Official Title:	**ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias**
NCT Number:	**NCT03338816**
Document Date:	**Clinical Study Protocol, 29 March 2021**

CLINICAL STUDY PROTOCOL

ALN-AS1-003

Protocol Title:	ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias
Investigational Drug:	ALN-AS1 (givosiran)
EudraCT Number:	2017-002432-17
IND Number:	126094
Protocol Date:	Original protocol 06 September 2017 Protocol Amendment 1 04 May 2018 Protocol Amendment 2 26 July 2018 Protocol Amendment 3 21 September 2018 Protocol Amendment 4 28 May 2019 Protocol Amendment 5 12 February 2020 Protocol Amendment 6 23 April 2020 Protocol Amendment 7 29 March 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PI

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

PI [redacted]

30 MAR 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-AS1-003 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Product Name

Givosiran (ALN-AS1)

Indication

Treatment of acute hepatic porphyrias (AHP) in adult and adolescent patients

Phase

Phase 3

Study center(s)

The study will be conducted at approximately 50 study centers worldwide.

Objectives

Primary

- Evaluate the effect of subcutaneous (SC) givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home in patients with acute intermittent porphyria (AIP)

Secondary

- Evaluate the effect of givosiran, compared to placebo, on urinary aminolevulinic acid (ALA) levels in patients with AIP
- Evaluate the effect of givosiran, compared to placebo, on urinary porphobilinogen (PBG) levels in patients with AIP
- Evaluate the effect of givosiran, compared to placebo, on hemin usage in patients with AIP
- Evaluate the effect of givosiran, compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP
- Evaluate the effect of givosiran, compared to placebo, in patients with AIP on the symptoms of pain, nausea, and fatigue
- Evaluate the effect of givosiran, compared to placebo, in patients with AIP on the Physical Component Summary (PCS) of the 12-item Short-Form Health Survey (SF-12)
- Evaluate the safety and tolerability of givosiran in patients with any AHP

Exploratory

- Evaluate the effects of givosiran, compared to placebo, in patients with AIP and in patients with any AHP over the 6-month treatment period on:
  - Rate of all porphyria attacks (requiring hospitalization, urgent healthcare visit, IV hemin administration at home, or treatment at home without IV hemin)

- Urinary aminolevulinic acid synthase (ALAS1) messenger RNA (mRNA) levels
- Analgesic usage
- Additional quality of life (QOL) measures, including missed days of work/school
- Patient experience questionnaire and patient's impression of health status change

- Assess the treatment effect of givosiran at evaluated doses during the open-label extension (OLE) period in patients with AIP and in patients with any AHP who had previously been randomized to placebo treatment
- Assess the long-term treatment effect of givosiran in patients with AIP and in patients with any AHP
- Characterize the pharmacokinetics (PK) and assess the antidrug antibodies (ADA) of givosiran in patients with any AHP

Endpoints

Primary

- Annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with AIP over the 6-month treatment period

Secondary

- Urinary ALA in patients with AIP at 3 months
- Urinary ALA in patients with AIP at 6 months
- Urinary PBG in patients with AIP at 6 months
- Annualized rate of administered hemin doses in patients with AIP over the 6-month treatment period
- Annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP over the 6-month treatment period
- Daily worst pain score as measured by Brief Pain Inventory-Short Form (BPI-SF) numeric rating scale (NRS) in patients with AIP over the 6-month treatment period
- Daily worst nausea score as measured by NRS in patients with AIP over the 6-month treatment period
- Daily worst fatigue score as measured by Brief Fatigue Inventory-Short Form (BFI-SF) NRS in patients with AIP over the 6-month treatment period
- Change from baseline in the PCS of the SF-12 in patients with AIP at 6 months

Exploratory

Exploratory endpoints will be measured in patients with AIP and in patients with any AHP over the 6-month treatment period and over the OLE period at doses evaluated:

- Rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home
- Rate of all porphyria attacks
- Rate of administered hemin doses

- Urinary ALA and PBG levels
- Urinary ALAS1 mRNA levels
- Daily worst pain, daily worst nausea, and daily worst fatigue score over 12 months
- PCS of the SF-12
- EQ-5D-5L index score
- Patient Global Impression of Change (PGIC)
- Porphyria Patient Experience Questionnaire (PPEQ)
- Analgesic usage (opioid and non-opioid)
- PK profile of givosiran
- Incidence and titer of ADAs

Safety

- Incidence, severity, seriousness, and relatedness of adverse events during the 6-month treatment period and in the OLE period

Study Design

This is a 2-part multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of givosiran in adults and adolescents (≥12 years of age) with a documented diagnosis of AIP. The efficacy and safety of givosiran will also be investigated in the other AHPs types, including Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), and ALA dehydratase deficient porphyria (ADP).

