Interim Data from a Randomized, Placebo Controlled, Phase 1 Study of Givosiran (ALN-AS1), an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyria

Eliane Sardh, MD, PhD1,2, Pauline Harper, MD, PhD1,2, Nabil Al-Tawil, MD1,3, Manisha Balwani, MD4, Karl Anderson, MD5, Joseph Bloomer, MD3, D. Montgomery Bissell, MD7, Robert Desnick, MD, PhD4, Charles Parker, MD3, John Phillips, PhD8, Herbert Bonkovsky, MD9, Craig Penz, MA10, Amy Chan10, PhD, Chang-Heok Soh, PhD10, William Querbes, PhD10, Amy Simon, MD10, Penelope Stein, MD, PhD11, and David Rees, MD11

1Karolinska University Hospital, Karolinska Institute; 2Stockholm, Sweden, Porphyria Centre Sweden; 3Karolinska Trial Alliance Phase 1 Unit; 4Icahn School of Medicine at Mount Sinai, New York, NY; 5University of Texas Medical Branch, Galveston, TX; 6University of Alabama, Birmingham, AL; 7University of California, San Francisco, CA; 8University of Utah, Salt Lake City, UT; 9Wake Forest University, Winston-Salem, NC; 10Alnylam Pharmaceuticals, Cambridge, MA; 11King’s College Hospital, London, United Kingdom

3 December 2016 | ASH | San Diego, CA
Acute Hepatic Porphyria Disease Overview

**Acute Hepatic Porphyria (AHP)**\(^1,2\)
- Inborn errors of heme synthesis from liver enzyme defects
- AIP most common, with prevalence 2-5 per 100,000, approximately 5-10% manifest
  - Autosomal dominant mutation in hydroxymethylbilane synthase (HMBS)

**Disease Pathophysiology**
- Increased ALAS1 levels leads to accumulation of toxic heme intermediates ALA/PBG that cause acute attacks

**Attack Manifestations**
- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis

**Treatment and Unmet Need**
- Acute treatment and prophylaxis with human hemin (IV)
- Unmet need for more efficacious and safer therapies for prophylaxis

---

Givosiran: Investigational RNAi Therapeutic Therapeutic Hypothesis

Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG

ALAS1 protein

ALAS1 protein

Givosiran (ALN-AS1) knockdown of ALAS1 reduces ALA/PBG production and prevents attacks

ALA/PBG induce porphyria symptoms

Givosiran (ALN-AS1) reduces ALA/PBG production and prevents attacks

Givosiran (ALN-AS1) ALAS1 siRNA Liver targeting ligand

ALAS1
Givosiran Phase 1 Study: Parts A and B
Study Design and Objectives


- 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
- 2.5 mg/kg x 1 SC, N=4

Part A and B Study Objectives:
- Primary: safety
- Secondary: PK and PD (ALA, PBG)
- Exploratory: ALAS1 mRNA by cERD

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

- 0.35 mg/kg, qMx2 SC, N=4
- 1.0 mg/kg, qMx2 SC, N=4

*0.035 mg/kg cohort dosed after 0.10 and 0.35 mg/kg cohorts
Updated Givosiran Phase 1 (Parts A,B) Study Results*

Parts A and B Study Summary

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

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

*S* Data transfer date: 07 Nov 2016

†5 subjects had >1 treatment assignment: 2 subjects repeated Part A; 3 subjects enrolled in Parts A and B
### Study Design
- Placebo-controlled, double-blind, randomized 3:1, multiple dose study in AIP patients with recurrent attacks
- Key Inclusion Criteria:
  - 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 of givosiran
- Characterize givosiran PK and PD

### Exploratory Objectives
- Clinical activity of givosiran on attack characteristics and treatment
- Characterize circulating ALAS1 mRNA from the liver in urine and serum

---

**Data cut-off is D168 for Cohort 1 (unblinded) and D84 for Cohort 2 (blinded)**

Clinicaltrials.gov: NCT02452372
## Demographics (N=8)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; mean (range)</td>
<td>39.4 (21-60)</td>
</tr>
<tr>
<td>Sex: Female, n (%)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Race: White/Caucasian, n (%)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Patient Reported Attack Number in last 12 mos; mean (range)</td>
<td>17.9 (0-50)</td>
</tr>
<tr>
<td>Hemin prophylaxis use prior to study, n (%)</td>
<td>5 (62)</td>
</tr>
</tbody>
</table>

## Baseline Disease Activity (N=8)

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PBG, mmol/mol Cr; mean (min, max)</td>
<td>48.6 (12.3, 88.2)</td>
</tr>
<tr>
<td>Baseline ALA, mmol/mol Cr; mean (min, max)</td>
<td>23 (2.6, 36.7)</td>
</tr>
</tbody>
</table>

*Data transfer date: 07 Nov 2016
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) Study Results*
Safety and Tolerability in AIP Patients with Recurrent Attacks

