A Phase 1/2 Open-Label Extension Study of Givosiran, an Investigational RNAi Therapeutic, in Patients with Acute Intermittent Porphyria

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Background and Rationale

Acute Hepatic Porphyria (AHP)[1,2]

- Acute hepatic porphyria (AHP) is a family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- Acute Intermittent Porphyria (AIP) is the most common, with mutation in hydroxymethylbilane synthase (HMBS) gene

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG (figure 1)
- ALA is believed to be the primary toxic intermediate that causes disease manifestations

Attacks, Chronic Manifestations, and Comorbidities[3-7]

- Patients can experience acute neurovisceral attacks which commonly manifest as severe, diffuse abdominal pain and can be life-threatening
- Patients may also experience nausea and fatigue, along with mental and autonomic symptoms
- Some patients experience chronic debilitating symptoms that negatively impact daily functioning and QoL
- Potential comorbidities include hypertension, chronic kidney disease and liver disease

Treatment and Unmet Need

- Glucose and hemin are used to treat acute attacks and by some specialists to prevent attacks
- Even with treatment, many patients with AHP continue to experience attacks, chronic manifestations, and significant disease burden
- There is an unmet need for therapies to prevent attacks and improve chronic disease manifestations

Therapeutic Hypothesis

- Givosiran (ALN-AS1) is a subcutaneously administered investigational RNAi therapeutic that specifically targets ALAS1 mRNA to reduce neurotoxic intermediates ALA and PBG for the potential treatment of AHP (figure 2)

Figure 1: Heme Biosynthesis Pathway

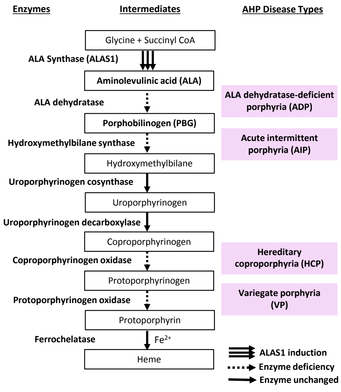
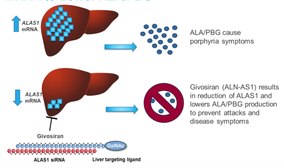


Figure 2: Therapeutic Hypothesis – Givosiran Reduces ALAS1 mRNA to Lower ALA/PBG

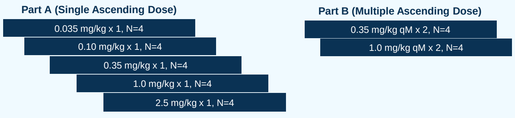


AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen

Study Design

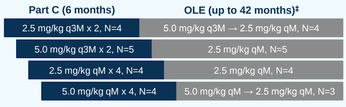
Parts A & B in Chronic High Excreter (CHE) Patients

- Randomized 3:1 (givosiran:placebo), single blind design
- Genetic confirmation of AIP
- Urine PBG level >4 mmol/mol Cr
- No attacks within 6 months of study drug



Part C and OLE in Recurrent Attack Patients

- Randomized 3:1 (givosiran:placebo), double-blind design
- Genetic confirmation of AIP
- Observational run-in (3 month) without scheduled hemin
- ≥2 attacks in past 6 months OR on prior hemin prophylaxis
- One attack in run-in required for randomization
- Patients completing Part C eligible to enroll in open label extension (OLE)



Clinicaltrials.gov: NCT02452372. Cr, Creatinine. qM; Monthly. q3M; Quarterly.
[†]2 patients participated twice in Part A and 3 patients participated in both Part A and Part B
[‡]All patients in OLE transitioned to 2.5 mg/kg qM; Safety Review Committee authorization before all dose escalations