Patients who are on hemin prophylaxis prior to enrollment will be eligible to participate if they meet the attack entry criteria. In this study, patients may be given hemin for the treatment of acute attacks if clinically indicated but may not use hemin prophylactically. Hemin prophylaxis is not permitted in this study because givosiran is intended as monotherapy to prevent attacks and the regular co-administration of hemin could confound efficacy and safety signals related to givosiran.

In the first part of the study, consenting (and assenting, where applicable) patients who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 2.5 mg/kg givosiran or placebo once monthly for a 6-month double-blind treatment period; both givosiran and placebo will be administered subcutaneously. Randomization into treatment groups will be stratified at study entry by AHP type (AIP [with mutation in the *HMBS* gene] vs HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene); all patients in the AIP group will be further stratified by each patient's use of hemin prophylaxis regimen at the time of screening and by each patient's historical annualized attack rate. Patients on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <7 attacks vs ≥7 attacks in the past 12 months. Patients who were not on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <12 attacks vs ≥12 attacks in the past 12 months.

No additional stratification factors will be considered for patients with HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene.

During the 6-month treatment period, patients will undergo efficacy and safety assessments every 2 weeks for the first month and monthly thereafter. After Month 6 visit procedures are completed in the treatment period, patients from both the givosiran and placebo arms will begin the second part of the study, the OLE period during which they will be treated with givosiran for up to 29 months. Patients who crossed over to the OLE period prior to the implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving a 2.5 mg/kg once monthly givosiran dose will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran.

After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group who experience inadequate disease control may be allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg) based on discussion and agreement by the Investigator and medical monitor, demonstration of tolerability to givosiran, and fulfillment of ALA and clinical activity criteria.

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. See Section 6.2.3.4 for further information on dose escalation.

For particular study visits, as specified in the Schedule of Assessments, and where applicable country and local regulations and infrastructure allow, study procedures, including study drug administration, may be conducted by a qualified home healthcare professional. Patients must demonstrate the ability to tolerate doses of the study drug at the study center before dosing at a location other than the study center is permitted. If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, givosiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations.

Patients or caregivers will be provided with an electronic diary (eDiary) to record severity of daily pain, nausea, and fatigue, as well as analgesic usage. Potential porphyria attacks will be reported by patients and caregivers through the eDiary when they occur; study centers will be notified when potential porphyria attacks are reported in the eDiary. In instances when the eDiary is not used to report potential porphyria attacks, study centers may be notified by telephone by patients, caregivers, or other healthcare providers. All potential porphyria attacks will be confirmed by the Investigator.

Patients may receive givosiran as long as they do not fulfill any of the study discontinuation criteria or until givosiran is commercially available in the patient's territory or the givosiran development program is discontinued (whichever comes first).

An external independent Data Monitoring Committee (DMC) will monitor safety over the course of the double-blind treatment period and until all patients have been in the OLE period for at least 6 months. Details for the committee will be provided in the committee charter.

Number of Planned Patients

The planned total enrollment for the study is approximately 74 patients, including approximately 70 AIP patients.

Diagnosis and Main Eligibility Criteria

This study will include adults and adolescents (≥12 years of age) with a documented diagnosis of AHP (including AIP, HCP, VP, or ADP) based on clinical features, documented evidence of urinary or plasma ALA or PBG elevations ≥4×upper limit of normal (ULN) within the past year prior to or during the Screening period and documented genetic evidence of a mutation in a porphyria-related gene. If the results of the patient's genetic testing do not identify a porphyria-related gene mutation, the patient may be eligible for the study based on clinical features accompanied by supportive biochemical criteria.

