  – Effective for Prophylaxis
ALN-AS1 for Acute Hepatic Porphyrias

Rachel Meyers, Ph.D.
SVP, Research
Acute Hepatic Porphyria (AHP) Program
Unmet Need, Product Opportunity, and Program Status

**AHPs are autosomal dominant disorders**
- Ultra-rare orphan disease
  - ~5,000 Patients with annual attacks U.S./EU
  - ~1000 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 to halt disease symptoms**
- Targets ALAS1, upstream of genetic defect
- Blocks toxic intermediates (ALA/PBG)
- ALN-AS1 to treat and/or prevent attacks
### ALN-AS1 for Acute Hepatic Porphyrias

**Alnylam Reproducible and Modular Platform**

|   | 1 | Genetically validated, liver-expressed target gene | **ALAS1** is upstream of genetic defect in acute hepatic porphyrias  
Up-regulation of ALAS1 results in accumulation of toxic intermediates that drive disease |
|---|---|---|---|
|   | 2 | Biomarker for POC in Phase 1 | Blood-based biomarkers are toxic intermediates that induce porphyria symptoms:  
• **ALA**  
• **PBG** |
|   | 3 | Definable path to approval and market | Streamlined clinical development plan  
Established Endpoints:  
• **ALA & PBG levels**  
• **Porphyria attack frequency and severity** |
RNAi Therapeutic Targeting ALAS-1
Potential Use for Prophylaxis and Acute Treatment

Recurrent Attack Setting (Prophylaxis)

Therapeutic Hypothesis
- Chronic suppression will blunt recurrent ALAS-1 upregulation that drives attacks
- Should result in chronic suppression of ALA/PBG
- Yields reduction in number and severity of attacks

Acute Attack Setting (Treatment)

Therapeutic Hypothesis
- Halt flux through pathway
- Quick reduction in ALA/PBG
- Rapid improvement in clinical symptoms
Prophylaxis with ALN-AS1 Inhibits Metabolite Production in Rat AIP Model

D0  D7  D14  D21  D25 (sac)

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

D18 PBGD LNP

ALAS1 mRNA

~50% ALAS1 lowering at 1mg/kg

Urinary ALA or PBG (mmol/mol creatinine) PBS=1

Leads to near-normal ALA & PBG

22
Prophylaxis with ALN-AS1 Inhibits Metabolite Production in Rat AIP Model

Based on pre-clinical data and biochemical response known to occur with heme, goal for ALN-AS1 dosing in clinic:
- Potential for near normalization of ALA and PBG
- While minimizing extent of ALAS1 mRNA reduction (predict ~ 50% required)
## ALN-AS1 Phase 1 Study: Design and Doses

### Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled, in ASHE

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dosing Schedule</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035 mg/kg*</td>
<td>x 1 SC, N=4</td>
<td>✔</td>
</tr>
<tr>
<td>0.10 mg/kg</td>
<td>x 1 SC, N=4</td>
<td>✔</td>
</tr>
<tr>
<td>0.35 mg/kg</td>
<td>x 1 SC, N=4</td>
<td>✔</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>x 1 SC, N=4</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dosing Schedule</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 mg/kg</td>
<td>qMx2 SC, N=4</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>qMx2 SC, N=4</td>
<td>✔</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Observation Phase</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in Observation (4 to 24 weeks)</td>
<td>✔</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>x 12 weeks SC, N=4-6</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>x 12 weeks SC, N=4-6</td>
</tr>
</tbody>
</table>

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

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

N = 1 in 1 mg/kg group at Days 21, 28
Biorad assay performed at Porphyria Center Sweden
ALN-AS1 Phase 1 Study Initial Results
Changes in ALAS1 mRNA and Urinary ALA/PBG Highly Correlated

ALAS1 mRNA vs. ALA

ALAS1 mRNA vs. PBG

R² = 0.82
P < 10⁻¹⁵

Treatment
- Placebo
- 0.035 mg/kg
- 0.1 mg/kg
- 0.35 mg/kg

Liver ALAS1 mRNA % Change from Baseline

Urine ALA % Change from Baseline

Liver ALAS1 mRNA % Change from Baseline

Urine PBG % Change from Baseline

Data in database as of 02 September 2015
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

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*Attacks defined as acute porphyria symptoms requiring increase in treatment (heme, pain medications, carbohydrates) or hospitalization*

ClinicalTrials.gov Identifier: NCT02240784
Attack Data

- 101 attacks total with mean duration of 7.9 days
- 41/68 (60%) patients reported 1+ attack during study

<table>
<thead>
<tr>
<th>Current Heme Prophylaxis</th>
<th>No (60%, n=41)</th>
<th>Yes (40%, n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Days on Study</td>
<td>137.7 (102.9)</td>
<td>180.5 (80.2)</td>
</tr>
<tr>
<td>Number of Attacks*</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>(total = 101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized Attack Rate</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>(per person)</td>
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</tbody>
</table>

- Patients on heme prophylaxis still experience attacks
- Majority of attacks are in hospital setting
- >70% of attacks treated with heme and/or pain meds (narcotics)
- Some attack symptoms present chronically in ~50% of patients
  - Most common chronic symptoms: pain, fatigue, anxiety and constipation

