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

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Acute Hepatic Porphyrias

Disease Overview

**Acute Hepatic Porphyrias (AHP)**\(^1,2\)
- Inborn errors of heme synthesis from liver enzyme defects
- AIP (Acute Intermittent Porphyria) most common, with a mutation in hydroxymethylbilane synthase (HMBS)

**Disease Pathophysiology**
- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG that cause disease manifestations

**Acute Attacks and Chronic 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**
- Glucose and hemin used to treat acute attacks and by some specialists to prevent attacks
- Unmet need for more efficacious, long acting, and safer therapies to prevent attacks and improve chronic disease manifestations

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RNA Interference (RNAi) Investigational Therapeutics

RNAi Mechanism of Action
- Harnesses natural pathway in cells
- Mediated by small interfering RNA (siRNA)
- Silence any gene in genome
- Distinct from gene therapy

GalNAc Ligand Mediates Liver Delivery
- N-acetyl galactosamine (GalNac) ligand has high affinity (nM) for receptor on hepatocytes (ASGPR)
- Administered subcutaneously (SC)
- Mediates robust silencing of target genes in liver

*Asialoglycoprotein receptor (ASGPR)
Givosiran: Investigational RNAi Therapeutic Therapeutic Hypothesis

Reduction of Liver ALAS1 Protein to Lower ALA/PBG

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 Phase 1 Study Design and Objectives

### Parts A and B (SAD/MAD) in Chronic High Excreter (CHE) patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Randomized, single-blind, placebo-controlled single (SAD) and multiple ascending dose (MAD) study CHE patients</em></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Objective**

- Safety and tolerability

**Secondary Objectives**

- Characterize givosiran pharmacokinetics (PK) and pharmacodynamics (PD), i.e. ALA and PBG lowering

**Exploratory Objectives**

- Characterize circulating ALAS1 mRNA from liver in urine and serum

### Part C (MD) in recurrent attack patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Placebo-controlled multiple dose (MD) study in recurrent attacks patients</em></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Objective**

- Safety and tolerability

**Secondary Objectives**

- Characterize givosiran PK and PD

**Exploratory Objectives**

- Clinical activity on attack characteristics and patient quality of life
- Characterize circulating ALAS1 mRNA (cERD) from liver in urine and serum
Givosiran Phase 1 Study
Key Study Eligibility Criteria

Part A and B Inclusion
• Male or female, ages 18-65 years
• AIP, with genetic diagnosis of HMBS mutation
• Urine PBG > 4 mmol/mol creatinine at screening

Part A and B Exclusion
• Attack* within 6 months of screening
• Hemin use in past 6 months
• Patients with new prescription medication regimen within 3 months of screening

Part C Only Inclusion
• Experienced at least 2 porphyria attacks in past 6 months or on hemin prophylaxis to prevent attacks
• If on hemin prophylaxis, willing to stop during study

Clinicaltrials.gov: NCT02452372; *Attack definition: intense abdominal or back pain requiring hospitalization, hemin use or treatment consisting of increased carbohydrate intake or pain medication
# Givosiran Phase 1 (Parts A and B) Study Design

## Dosing Regimen

### Part A: SAD
- Randomized, placebo-controlled 3:1 in CHE patients

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035* mg/kg x 1 SC</td>
<td></td>
</tr>
<tr>
<td>0.10 mg/kg x 1 SC</td>
<td></td>
</tr>
<tr>
<td>0.35 mg/kg x 1 SC</td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg x 1 SC</td>
<td></td>
</tr>
<tr>
<td>2.5 mg/kg x 1 SC</td>
<td></td>
</tr>
</tbody>
</table>

*0.035 mg/kg cohort dosed after 0.10 and 0.35 mg/kg cohorts

### Part B: MAD
- Randomized, placebo-controlled 3:1 in CHE patients

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 mg/kg, qMx2 SC</td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg, qMx2 SC</td>
<td></td>
</tr>
</tbody>
</table>