In addition to clinical, biochemical, and genetic features of AHP, patients are also required to have had at least 2 porphyria attacks in the last 6 months prior to screening that required hospitalization, urgent healthcare visit, or IV hemin treatment at home.

Investigational Product, Dose and Mode of Administration

Givosiran is a synthetic chemically modified small interfering RNA (siRNA) targeting ALAS1 mRNA and bearing a triantennary N-acetyl galactosamine ligand conjugated to the sense strand.

Patients randomized to receive givosiran will be administered 2.5 mg/kg SC monthly during the 6-month treatment period; patients will receive 1.25 mg/kg or 2.5 mg/kg SC monthly during the OLE period

Reference Therapy, Dose and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration).

Duration of Treatment

The estimated total time on study for each patient is up to 38 months, including up to 2 months of screening, up to 35 months of treatment (6-month treatment period (double-blind) + up to a 29-month open-label extension period), and a 1-month follow-up period.

A patient will be considered to have completed the primary analysis period of the study at the time of completion of the Month-6 treatment assessments.

Statistical Methods

The study was designed with the assumption of a mean annualized attack rate of 8, a standard deviation (SD) of 5 in the placebo arm, and a mean annualized attack rate of 4.4 with an SD of 3 in the givosiran arm. This study will have at least 90% power to detect a 45% reduction in the annualized attack rate with givosiran at a 2-sided 5% significance level, using a negative binomial model with 70 patients. This study design will still have at least 80% power even if the dropout rate is as high as 15% under the same assumptions.

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using an alpha spending function for the interim analysis and a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the final analysis significance level. If the primary analysis of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section.

If a test of the primary or a secondary endpoint is not statistically significant at the final analysis significance level, the testing of remaining endpoints in the sequence will stop.

The primary endpoint of the study is the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in AIP patients over the initial 6-month treatment period. The annualized attack rate will be calculated as the total number of primary endpoint events, divided by the total number of days in the treatment period, and multiplied by the number of days in a year.

The primary analysis of the primary endpoint is the comparison of the mean annualized attack rate for the placebo and givosiran arms using a negative binomial regression model that will include fixed effects for the treatment arm and stratification factors (status of hemin prophylaxis use prior to study entry and historical attack rate). The number of days that patients spend in the 6-month treatment period will be included in the model as an offset variable. This analysis will include all randomized patients with AIP (with mutation in the *HMBS* gene) who received at least 1 dose of givosiran/placebo, grouped according to their randomly assigned treatment arm (the AIP full analysis set [FAS_{AIP}]).

An estimated ratio of mean annualized attack rates between treatment arms, with its corresponding 95% confidence interval, will be estimated from the negative binomial regression model. Descriptive statistics for the median and interquartile range of the annualized attack rate will also be presented for each treatment arm.

Sensitivity analyses will be detailed in the statistical analysis plan (SAP).

The analysis of the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP who received at least 1 dose of givosiran/placebo (the AHP full analysis set [FAS]) during the 6-month treatment period and the annualized rate of hemin doses will be conducted using the same approach as the primary analysis.

For the analysis of urinary ALA-related endpoints, ALA levels will be compared between treatment arms using a mixed-effects model repeated measures (MMRM) with baseline ALA as a continuous covariate, the fixed effect terms including treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), visit, and treatment by visit interaction. PBG-related endpoints will also be analyzed using this methodology.

Daily pain, nausea, and fatigue scores will be analyzed separately using the area under the curve (AUC) approach: the AUC over 6 months in the respective score will be calculated for each patient, and the mean AUC will be compared between treatment arms in an ANCOVA model.

The change from baseline in PCS of SF-12 at 6 months will be analyzed using an MMRM. Details on the MMRM model for each continuous secondary endpoint and the covariates to be included will be described in the SAP.

Safety results will be summarized descriptively.

An unblinded interim analysis will be conducted when approximately 30 AIP patients have completed at least 3 months of the treatment period. The endpoint for this interim analysis is the ALA level at 3 months. The ALA level at 3 months will be compared between treatment arms using an analysis of covariance (ANCOVA) model with the fixed effect of treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), and with baseline ALA as a covariate. An alpha-spending function will be used to adjust the significance level to ensure the overall type I error rate is not inflated; the error spending function will be specified in the statistical analysis plan. The significance level for the comparison at the interim is 0.001 (2 sided).