Demographics and Baseline Characteristics

Table 1: Phase 1 Baseline Characteristics

	Parts A & B (N=23[†])	Part C Placebo (N=4)	Part C Givosiran (N=13)
Age, years, median (range)	47 (30–64)	42 (27–60)	36 (21–59)
Female, n (%)	18 (78)	2 (50)	13 (100)
Weight, kg, mean (SD)	75.9 (15.9)	91.4 (20.8)	70.9 (14.5)
Race, n (%)			
White/Caucasian	22 (96)	4 (100)	10 (77)
Asian	1 (4)	0 (0)	1 (8)
Black/African American	0 (0)	0 (0)	2 (15)
Prior porphyria therapy, n (%)			
Hemin prophylaxis		2 (50)	6 (46)
GnRH analogue use	NA	0 (0)	4 (31)
Chronic opioid use		2 (50)	7 (54)
Porphyria attacks in past 12 months, median (range)	NA	10.0 (5–50)	9.0 (0–36)
ALA, mmol/mol Cr, mean (SEM)[‡]	10.3 (1.5)	18.7 (5.5)	17.5 (4.0)
PBG, mmol/mol Cr, mean (SEM)[‡]	23.8 (3.6)	43.8 (4.6)	48.1 (7.1)
ALAS1 mRNA, fold relative to normal, mean (SEM)[§]	2.4 (0.2)	2.8 (0.3)	3.7 (0.3)

[†]2 patients participated twice in Part A and 3 patients participated in both Part A and Part B
[‡]Upper Limit of Normal: ALA=1.5 mmol/mol Cr; PBG=0.14 mmol/mol Cr determined based on samples collected from 150 normal healthy subjects analyzed by LC-MS/MS
SD; Standard deviation. GnRH; Gonadotropin-releasing hormone. SEM; Standard error of mean.

Phase 1 Study Results

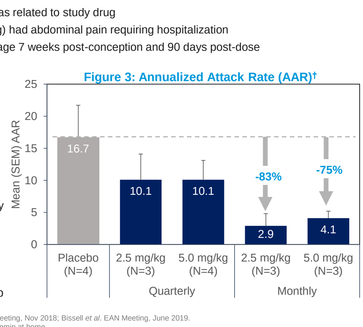
Clinical Activity in Recurrent Attack Patients (Part C)

- Monthly dosing resulted in:
- ~ 60 – 70% reduction of induced ALAS mRNA
- Robust and sustained lowering of ALA and PBG of >80%
- Mean reductions in AAR up to 83% (Figure 3) and annualized hemin use (not shown) up to 88% relative to placebo

Safety

- 6 patients had SAEs, with none assessed as related to study drug
  - Part A: 2 patients (0.035 and 0.10 mg/kg) had abdominal pain requiring hospitalization
  - Part B: 1 patient (1 mg/kg) had miscarriage 7 weeks post-conception and 90 days post-dose
  - Part C: 3 patients
    - 1 patient (2.5 mg/kg qM) had opioid bowel dysfunction
    - 1 patient (5 mg/kg q3M) had influenza infection
    - 1 patient (5 mg/kg qM) had bacteremia from portacath, associated with auditory hallucinations. Patient subsequently had fatal hemorrhagic pancreatitis, assessed as unlikely related to study drug due to presence of gallbladder sludge (previously reported)
- No other discontinuations due to AEs or other clinically significant changes in EKG, clinical laboratory or physical examination
- Review of AEs reveals no clear relationship to dose

Figure 3: Annualized Attack Rate (AAR)[†]



*Sardh *et al.* EASL Meeting, Apr 2018; Anderson *et al.* AASLD Meeting, Nov 2018; Bissell *et al.* EAN Meeting, June 2019.
[†]Attacks requiring hospitalization, urgent health care visit, or IV hemin at home

Phase 1/2 Open Label Extension (OLE) Results

Phase 1/2 OLE Study Patient Overview

- All eligible patients from Phase 1 Part C enrolled into OLE
- As of April 19, mean time in OLE of 22.8 months (median 24.7 months)
- Max time in OLE of 29.6 months, with max of 35.0 months of total treatment in Phase 1 and OLE

Data as of 19Apr2019

Phase 1/2 Open Label Extension (OLE) Results Cont.

