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

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Introduction

AHP

- Rare genetic disorders due to hepatic deficiency in one of the heme biosynthesis enzymes[1,2]
  - Acute intermittent porphyria (AIP) is the most common type of AHP[3,4]
- Induction of δ-aminolevulinic acid synthase 1 (ALAS1) leads to accumulation of toxic heme intermediates δ-aminolevulinic acid (ALA) and porphobilinogen (PBG)[1,2]

Attacks, Chronic Manifestations, and Comorbidities

- Acute neurovisceral attacks commonly manifest as severe, diffuse abdominal pain, often accompanied by nausea, and motor weakness[5–7]
- Chronic debilitating symptoms can negatively impact daily functioning and quality of life[5,7]
- Comorbidities include chronic neuropathy, hypertension, chronic kidney disease, and liver disease[3,5,8–10]

Unmet Need

- Hemin used to treat acute attacks and sometimes as off-label treatment to prevent attacks[6,11]
- Unmet need for therapies to prevent attacks and chronic disease manifestations

Givosiran

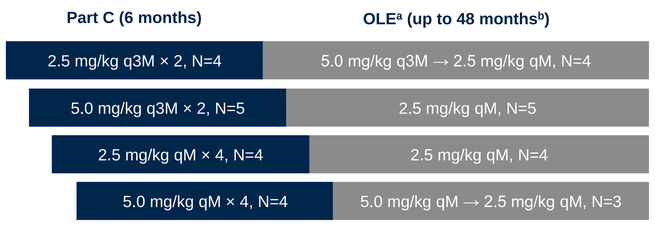
- Subcutaneously administered RNAi therapeutic that specifically targets *ALAS1* messenger RNA in the liver to reduce disease-causing neurotoxic intermediates ALA and PBG[12]
- Givosiran approved for the treatment of AHP in adults in the U.S. and in adults and adolescents aged 12 years and older in the EU[13,14]

Methods

Study Design and Objective

- A Phase 1 study evaluated the safety, tolerability, and pharmacokinetics/pharmacodynamics of givosiran (NCT02452372)[15]
- Part C was the double-blind, randomized, placebo-controlled (3:1 givosiran:placebo) portion of the study in patients with AIP experiencing recurrent attacks (≥2 attacks in past 6 months or on prior hemin prophylaxis)
- Patients completing Part C of the Phase 1 study were eligible to enroll in the Phase 1/2 open-label extension (OLE) study (NCT0294983)
- Here the interim safety and clinical activity data are described for patients in the ongoing Phase 1/2 OLE study once all active patients have completed at least their Month 24 visit (as of 16 October 2019)

Figure 1: Study Design: Phase 1 Part C and Phase 1/2 OLE



[a]All patients in OLE transitioned to the intended clinical dose of 2.5 mg/kg qM by August 2017; Safety Review Committee authorization before all dose modifications. [b]Treatment period

Results

- All eligible patients from Phase 1, Part C enrolled into OLE (N=16)
  - 12 had received givosiran in the Phase 1 study (givosiran-treated)
  - 4 had received placebo in the Phase 1 study (placebo cross-over)

Overall Exposure As of October 16 2019

- Mean duration on givosiran in OLE 27.9 months (median 30.6 months)
- Maximum duration on givosiran in OLE 35.5 months, with maximum of 41.0 months of total treatment in Phase 1 and OLE combined
- Patients received givosiran 2.5 mg/kg for a median 26.7 (range, 2.1–33.2) months with a cumulative 33.5 patient-years of exposure
- 15 patients received givosiran 2.5 mg/kg for ≥12 months, 13 patients for ≥24 months
  - Median 26.5 (range, 1–34) cumulative doses, total of 405

Results (continued)

Table 1. Demographics and Baseline Characteristics

	Placebo Cross-Over (N=4)	Givosiran-Treated (N=12)	Total Givosiran (N=16)
Age, years, median (range)	42.0 (27–60)	37.5 (21–59)	39.5 (21–60)
Female, n (%)	2 (50)	12 (100)	14 (88)
BMI, kg/m^2, mean (SD)	31.1 (4.6)	26.6 (5.8)	27.7 (5.7)
Race, n (%)			
White/Caucasian	4 (100)	9 (75)	13 (81)
Asian	0	1 (8)	1 (6)
Black/African American	0	2 (17)	2 (13)
Prior porphyria therapy, n (%)			
Hemin prophylaxis	2 (50)	6 (50)	8 (50)
GnRH analog use	0	4 (33)	4 (25)
Chronic opioid use	2 (50)	7 (58)	9 (56)
Porphyria attacks in past 12 months, median (range)[a]	10.0 (5–50)	9.5 (0–36)	10.0 (0–50)
ALA, mmol/mol creatinine, mean (SD)[b]	18.7 (11.0) (n=4)	18.8 (13.9) (n=11)	18.8 (12.8) (n=15)
PBG, mmol/mol creatinine, mean (SD)[b]	43.8 (9.2) (n=4)	50.1 (24.9) (n=11)	48.4 (21.7) (n=15)