Stopping for efficacy or futility is not planned in this study. To ensure that the study is adequately powered for the primary endpoint comparison at the final analysis, the annualized attack rates may also be evaluated in a blinded manner for sample size reassessment at the time of the interim analysis. Details will be described in the SAP.

Table 1: Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6)

		6-Month Treatment Period							
Study Visit	**Screening Period**	**Randomization[a]**	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6[b,c]**
Study Day (±Visit Window)	**Day -60 to Day -1**	**(Baseline) Day 1**	**Day 15 (±2)**	**Day 29 (±7)**	**Day 57 (±7)**	**Day 85 (±7)**	**Day 113 (±7)**	**Day 141 (±7)**	**Day 169 (±7)**
Informed Consent (and Assent, if applicable)	X								
Medical History[d]	X	X							
Demographics	X								
Inclusion/Exclusion Criteria	X								
Randomization		X							
Physical Examination[e]	X	X		X	X	X			X
Body Weight, Height, and BMI[f]	X	X		X	X	X	X	X	X
FSH and Serology[g]	X								
Vital Signs[h]	X	X	X	X	X	X	X	X	X
Single 12-Lead ECG[i]	X								
Triplicate 12-Lead ECG[j]		X						X	X
Clinical Laboratory Assessment[k]	X	X	X	X	X	X	X	X	X
Pregnancy Test[l]	X	X		X	X	X	X	X	X
Study Drug Administration[m]		X		X	X	X	X	X	X[d]
Urine Sample for ALA and PBG[n]	X	X	X	X	X	X	X	X	X
Urine ALAS1 mRNA[n]	X		X	X	X	X			X
Samples for Exploratory Biomarkers (urine, plasma, serum)[o]		X				X			X
DNA Sample for Porphyria Genotyping[p]	X								
Exploratory DNA Sample (optional)[q]		X							
Serum ADA[r]		X		X		X			X
Blood Sample for PK[s]		X		X		X		X	X
Urine Sample for PK (patients at East Asian Study Centers only)[t]		X							X

Table 1: Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6)

		6-Month Treatment Period							
Study Visit	**Screening Period**	**Randomization[a]**	**Week 2**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6[b] [c]**
Study Day (±Visit Window)	**Day -60 to Day -1**	**(Baseline) Day 1**	**Day 15 (±2)**	**Day 29 (±7)**	**Day 57 (±7)**	**Day 85 (±7)**	**Day 113 (±7)**	**Day 141 (±7)**	**Day 169 (±7)**
QOL Assessments[u]	X					X			X
PGIC[v]									X
PPEQ[w]									X
Daily Electronic Diary Entries[x]	X	Daily							
Adverse Events[y]		Continuous							
Concomitant Medications	Continuous								

Abbreviations: ADA=anti-drug antibody; AE=adverse event; ALAS1=aminolevulinic acid synthase 1; ALA= aminolevulinic acid; ALT=alanine aminotransferase; BMI=body mass index; DNA=deoxyribonucleic acid; EC=ethics committee; ECG=electrocardiogram; EOS=end of study; FSH=follicle-stimulating hormone; HCV=hepatitis C virus; INR=international normalized ratio; IRB=institutional review board; LFT=liver function test(s); M=month; mRNA=messenger ribonucleic acid; PBG= porphobilinogen; PGIC=Patient Global Impression of Change; PK=pharmacokinetics; PPEQ = Porphyria Patient Experience Questionnaire; QOL=quality of life; SAE=serious adverse event; SC=subcutaneous; TBL=total bilirubin.

Notes:

- White boxes represent visits to the clinical study center; grey boxes represent study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow. In the event that a patient is unable to come to the study center for a scheduled clinical study visit or the procedure (s) cannot be completed during the visit, vital sign assessments, laboratory sample collection, and/or study drug administration may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor.
- If, in the Investigator's judgment, lab abnormalities are likely to be transient, laboratory tests can be retested. INR and other laboratory values can be retested during Screening providing the patient can be evaluated for eligibility and randomized within the allowed Screening period.
- A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued, variability in ALT measurements) will be allowed to return for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

[a] Randomization may occur on Day 1 or on the business day prior.