Clinicaltrials.gov: NCT02452372
SAD, single ascending dose; CHE, Chronic High Excreter; MAD, and multiple ascending dose
### Demographics and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>N=23* (Givosiran:Placebo=21:7)</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>47 years (30-64)</td>
</tr>
<tr>
<td>Sex: Female, n (%)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Race: White/Caucasian n (%)</td>
<td>22 (96)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Genotype (n)</td>
<td>8 different mutations identified: 593G&gt;A (13) 87+1G&gt;A (4) 499-1G&gt;A (1) 517C&gt;T (1) 647G&gt;A (1) 847_848delTG (1) Variant exon 11 673C&gt;T (1) Exon 3 shift IVS3+1G&gt;T(1)</td>
</tr>
<tr>
<td>Mean baseline ALA (range)</td>
<td>11.0 mmol/mol Cr (2.9-24.6)^</td>
</tr>
<tr>
<td>Mean baseline PBG (range)</td>
<td>22.0 mmol/mol Cr (4.5-50.5)^</td>
</tr>
</tbody>
</table>

*5 patients had >1 treatment assignment: 2 patients repeated Part A; 3 patients enrolled in Part A and B

^Upper Limit of Normal: ALA<3.9 or 3.8 mmol/mol Cr; PBG<1.6 or 1.5 mmol/mol Cr (site dependent)

Biorad assay performed at Porphyria Centers in Sweden and UK
Interim Givosiran Phase 1 (Parts A and B) Study Results
Safety and Tolerability*

Part A
- 11 patients reported AEs; all mild/moderate except 1 severe unrelated AE of abdominal pain
- AEs reported in ≥2 patients: abdominal pain, diarrhea, nasopharyngitis, and hypoesthesia
- 4 patients had related AEs
  - Diarrhea, dyspepsia, hematochezia, hypoesthesia, ISRs (erythema and pain), mild decreased GFR/increased creatinine
- ISRs were mild and transient

Part B
- 6 patients reported AEs, all AEs mild/moderate severity except 1 unrelated AE of bursitis
- AEs reported in ≥2 patients: nasopharyngitis, pruritus and rash
- 3 patients reported related AEs: pruritus and rash
- No ISRs reported

No drug-related SAEs or discontinuations due to AEs
- 2 patients (0.035 and 0.10 mg/kg dose) hospitalized for SAE of “abdominal pain”; both assessed as unlikely related (noted above)
- 1 patient (1 mg/kg dose) miscarried 7 weeks post-conception (90 days post-givosiran) during follow-up; assessed as unlikely related

No clinically significant changes in vital signs, EKG, clinical laboratory or physical examination

*All Safety Data in database as of 5 May 2017; AEs- Adverse Event; ISRs- Injection Site Reaction; GFR- glomerular filtration rate; SAE- Severe Adverse Event; EKG- electrocardiogram.
Method for Liver ALAS1 mRNA Detection in Serum or Urine Circulating Extracellular RNA Detection (cERD)

- Exosomes shed into bodily fluids from different cells contain mRNA from non-human primate tissue of origin
- Correlation of liver and serum ALAS1 mRNA shown in preclinical studies
- Exosomes may enable porphyria disease monitoring by following circulating ALAS1 mRNA in serum/urine

Interim Givosiran Phase 1 (Part A) Study Results
Pharmacodynamics, Serum ALAS1 mRNA

Rapid, dose-dependent lowering of induced ALAS1 mRNA

- Serum ALAS1 mRNA levels induced ~2 times in CHE compared to normal healthy (NH) levels
- 64 ± 1% mean (SEM) maximal ALAS1 mRNA reduction with single 2.5 mg/kg dose
- Remaining ALAS1 mRNA levels after 1 or 2.5 mg/kg dose similar to NH levels