[a]Represents all porphyria attacks including attacks requiring hospitalization, urgent healthcare visit, intravenous hemin treatment at home, or treatment at home without hemin. [b]Upper limit of normal: ALA=1.5 mmol/mol creatinine; PBG=0.14 mmol/mol creatinine; determined based on samples collected from 150 normal healthy subjects analyzed by liquid chromatography tandem mass spectrometry[5]

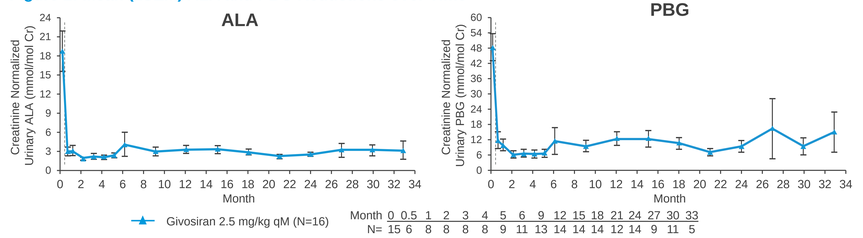
Safety and Tolerability

- AEs reported in 16 (100%) patients; majority of AEs were mild or moderate
- AEs reported in >3 patients were abdominal pain, nasopharyngitis, fatigue, injection-site erythema, nausea, headache, myalgia, diarrhea, injection site pruritus, and international normalized ratio increase
- Most common related AEs were injection site reactions (ISRs) in 7 (44%) patients; all mild or moderate
  - Symptoms in 2 or more patients: erythema, pruritus, rash, and swelling at the injection site
  - None led to treatment discontinuation or withdrawal from study
- Serious adverse events (SAEs) reported in 6 (38%) patients
  - 1 patient with history of asthma and atopy had a SAE of anaphylactic reaction considered related to the study drug. The event resolved with medical management and the patient discontinued the study (previously reported)
  - No other SAEs were considered related to study drug
- No deaths, no other treatment discontinuations due to AEs
- Transient elevations of ALT above upper limit of normal (ULN) in 6 patients; none >3xULN
  - All resolved during continued treatment with givosiran
- Fluctuations in creatinine and eGFR were noted. Generally, the magnitude of these changes were small
  - No dosing interruption due to changes in renal function
- No other clinically relevant laboratory changes

Sustained Lowering of ALA and PBG with Long-Term Givosiran Dosing (Fig. 2)

- Monthly dosing at 2.5 mg/kg continued to provide robust and sustained lowering of ALA and PBG toward normal levels
- Respective mean reductions in ALA and PBG from baseline: 84% and 80% at Month 12, 89% and 90% at Month 30

Figure 2: Mean (±SEM) ALA and PBG Reductions over Time[a]



[a]The N=15 at Month 0 is due to a missing data point at baseline in Phase 1, Part C study. 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. Data cut-off 16 October 2019. The vertical dashed line indicates the gap in time between Phase 1 Part C baseline and the first visit in Phase 1/2 OLE study.

Clinical Activity Maintained or Enhanced with Long-term Givosiran Dosing

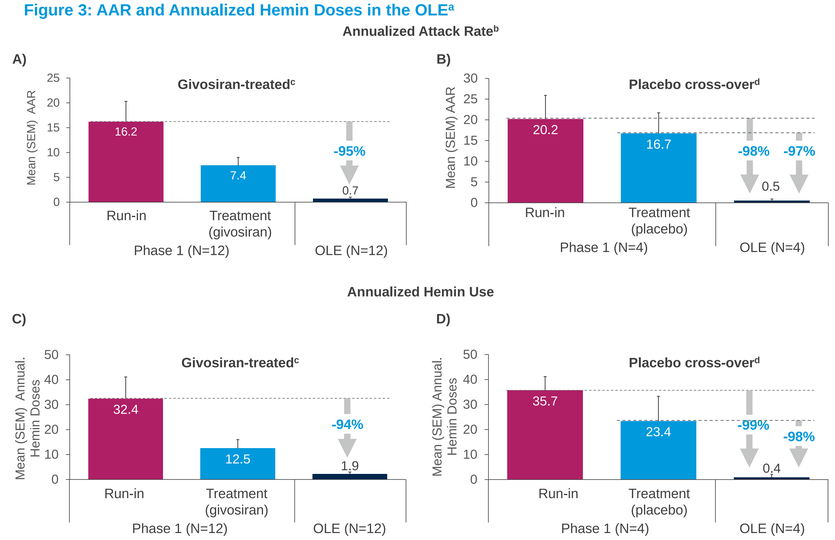
Givosiran-Treated Patients with Extended Dosing (n=12)