[b] Patients who discontinue treatment during the 6-month treatment period will be asked to complete the remainder of scheduled study visits and assessments (except for study drug administration) through Month 6, as well as a safety follow-up assessment at 3 months after the final dose of study drug (Table 3).

[c] Patients who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving 2.5 mg/kg once monthly will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran.

[d] Medical history collected will incorporate the patient's porphyria history, including their typical attack characteristics, triggers, and treatment, as well as central venous access history, iron overload history, and prior liver disease history.

[e] A complete physical examination will be performed at Screening, Day 1, and Month 6. At all other visits, a targeted physical examination will be performed as described in Section 7.5.3. The physical examination will be performed prior to dosing.

[f] Dosing weight (in kilograms) will be collected during the clinical study center visits. Weight collected at either the previous study center visit or current study center visit may be used for dose calculations. The Screening Visit weight will be used for dose-calculation on Study Day 1. Height (in centimeters) will be measured and BMI calculated at clinic visits every 6 months (on Day 1 and Month 6). BMI will be automatically calculated within the database.

[g] Serology includes hepatitis B surface antibody (HbsAb), hepatitis B surface antigen (HbsAg), and anti-HCV antibody. FSH testing may be performed to confirm suspected post-menopausal status.

[h] Vital signs include blood pressure, heart rate, body temperature, and respiratory rate and will be measured when patients are in a seated or supine position (should be consistent across study visits with each patient) after the patient has rested for 10 min. On the Day 1 and Month 6 visit, vital signs will be collected predose and 2 hours postdose (± 15 minutes). On all other dosing days, vital signs will be collected predose.

[i] Single 12-lead ECG will be performed in the supine position after the patient has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.

[j] Triplicate 12-lead ECGs will be performed at predose and 2-hours (± 15 minutes) post-dose on the Day 1, Month 5, and Month 6 visits, using validated ECG services equipment from a central facility; triplicate measurements should be separated by approximately 1 minute with the patient in the supine position after he or she has rested comfortably for 5 minutes. When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECG assessments should be performed before blood samples are drawn. In a prespecified subset of approximately 24 patients at prespecified study centers (including all patients at East Asian study centers [in Japan, South Korea, and Taiwan]), an additional ECG (with paired PK assessment) at 24 hours (±2 hours) post-dose will be collected at Day 1 and Month 6.

[k] Clinical laboratory parameters will include: serum chemistry including LFTs, lipase, amylase, hematology, coagulation, and urinalysis. Blood and urine samples for clinical laboratory evaluations will be collected predose. Serum ferritin assessments will be collected at Study Day 1 and Month 6. D-dimer assessments will be performed at Screening, Day 1, Month 3, and Month 6; as a clinical research parameter only, d-dimer results will not be communicated to the study centers. Results from ALT, TBL, and INR tests collected within the 14 days prior to dosing must be reviewed by the Investigator before study drug administration. Locally analyzed results may be reviewed to allow study drug administration, but additional samples for central analysis must also be collected on the day of dosing prior to dose administration.

[l] For females of child-bearing potential, a serum pregnancy test will be performed at Screening; thereafter, serum or urine pregnancy tests will be performed monthly. Results must be available before dosing.

[m] At the Month 6 visit, the first open-label dose of givosiran in the extension study will be administered after all scheduled 6-month assessments (for the completion of the double-blind period) have been performed. The urine ALA and PBG sample must be collected prior to the first open-label dose of givosiran. If the ALA and PBG sample collection is delayed due to hemin usage within 4 days of the Month 6 visit, the open-label dose should be delayed as well.

[n] In patients who were on hemin prophylaxis prior to study, collection of the Screening urine samples for ALA, PBG, and ALAS1 mRNA must occur when the patient is not having an attack, and ≥4 days after prophylactic hemin discontinuation and after their last hemin dose Two screening urine samples (collected on 2 different days) should be collected for ALA/PBG; one screening urine sample should be collected for ALAS1 mRNA. During the study, spot urine samples for ALA, PBG, and ALAS1 mRNA measurement should be collected prior to study drug dosing; however, if hemin is used for an attack, scheduled urinary ALA, PBG and ALAS1 mRNA will be collected 4 days (+4 days) after the patient's last hemin dose. At the Month 6 visit, the first open-label dose of givosiran should not be administered until the Month 6 urine sample for ALA, PBG have been collected. Where applicable country and local regulations and infrastructure allow, Screening and on-study urine samples for ALA, PBG, and ALAS1 mRNA assessments may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit.

