Supplementary Table 1. Phase 1 and 3 Open Label Extension (OLE) Study Design

A. Phase 1, Parts A and B

Key study inclusion:

- No attacks within 6 months of study drug (chronic high excretor)
- Urine PBG level >4 mmol/mol Cr
- Genetic confirmation of AIP

Study design:

- Single-blind
- Randomized 3:1 (givosiran:placebo)

Part A (Single Ascending Dose)	**Part B (Multiple Ascending Dose)**
0.035 mg/kg X1, N=4	0. 35 mg/kg Q month X2, N=4
0.10 mg/kg X1, N=4	1.0 mg/kg Q month X2, N=4
0.35 mg/kg X1, N=4	
1.0 mg/kg X1, N=4	
2.5 mg/kg X1, N=4	

B. Phase 1, Part C

Key study inclusion:

- ≥2 attacks in past 6 months OR on prior hemin prophylaxis. One attack in run-in required for randomization
- Genetic confirmation of AIP
- Observational run-in (3 month) without scheduled hemin
- Patients completing Part C eligible to enroll in OLE
- Genetic confirmation of AIP

Study design:

- Double blind
- Randomized 3:1 (givosiran:placebo)

Part C (6 months)	**OLE (up to 42 months)**
2.5 mg/kg q3 monthsX2, N=4	2.5 mg/kg q3M → 2.5 mg/kg qM, N=4
5.0 mg/kg q 3 monthsX2, N=5	2.5 mg/kg qM, N=5
2.5 mg/kg q month X4, N=4	2.5 mg/kg qM, N=4
5.0 mg/kg q monthX4, N=4	5.0 mg/kg qM → 2.5 mg/kg qM, N=3

C. Phase 3 Study Design

Key study inclusion:

- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks in past 6 months
- Willing to discontinue and/or not initiate hemin prophylaxis

Study design:

- Double blind, Placebo controlled
- Randomized 1:1 (givosiran:placebo)

6 month double blind period	**Open label extension (30 month)**
2.5 mg/kg QM	2.5 mg/kg QM
Placebo SC QM	2.5 mg/kg QM

Adapted from:

Eliane Sardh, MD, PhD[1,2], Pauline Harper, MD, PhD[1,2], Manisha Balwani, MD[3], Penelope Stein, MD, PhD[4], David Rees, MD[4], Joseph Bloomer, MD[5], D. Montgomery Bissell, MD[6], Robert Desnick, MD, PhD[3], Charles Parker, MD[7], John Phillips, PhD[7], Herbert Bonkovsky, MD[8], Nabil Al-Tawil, MD[1,9], Stephanie Rock, PhD[10], Craig Penz, MA[10], Amy Chan, PhD[10], Qiuling He, PhD[10], William Querbes, PhD[10], Amy Simon, MD[10] and Karl Anderson, MD[11] A Phase 1/2, Randomized, Placebo Controlled and Open Label Extension Studies of Givosiran, an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Acute Intermittent Porphyria. 16 June 2018 | EAN Lisbon, Portugal

Balwani M, Gouya L, Rees DC, Stein P, Stölzel U, Aguilera Peiro P, Bissell DM, Bonkovsky HL, Keel S, Parker C, Phillips JD, Silver S, Windyga J, D'Avola D, Ross G, Stewart P, Ritchie B, Oh J, Harper P, Wang JD, Langendonk JG, Ivanova A, Horie, Y, Anderson KE, Ventura P, Chan A, Penz C, Simon A' Kim J, Dinh Q', Liu G, Garg P, Vaishnaw A, and Sardh E on behalf of the ENVISION investigators. ENVISION, a Phase 3 Study to Evaluate the Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic Targeting Aminolevulinic Acid Synthase 1, in Acute Hepatic Porphyria Patients. 13 April 2019 | EASL | Vienna, Austria