Safety and Tolerability

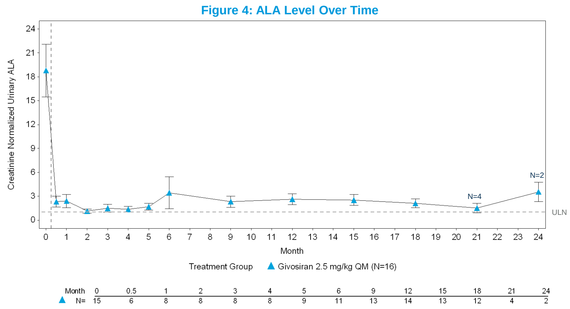
- 100% (16/16) patients reported at least 1 AE
- 6 patients with 10 SAEs
  - 1 patient with upper extremity DVT, unlikely related to study drug due to prior indwelling central venous catheter and venous damage from chronic hemin usage*
  - 1 patient with anaphylactic reaction, assessed as definitely related to study drug*:
    - Occurred after third dose of givosiran (first dose in OLE at 2.5 mg/kg); patient previously received two doses (5 mg/kg q3M) in Phase 1 study
    - Past history of asthma and atopy
    - Event resolved with medical management, and patient permanently discontinued from study
  - 1 patient with synovitis, assessed as not related to study drug
  - 1 patient with abdominal pain, assessed as unlikely related to study drug
  - 1 patient had four events: two episodes of pyrexia related to suspected indwelling central venous catheter infection and to chlamydia bronchitis, clostridium difficile, and dyspnea, all assessed as unlikely related
  - 1 patient had two events: change in mental status due to possible glucocorticoid toxicity for an acute bacterial sinusitis, assessed as unlikely related, and sinusitis bacterial assessed as unrelated
- AEs in >3 patients: abdominal pain, fatigue, injection site erythema, nausea, nasopharyngitis, headache, myalgia, diarrhea, injection site pruritus, and international normalized ratio increased
- 7 patients had injection site reactions, most commonly erythema and all mild to moderate
- No clinically significant laboratory changes, including LFTs

Data as of 19Apr2019
*Previously reported Sardh *et al.* EASL Meeting, Apr 2018,Anderson *et al.* AASLD Meeting, Nov 2018; Bissell *et al.* EAN Meeting, June 2019

Consistent and Durable Lowering of ALA Toward Normal Levels with Long-term Givosiran Dosing

- Monthly dosing at 2.5 mg/kg led to robust and sustained lowering of ALA toward normal levels, with a mean reduction from baseline of 84% at Month 12 and a reduction of 91% at Month 18 (Figure 4)
- Monthly dosing at 2.5 mg/kg led to robust and sustained lowering of PBG toward normal levels, with a reduction from baseline of 80% at Month 12 and a reduction of 86% at Month 18 (data not shown)

Figure 4: ALA Level Over Time



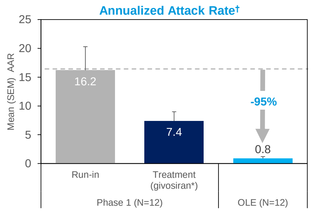
[†]The different Ns at each month reflect differences in (1) when patients transitioned to 2.5 mg/kg dose on study, and (2) the duration of patients on study. The N=15 at 0 month reflects a missing data point at pre-study baseline.

Phase 1 and Interim OLE Study Results in Recurrent Attack Patients

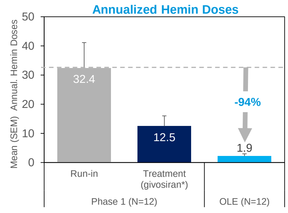
Clinical Activity Maintained or Enhanced in Givosiran Treated Patients with Extended Dosing in the OLE Study

- Mean reductions in AAR of 95% and annualized hemin use of 94% observed in OLE relative to Phase 1 Run-in
- 5/12 (42%) patients with AAR = 0, for a mean of 18.1 months

Annualized Attack Rate[†]



Annualized Hemin Doses

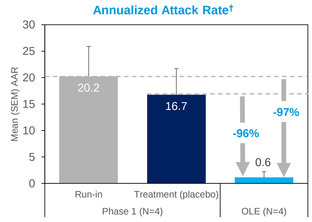


Data as of 19Apr2019. OLE: Open-label extension. AAR: Annualized attack rate
[†]Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. *Aggregated across all dose groups. Mean time in Phase 1 Run-in and Treatment of 103 days and 165 days, respectively; mean time in OLE of 733 days.