[o] Where allowed per local regulations and IRB/EC approval, serum, plasma, and urine samples for exploratory biomarker testing, and measuring homocysteine levels, will be collected prior to dosing.
[p] Genetic testing of porphyria-related genes is only required in patients without prior documented genetic testing for porphyria. See Section 7.6.2 for details.
[q] Where allowed per local regulations, IRB/IEC approval, and patient consent (and assent, where applicable), a voluntary blood sample may be collected for later DNA analysis. See Section 7.6.2 for details.
[r] Sample to be collected predose.
[s] Blood samples for PK analysis will be collected in all patients at the time points listed in Table 8. An additional 24-hour (±2 hour) PK assessment (with paired ECG measurement) will be performed on Day 1 and Month 6 in approximately 24 patients from preselected study centers. In patients at East Asian study centers (in Japan, South Korea, or Taiwan), blood samples for PK analysis will be collected at the time points listed in Table 9 (which includes all those time points listed in Table 8).
[t] In patients at East Asian study centers, spot (predose) and pooled (postdose) urine samples will be collected for PK analysis on Day 1 and Month 6 at the time points listed in Table 10.
[u] QOL questionnaires to be completed include SF-12, EQ-5D-5L, and days of missed work/school.
[v] The PGIC assesses a patient's perceived overall health status change since the beginning of the study using a single-item scale.
[w] The PPEQ is a set of questions to assess treatment experience and impacts to the patient's life that are not collected by the other QOL assessments.
[x] During the screening period, patients and caregivers will record a minimum of 4 days of eDiary entries for pain, nausea, fatigue, and analgesic use to provide a baseline. These baseline entries must be collected on days when the patient is not experiencing a porphyria attack. During the treatment period through the Month 12 visit, eDiary entries for pain, nausea, fatigue and analgesic use will occur daily. Potential porphyria attacks will be reported in the eDiary when they occur throughout the duration of the study (from screening through the EOS visit). eDiary training will be completed at the study center at Screening. Further details on eDiary training can be found in the Study Manual.
[y] Serious adverse events (SAEs) will be collected starting at the time that informed consent is signed and through the duration of the study; AEs will be collected starting at the time the first dose of study drug is administered (Study Day 1) through the duration of the study

Table 2: Schedule of Assessments – Open-Label Extension Period: After Month 6 through Month 18

	Open-Label Extension Period[a] (After Month 6 through Month 18)									
Study Visit (M)	**Month 6.5**	**Month 7**	**Month 8**	**Month 9**	**Month 10/11**	**Month 12**	**Month 13[b]/14**	**Month 15**	**Month 16/17**	**Month 18**
Study Day (±Visit Window)	**Day 183 (±7)**	**Day 197 (±7)**	**Day 225 (±7)**	**Day 253 (±7)**	**Day 281/ Day 309 (±7)**	**Day 337 (±7)**	**Day 365/ Day 393 (±7)**	**Day 421 (±7)**	**Day 449/ Day 477 (±7)**	**Day 505 (±7)**
Physical Examination[c]		X	X	X		X				X
Body Weight, Height and BMI[d]		X	X	X		X		X		X
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X
Triplicate 12-Lead ECG[f]						X				
Clinical Laboratory Assessments[g]	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[h]		X	X	X	X	X	X	X	X	X
Study Drug Administration[i]		X	X	X	X	X	X	X	X	X
Urine Sample for PBG and ALA[jk]	X	X	X	X	X	X	X	X	X	X
Urine ALAS1 mRNA[j]	X	X	X	X		X				X
Samples for Exploratory Biomarkers (urine, plasma, serum)[l]				X		X				
Blood Sample for PK[m]		X				X				X
Serum ADA[n]		X				X				X
QOL Assessments[o]				X		X				X
PGIC[p]						X				
PPEQ[q]						X				X
Electronic Diary Entries[r]	Daily						When potential attacks occur			
AEs	Continuous									
Concomitant Medications	Continuous									