Data as of 14 AUG 2015
## Unmet Needs in Acute Hepatic Porphyrias

<table>
<thead>
<tr>
<th>Porphyria</th>
<th>Population:</th>
<th>Current Treatment:</th>
<th>Major Unmet Medical Needs:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Intermittent Porphyria</strong></td>
<td>Prophylaxis for patients with acute attacks</td>
<td>Heme (US)</td>
<td>Diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heme Ariginate (EU)</td>
<td>Effective prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV Glucose</td>
<td>Unstable heme products causes side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potential for tachyphylaxis</td>
</tr>
<tr>
<td><strong>Variegate Porphyria</strong></td>
<td>Treatment of patients with acute attacks</td>
<td>Heme (US)</td>
<td>Diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heme Ariginate (EU)</td>
<td>Rapid resolution of attack symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV Glucose</td>
<td>Impact of cutaneous symptoms to lifestyle</td>
</tr>
<tr>
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<td>Unstable heme products causes side effects</td>
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<tr>
<td><strong>Hereditary Coproporphyria</strong></td>
<td>Treatment of patients with acute attacks</td>
<td>Heme (US)</td>
<td>Diagnosis</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unstable heme products causes side effects</td>
</tr>
</tbody>
</table>
Significant opportunity to treat and potentially prevent attacks

- Orphan disease with substantial morbidity
  - IV Heme products have poor stability, limited efficacy and significant side effects
  - Heme not indicated for prophylaxis, use is controversial due to safety profile and potential tachyphylaxis

- Potential for long-term growth through improved diagnosis
  - Significant number of patients are undiagnosed or poorly managed
    - Mean time to diagnosis ~15 years
  - Porphyria Centers of Excellence (i.e., American Porphyria Consortium) support rapid adoption of new therapies

- Value supported by significant burden of disease (hospital visits, impact to productivity) and cost of current standard of care

- Strong patient advocacy from the American Porphyria Foundation and other patient organizations around the world
Porphyria Epidemiology
Alnylam Initial Focus on Recurrent and Sporadic AIP Patients

High unmet medical need provides opportunity for rapid penetration
• Small identifiable patient population with life threatening recurrent attacks
  ◦ Many patients choose to not use existing standard of care (heme) due to tolerability, efficacy issues
  ◦ Emerging natural history data suggest high incidence of “at-home” attacks and chronic symptoms
• Potential for patients with sporadic attacks to be treated
• Focused number of Porphyria Centers of Excellence support rapid adoption
• No other promising products currently in development

Acute Hepatic Porphyria Population Estimates – Major Markets (US, Europe, Japan, Brazil)

Patients with other AHP likely to have fewer recurrent attacks based on published literature

*Truven Marketscan US data; extrapolated to other geographies
## Porphyria is Compelling Commercial Opportunity Supported by Close Analogue: HAE

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence*</th>
<th>Clinical Manifestations</th>
<th>Current Standard of Care</th>
<th>Global Market (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Intermittent Porphyria (AIP)</strong></td>
<td>1:75,000 Autosomal dominant</td>
<td>• Intermittent and recurrent neuro-visceral attacks&lt;br&gt;• Intense abdominal pain&lt;br&gt;• Neurological and/or psychological symptoms</td>
<td>Panhematin (Plasma derived Heme, IV, acute treatment)</td>
<td>&lt;$100M</td>
</tr>
<tr>
<td><strong>Hereditary Angio-Edema (HAE)</strong></td>
<td>1:100,000 Autosomal dominant</td>
<td>• Transitory and recurrent subcutaneous and/or submucosal edemas&lt;br&gt;• Swelling and/or abdominal pain</td>
<td>Cinryze (C1 esterase inhibitor, IV, prophylaxis)&lt;br&gt;Berinert; Ruconest (C1 esterase inhibitor, IV acute)&lt;br&gt;Firazyr; Kalbitor (Kallikrein inhibitor, SC, acute)</td>
<td>$1B</td>
</tr>
</tbody>
</table>

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* Orphanet
** CMS.gov; assuming monthly attacks treated at recommended dose
*** CMS.gov; prophylactic treatment
# ALN-AS1 Target Product Profile

<table>
<thead>
<tr>
<th>ALN-AS1</th>
<th>Target Product Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>• Prevention of attacks in patients with acute hepatic porphyria</td>
</tr>
<tr>
<td><strong>Dose and Regimen</strong></td>
<td>• ≤2.5 mg/kg, once monthly (qM) or once every 3 months (qQ)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>• Low volume, subcutaneous via auto-injector</td>
</tr>
</tbody>
</table>
| **Efficacy** | • Primary  
  • Significant reduction in frequency of attacks  
  • Secondary  
  • Diminished severity of any breakthrough attacks  
  • Reduced use of heme and pain medications  
  • Decreased hospitalizations  
  • Improved quality of life |
| **Safety** | • Very low incidence of mild-moderate ISRs  
  • No significant impact on liver or kidney function |

Target product profiles for investigational RNAi therapeutics reflect current thinking on desired product characteristics and are subject to change.
Potential Phase 3 Study Design for ALN-AS1*
Initial Focus on Prophylaxis for Recurrent AIP Patients

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

Endpoints (at 9 months)
- Change in annualized attack rate compared to baseline at 9 months
- ALA, PBG and ALAS1 levels
- Hematin and pain medication usage
- Hospitalization
- EQ-5D-5L QoL
- Safety and tolerability

All completers eligible for ALN-AS1 treatment in Phase 3 OLE study

*Preliminary plans subject to further diligence and health authority feedback
ALN-AS1 Program Summary & Next Steps

**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 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

**Potential for Streamlined Phase 3 Study with clear and measurable endpoints**
- Natural history study informing Phase 3 endpoints

**Significant opportunity to potentially prevent attacks**
- Standard of care inadequate to manage disease
- Potential for growth with improved diagnosis and strong patient advocacy groups

**Next Steps**
- Part B of Phase 1, MAD portion ongoing in Sweden and UK
- Part C of Phase 1, MD portion in recurrent attack patients planned in Sweden, UK and US