No drug-related SAEs in Cohorts 1-4

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

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

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*
Clinical Activity Data: Cohort 1, Placebo Patient

<table>
<thead>
<tr>
<th>Period</th>
<th>Weeks</th>
<th>Attacks</th>
<th>Attacks Annualized</th>
<th>Max Attack-Free Interval (Days)</th>
<th>Hemin Doses</th>
<th>Hemin Doses Annualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In</td>
<td>12</td>
<td>8</td>
<td>34</td>
<td>9</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Treatment</td>
<td>22</td>
<td>11</td>
<td>26</td>
<td>16</td>
<td>12</td>
<td>29</td>
</tr>
</tbody>
</table>

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*
Clinical Activity Data: Cohort 1, Givosiran – Patient 1

### Periods Summary

<table>
<thead>
<tr>
<th>Period</th>
<th>Weeks</th>
<th>Attacks</th>
<th>Attacks Annualized</th>
<th>Max Attack-Free Interval (Days)</th>
<th>Hemin Doses</th>
<th>Hemin Doses Annualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In</td>
<td>12</td>
<td>9</td>
<td>38</td>
<td>10</td>
<td>24</td>
<td>102</td>
</tr>
<tr>
<td>Treatment</td>
<td>22</td>
<td>6</td>
<td>14</td>
<td>42</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*  
Clinical Activity Data: Cohort 1, Givosiran – Patient 2

<table>
<thead>
<tr>
<th>Period</th>
<th>Weeks</th>
<th>Attacks</th>
<th>Attacks Annualized</th>
<th>Max Attack-Free Interval (Days)</th>
<th>Hemin Doses</th>
<th>Hemin Doses Annualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In</td>
<td>12</td>
<td>11</td>
<td>47</td>
<td>6</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>Treatment</td>
<td>25</td>
<td>7</td>
<td>15</td>
<td>62</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*
Clinicl Activity Data: Cohort 1, Givosiran – Patient 3

<table>
<thead>
<tr>
<th>Period</th>
<th>Weeks</th>
<th>Attacks</th>
<th>Attacks Annualized</th>
<th>Max Attack-Free Interval (Days)</th>
<th>Hemin Doses</th>
<th>Hemin Doses Annualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-In</td>
<td>12</td>
<td>8</td>
<td>35</td>
<td>10</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Treatment</td>
<td>25</td>
<td>1</td>
<td>2</td>
<td>169</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*  
Summary of Clinical Activity Data Cohorts 1 and 2 in AIP Patients

Givosiran Treated Period Relative to Run-in

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

*Data transfer date: 07 Nov 2016
Interim Givosiran Phase 1 (Part C) Study Results*

Cohorts 1 and 2 Summary and Next Steps

**Givosiran safety and tolerability**
- No drug-related SAEs or discontinuations due to AEs
- No dose-dependent AEs or clinically significant changes in vital signs, EKG, clinical laboratory parameters or physical examination
- Cohort 3: one unlikely related fatal SAE of acute pancreatitis complicated by a pulmonary embolism

**Givosiran showed robust clinical activity in AIP patients with recurrent attacks**
- Data suggest modest lowering, and/or blunting of further increases during attacks, of ALA/PBG may be sufficient for clinical activity
- Cohort 1 Data in Givosiran-treated patients:
  - 74% reduction in annualized attack rate compared to run-in
  - 75% reduction in annualized hemin usage compared to run-in
  - 10.5x maximum attack free interval (~82 days longer on average) compared to run-in
- Aggregated Cohort 2 Blinded Data:
  - Supportive data demonstrating reduction in attack rate and hemin usage compared to run-in

**Next Steps**
- Complete dosing of Cohorts 3 and 4
- Ongoing open label extension study for longer term safety and clinical activity data
- Initiate Phase 3 study in late 2017, subject to successful global regulatory interactions

*Data transfer date: 07 Nov 2016*
Acknowledgements

Thank you to the patients, investigators, and study staff who participated in this study.

<table>
<thead>
<tr>
<th>Investigator(s)</th>
<th>Institution</th>
<th>City/Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliane Sardh</td>
<td>Karolinska University Hospital</td>
<td>Stockholm, Sweden</td>
</tr>
<tr>
<td>Nabil Al-Tawil</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>David Rees</td>
<td>King’s College</td>
<td>London, UK</td>
</tr>
<tr>
<td>Penelope Stein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manisha Balwani</td>
<td>Mt. Sinai Icahn School of Medicine</td>
<td>New York, USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karl Anderson</td>
<td>University of Texas Medical Branch</td>
<td>Galveston, TX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joseph Bloomer</td>
<td>University of Alabama, Birmingham</td>
<td>Birmingham, AL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montgomery Bissell</td>
<td>University of California, San</td>
<td>San Francisco, CA</td>
</tr>
<tr>
<td>Bruce Wang</td>
<td>Francisco</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>