Abbreviations: ADA=anti-drug antibody; AE=adverse event; ALAS1=aminolevulinic acid synthase 1; ALA=aminolevulinic acid; ALT=alanine aminotransferase; BMI=body mass index; D=day; EC=ethics committee; ECG=electrocardiogram; IRB=institutional review board; INR=international

normalized ratio; LFT=liver function test(s); M=month; mRNA=messenger ribonucleic acid; PBG=porphobilinogen; PGIC=Patient Global Impression of Change; PK=pharmacokinetics; PPEQ=Porphyria Patient Experience Questionnaire; Q=every; QOL=quality of life; SC=subcutaneous; TBL=total bilirubin
Note:

- White boxes represent visits to the clinical study center; grey boxes represent study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow. In the event that a patient is unable to come to the study center for a scheduled clinical study visit or the procedure (s) cannot be completed during the visit, vital sign assessments, laboratory sample collection, and/or study drug administration may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor
- Study procedures, including givosiran administration, may occur at the patient's home at the discretion of the Investigator, based on safety and tolerability.

[a] Patients who discontinue treatment will be asked to complete their next clinic visit, as well as a safety follow-up assessment at 3 months (84 [± 7] days) after their last dose of givosiran.

[b] Starting at Month 13, patients on the once monthly1.25 mg/kg dose may have their monthly dose increased to 2.5 mg/kg based on Investigator judgement with consideration of the criteria described in Section 6.2.3.4.

[c] A complete physical examination will be performed at the Month 12 and Month 18 visit. At all other visits, a targeted physical examination will be performed. The physical examination will be performed prior to dosing.

[d] Dosing weight (in kilograms) will be collected during the clinical study center visits. Weight collected at either the previous study center visit or current study center visit may be used for dose calculations. Height (in centimeters) will be measured and BMI will be calculated at clinic visits every 6 months. BMI will be automatically calculated within the database.

[e] Vital signs include blood pressure, heart rate, body temperature, and respiratory rate and will be collected predose. Vital signs will be measured when patients are in a seated or supine position (should be consistent across study visits with each patient) after the patient has rested for 10 min.

[f] Triplicate 12-lead ECGs will be performed at predose and 2-hours (± 15 minutes) post-dose at the Month 12 visit, using validated ECG services equipment from a central facility; triplicate measurements should be separated by approximately 1 minute, with the patient in the supine position after he or she has rested comfortably for 5 minutes. When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECG assessments should be performed before blood samples are drawn.

[g] Clinical laboratory parameters will include: serum chemistry including LFTs, lipase, amylase, hematology, coagulation, and urinalysis. Blood and urine samples for clinical laboratory evaluations will be collected predose. Serum ferritin assessments will be collected at the Month 12 and Month 18 visits. D-dimer assessments will be performed at the Month 9 and Month 12 visits; as a clinical research parameter only, d-dimer results will not be communicated to the study centers. Results from ALT, TBL, and INR tests collected within the 14 days prior to dosing must be reviewed by the Investigator before study drug administration. Locally analyzed results may be reviewed to allow study drug administration, but additional samples for central analysis must also be collected on the day of dosing prior to the dose administration.

[h] Serum or urine pregnancy tests will be performed for females of child-bearing potential. Results must be available before dosing.

[i] Patients who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving 2.5 mg/kg once monthly will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran.

[j] Spot urine samples for ALA, PBG, and ALAS1 mRNA measurement during the study should be collected predose; however, if hemin is used for an attack, scheduled urinary ALA, PBG and ALAS1 mRNA will be collected 4 days (+4 days) after the patient's last hemin dose. Where applicable country and local regulations and infrastructure allow, urine samples for ALA, PBG, and ALAS1 mRNA assessments may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit.