ALAS1 mRNA by cERD

CHE, Chronic high excreters
*Derived from healthy individuals not in study
Interim Givosiran Phase 1 (Part A) Study Results
Pharmacodynamics, ALA and PBG

Rapid, dose-dependent, and durable lowering of ALA and PBG

- Single givosiran dose results in:
  - Mean (SEM) maximal reduction of 86 ± 2% ALA and 95 ± 0.4% PBG with 2.5 mg/kg dose
  - Durable ALA and PBG lowering, supporting monthly or quarterly dosing
  - Normalization of ALA/PBG at 2.5 mg/kg dose levels

Interim Givosiran Phase 1 (Part A) Study Results
ALAS1 mRNA and Urinary ALA/PBG

Serum ALAS1 mRNA Highly Correlated to Urinary ALA and PBG

**ALAS1 mRNA vs ALA**

- *Regression Line*
- Placebo
- 0.035 mg/kg
- 0.10 mg/kg
- 0.35 mg/kg
- 1.0 mg/kg
- 2.5 mg/kg

**ALAS1 mRNA vs PBG**

- *Regression Line*
- Placebo
- 0.035 mg/kg
- 0.10 mg/kg
- 0.35 mg/kg
- 1.0 mg/kg
- 2.5 mg/kg

R² = 0.79
p<0.001

R² = 0.87
p<0.001
Interim Givosiran Phase 1 Study Results
Summary: Parts A and B

Safety
• Givosiran generally well-tolerated
• Most common AEs were abdominal pain, diarrhea, nasopharyngitis, hypoesthesia
• No drug-related SAEs or discontinuations due to AEs
• No dose-dependent AEs or clinically significant changes in vital signs, EKG, labs or physical exam

Non-invasive method to quantify liver ALAS1 mRNA expression demonstrated
• CHE patients have 2 times ALAS1 mRNA induction compared to NH levels
• May provide another method, in addition to ALA and PBG, to follow disease activity in some porphyria patients

Rapid, dose-dependent, and durable reductions in ALAS1 mRNA and urinary ALA and PBG with single and multiple givosiran doses
• 64% ALAS1 lowering with a single 2.5 mg/kg dose; 54% with multiple 1.0 mg/kg doses
• 86% ALA and 95% PBG lowering with a single 2.5 mg/kg dose
• 84% ALA and 89% PBG lowering with multiple 1.0 mg/kg doses

AEs, Adverse Event; EKG, electrocardiogram; SAEs, Severe Adverse Event; ALA, CHE, chronic high excreters; NH, normal healthy; All Safety Data in database as of 5 May 2017
### Givosiran Phase 1 (Part C and OLE) Study

#### Study Design and Objectives

**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

### Study Design and Objectives Table

<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Run-in Period</th>
<th>Cohort 1, 2.5 mg/kg q3M x 2, N=4</th>
<th>5.0 mg/kg q3M, N=4</th>
</tr>
</thead>
<tbody>
<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>

**OLE, Open label Extension**
Clinicaltrials.gov: NCT02452372
### 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>Patient Reported Attacks in last 12 mos, mean (range)</td>
<td>22.3 (5-50)</td>
<td>13.5 (0-36)</td>
<td>8.5 (4-12)</td>
</tr>
<tr>
<td>Hemin Prophylaxis Use Prior to Study, n (%)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Baseline PBG, mmol/mol Cr mean, (range)*</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>Baseline ALA, mmol/mol Cr mean, (range)*</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></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 and OLE) Study Results
Safety and Tolerance

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 is 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

All Safety Data in database as of 5 May 2017
Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Pharmacodynamics, Serum ALAS1 mRNA

Rapid, Dose-dependent and Durable ALAS1 Lowering

- ALAS1 mRNA levels induced ~4 times in recurrent attack patients compared to NH levels
- 70 ± 3% Mean (SEM) maximal ALAS1 reduction in 5 mg/kg QM dose group (Cohort 3)
- Remaining ALAS1 mRNA levels with multiple doses near NH levels (dashed line)