- Mean reductions in AAR of 95% and annualized hemin use of 94% in OLE relative to Phase 1 run-in (Fig. 3A and C)
- 5/12 (42%) patients experienced no attacks (AAR=0) over a mean OLE duration of 22.8 months

Placebo-Treated Patients Who Crossed Over to Givosiran in OLE (n=4)

- Mean reductions in AAR of 98% and annualized hemin use of 99% relative to Phase 1 run-in (Fig. 3B and D)
  - Mean reductions of 97% in AAR and 98% in annualized hemin use relative to placebo treatment period (Fig. 3B and D)
- 2/4 (50%) patients experienced no attacks (AAR=0) over a mean OLE duration of 30.8 months

Figure 3: AAR and Annualized Hemin Doses in the OLE[a]

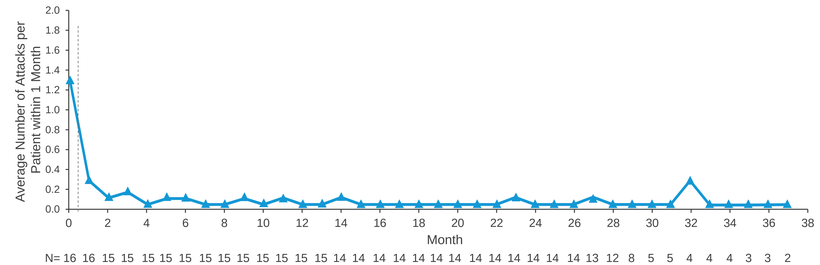


[a]Data cut-off 16 October 2019. [b]Attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home. [c]Aggregated across all dose groups. Mean time in Phase 1 run-in and treatment of 103 days and 165 days, respectively; mean time in OLE of 822 days. [d]Mean time in Phase 1 run-in and treatment of 77 days and 175 days, respectively; mean time in OLE of 913 days

Sustained Reduction of Attack Rate Over Time

- Ongoing monthly dosing at 2.5 mg/kg maintained the reduction in mean attack rate out to Month 37* (Fig. 4)

Figure 4: Average Number of Attacks[a] per Patient per Month



[a]Attacks requiring hospitalization, urgent healthcare 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 2.5 mg/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 Phase 1/2 OLE study
*1 month = 28 days is used for categorization

Summary

- These data represent patients with the longest treatment experience with givosiran to date, with a mean time in the Phase 1/2 OLE of 27.9 months and up to a total of 41.0 months of treatment in the combined Phase 1 and Phase 1/2 OLE studies.
- Long-term treatment with givosiran demonstrated:
  - Maintenance, and potentially enhancement, of clinical activity with continuous monthly dosing at 2.5 mg/kg
  - Consistent and durable ALA and PBG reductions of ≥89% at Month 30 and reductions in AAR and annualized hemin use of >90%
  - An acceptable and consistent safety profile, with no new safety findings
- These long-term results are consistent with the results of the ENVISION Phase 3, global, placebo-controlled study (NCT03338816) 6-month double-blind period and 12-month interim OLE period[17,18]

Abbreviations: AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; ALAS1, δ-aminolevulinic acid synthase 1; BMI, body mass index; EU, European Union; GnRH, gonadotropin-releasing hormone; IV; intravenously; OLE, open-label extension; PBG, porphobilinogen; qM, monthly; q3M, quarterly; RNAi, RNA interference; SD, standard deviation; SEM, standard error of the mean; ULN, upper limit of normal; US, United States. **Acknowledgments:** Medical writing services, provided by Stephen Whiting, Ph.D. of Adelphi Communications Ltd, UK, were funded by Alnylam Pharmaceuticals, Cambridge, MA, USA, in accordance with Good Publication Practice (GPP3) guidelines. **Funding:** This study was sponsored by Alnylam Pharmaceuticals. **References:** 1. Puy et al. *Am J Hum Genet* 1997;60:1373–83; 2. Balwani & Desnick. *Blood* 2012;120:4496–504; 3. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 4. Elder et al. *J Inherit Metab Dis* 2013;36:849–57; 5. Gouya et al. *Hepatology* 2020;71:1546–58; 6. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 7. Simon et al. *Patient* 2018;11:527–37; 8. Stewart. *J Clin Pathol* 2012;65:976–80; 9. Pallet et al. *Kidney Int* 2015;88:386–95; 10. Andersson et al. *J Intern Med* 1996;240:195–201; 11. Stein et al. *Br J Haematol* 2017;176:527–38; 12. Chan et al. *Mol Ther Nucleic Acids* 2015;4:e263; 13. GIVLAARI US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed June 26, 2020); 14. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed June 26, 2020); 15. Sardh et al. *NEJM* 2019;380:549–58; 16. Bonkovsky et al. ICPP 2019; 17. Balwani et al. *NEJM* 2020;382:2289–301; 18. Sardh et al. Oral presentation at: Alnylam Scientific Webinar Session; June 2020 (virtual).