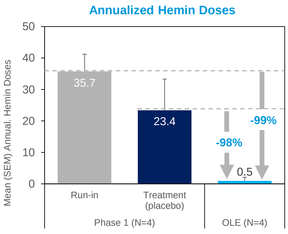
Clinical Activity Demonstrated in Placebo Patients Crossing Over to Givosiran Treatment in OLE

- Patients crossing over to givosiran in OLE had a 97% mean reduction in AAR and 99% mean reduction in annualized hemin use relative to Phase 1 Run-in periods; patients also had a 96% mean reduction in AAR and a 98% mean reduction in hemin use relative to treatment period
- 2/4 (50%) patients with zero attacks, for a mean of 24.9 months

Annualized Attack Rate[†]



Annualized Hemin Doses

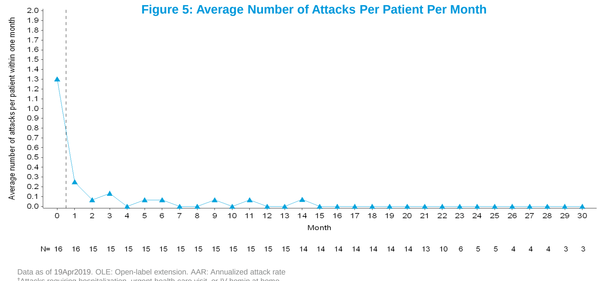


Data as of 19Apr2019. OLE: Open-label extension. AAR: Annualized attack rate
[†]Attacks requiring hospitalization, urgent health care visit, or IV hemin at home. Mean time in Phase 1 Run-in and Treatment of 77 days and 175 days, respectively; mean time in OLE of 733 days

Sustained Reduction of Attack Rate in Recurrent Attack Patients Over Time

- Ongoing monthly dosing at 2.5 mg/kg maintained the reduction in mean attack rate out to Month 30, with median patient-level AAR of 0.22

Figure 5: Average Number of Attacks Per Patient Per Month



Data as of 19Apr2019. OLE: Open-label extension. AAR: Annualized attack rate
[†]Attacks requiring hospitalization, urgent health care visit, or IV hemin at home
Month 0: Run-In Period in Phase 1 Part C, and the estimate is calculated as total number of attacks/total duration in months.
Month 1 and beyond are categorized relative to the first dose of givosiran 2.5mg/kg QM in Phase 1/2 OLE, and the estimate is calculated as total number of attacks/total number of patients reached that month.
The dashed line indicates the gap in time between Phase 1 Part C baseline and the first visit in Study Phase 1/2 OLE.
One month = 28 days is used in categorization.

Summary

- In Phase 1 study, givosiran treatment lowered elevated ALA and PBG, and reduced attacks and hemin use in recurrent attack patients
- Dose regimen of 2.5 mg/kg qM was selected for Phase 1/2 OLE and further clinical development
- Increasing patient experience, with mean time in Phase 1/2 OLE, as of April 19, 2019, of 22.8 months and up to 30.9 months of total treatment in Phase 1 and Phase 1/2 OLE
- Interim Phase 1/2 OLE study results demonstrated:
  - Maintenance, and potentially enhancement, of clinical activity with continuous monthly dosing at 2.5 mg/kg
    - Consistent and durable ALA and PBG lowering of ≥80% at Month 12 and of >85% at Month 18
    - Reductions in AAR and hemin use of >90%
  - Safety profile supportive of continued clinical development
- Ongoing dosing with givosiran maintained the reduction of mean attack rate in patients out to Month 30

References

1. Bonkovsky, et al., Am J Med. 2014;127:1233-41; 2. Elder, et al., JIMD. 2013;36:849-57; 3. Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 4. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 5. Stewart. J Clin Pathol. 2012;65:976-80. 6. Simon, et al., Patient. 2018;11:527-37. 7. Naik, et al., Mol Genet Metab. 2016;119:278-83. 8. Chan, et al., Molecular Therapy—Nucleic Acids.