ALAS1 mRNA levels in CHE and Recurrent Attack Patients

ALAS1 mRNA Levels Post-Dosing in Recurrent Attack Patients

Data cut date of 21 Apr 2017

## 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)</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)</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

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

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

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Interim Givosiran Phase 1 (Part C, Cohorts 1-3) Study Results
Clinical Activity, Annualized Hemin Doses

73% Mean Decrease in Annualized Hemin Doses

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 Quartiles**
- ALA Lowering ≤0%
- ALA Lowering >0-25%
- ALA Lowering >25-50%
- ALA Lowering >50-75%
- ALA Lowering >75%

**Mean (SEM) Annualized Attack Rate**
- ALA Lowering ≤0%: 17.6 (3.5)
- ALA Lowering >0-25%: 19.6 (6.2)
- ALA Lowering >25-50%: 11.9 (4.2)
- ALA Lowering >50-75%: 5.5 (2.3)
- ALA Lowering >75%: 3.8 (1.4)

**Number of Attacks**
- 25
- 10
- 8
- 6
- 8

**Patient-years**
- 1.4
- 0.5
- 0.7
- 1.1
- 2.1

*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
Interim Givosiran Phase 1 (Part C, Cohorts 1-2 OLE) Study Results

Clinical Activity

Givosiran activity maintained, potential for further reductions in attack rate with extended dosing

**Mean Annualized Attack Rate**

Cohorts 1 and 2

- **Run-In** N=6: 27
- **Treatment** N=6: 9
- **OLE** N=6: 5

**Mean Annualized Hemin Doses**

Cohorts 1 and 2

- **Run-In** N=6: 41
- **Treatment** N=6: 10
- **OLE** N=6: 4

Data cut date of 21 Apr 2017

<table>
<thead>
<tr>
<th></th>
<th>Run-In</th>
<th>Treatment</th>
<th>OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Days on Study</td>
<td>90</td>
<td>169</td>
<td>111</td>
</tr>
</tbody>
</table>
Interim Givosiran Phase 1 (Part C, Cohorts 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>Annualized Attack Rate</td>
<td>29</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Annualized Attack Rate N=2</td>
<td>29</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Mean Days on Study</td>
<td>77</td>
<td>169</td>
<td>31</td>
</tr>
</tbody>
</table>

Data cut date of 21 Apr 2017
Interim Givosiran Phase 1 Study Results
Summary: Part C (Cohorts 1-3) and OLE (Cohorts 1-2)

**Givosiran is generally well tolerated**
- No drug-related SAEs or discontinuations due to AEs
  - One fatal SAE of pancreatitis unlikely related to study drug (previously reported)
- No dose-dependent AEs or other clinically significant changes in laboratory or physical examination related to study drug
- Most common AEs: Abdominal pain, headache, nasopharyngitis, nausea, vomiting

**Givosiran has very encouraging clinical activity in AIP patients with recurrent attacks**
- Rapid, dose-dependent and durable lowering in ALAS1, ALA and PBG to near normal levels seen after multiple givosiran doses (2 to 4 doses)
- Consistent clinical activity in givosiran-treated patients across three cohorts
  - 63\% reduction in annualized attack rate
  - 73\% reduction in annualized hemin doses
- Attack rate reduction closely associated with the extent of ALA and PBG lowering

**Interim OLE data demonstrates further safety and clinical activity**
- Continued safety and tolerability with longer term givosiran dosing consistent with Phase 1
- Decreases in attack rates and hemin use maintained in OLE
  - Initial results suggest potential for further reductions in attack rate with extended dosing

*All Safety Data as of 5 May 2017*
Next Steps

- Complete treatment in patients in Part C Cohort 4 and 5
- Enroll all patients into OLE for longer term safety and clinical activity data
- Initiate Phase 3 study in late 2017, pending successful global regulatory feedback
Acknowledgements

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

<table>
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