[k] For patients on the once monthly 1.25 mg/kg dose who have demonstrated tolerability to givosiran, but have inadequate clinical response, ALA measurements from a previous visit or a local laboratory may be used by Investigators considering dose escalation to 2.5 mg/kg once monthly. Dose escalation for patients on the 1.25 mg/kg monthly dose may be considered starting at Month 13. See Section 6.2.3.4 for further information on dose escalation criteria.
[l] Where allowed per local regulations and IRB/EC approval, serum, plasma, and urine samples for exploratory biomarker testing, and measuring homocysteine levels, will be collected prior to dosing.
[m] Blood samples for PK analysis will be collected predose and at the timepoints listed in Table 8 or Table 9.
[n] Samples will be collected predose.
[o] QOL questionnaires to be completed include SF-12, EQ-5D-5L, and missed days of work/school
[p] The PGIC assesses a patient's perceived overall health status change since the beginning of the study using a single-item scale.
[q] The PPEQ is a set of questions to assess treatment experience and impacts to the patient's life that are not collected by the other QOL assessments.
[r] Electronic diary entries (including pain, nausea, and fatigue measurement by NRS and analgesics question) will be completed daily by patients and caregivers through the Month 12 visit; potential porphyria attacks will be reported in the eDiary when they occur by patients and caregivers throughout the duration of the study (from screening through the EOS visit). Patients/caregivers will be trained on the new approach for using the ediary after Month 12.

Table 3: Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study

	Open-Label Extension Period (Month 19 through End of Study)												
Study Visit	**Month 19/20**	**Month 21**	**Month 22/23**	**Month 24**	**Month 25/26**	**Month 27**	**Month 28/29**	**Month 30**	**Month 31/32**	**Month 33**	**Month 34/35**	**Month 36/ EOS/ ET**	**Safety Follow-up[a]**
Study Visit (±Visit Window)	**Day 533/561 (±14)**	**Day 589 (±14)**	**Day 617/645 (±14)**	**Day 673 (±14)**	**Day 701/729 (±14)**	**Day 757 (±14)**	**Day 785/813 (±14)**	**Day 841 (±14)**	**Day 869/897 (±14)**	**Day 925 (±14)**	**Day 953/981 (±14)**	**Day 1009 (±14)**	
Physical Examination[b]				X				X				X	X
Body Weight, Height and BMI[c]				X				X				X	
Vital Signs[d]		X		X		X		X		X		X	X
Single 12-Lead ECG[e]													
Clinical Laboratory Assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[h]	X	X	X	X	X	X	X	X	X	X	X		
Urine Sample for PBG and ALA[i]		X		X		X		X		X		X	X
Urine ALAS1 mRNA[i]				X				X				X	
Samples for Exploratory Biomarkers (urine, plasma, serum)[j]				X								X	
Blood Sample for PK[k]				X									
Serum ADA[l]				X								X	
QOL Assessments[m]				X				X				X	
PPEQ[n]				X									
Electronic Diary Entries[o]	When potential attacks occur												
Adverse Events	Continuous												
Concomitant Medications	Continuous												

Table 3: Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study

	Open-Label Extension Period (Month 19 through End of Study)												
Study Visit	**Month 19/20**	**Month 21**	**Month 22/23**	**Month 24**	**Month 25/26**	**Month 27**	**Month 28/29**	**Month 30**	**Month 31/32**	**Month 33**	**Month 34/35**	**Month 36/ EOS/ ET**	**Safety Follow-up[a]**
Study Visit (±Visit Window)	**Day 533/561 (±14)**	**Day 589 (±14)**	**Day 617/645 (±14)**	**Day 673 (±14)**	**Day 701/729 (±14)**	**Day 757 (±14)**	**Day 785/813 (±14)**	**Day 841 (±14)**	**Day 869/897 (±14)**	**Day 925 (±14)**	**Day 953/981 (±14)**	**Day 1009 (±14)**	

Abbreviations: ADA=anti-drug antibody; ALA=aminolevulinic acid; ALAS1=aminolevulinic acid synthase 1; BMI=body mass index; EC=ethics committee; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; IRB=institutional review board; INR=international normalized ratio; LFT=liver function test(s); M=month; mRNA=messenger ribonucleic acid; PBG=porphobilinogen; PK=pharmacokinetics; QOL=quality of life; SC=subcutaneous.

Note:
- White boxes represent visits to the clinical study center; grey boxes represent study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow. In the event that a patient is unable to come to the study center for a scheduled clinical study visit or the procedure (s) cannot be completed during the visit, vital sign assessments, laboratory sample collection, and/or study drug administration may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor.
- Study procedures, including givosiran administration, may occur at the patient's home at the discretion of the Investigator, based on safety and tolerability. In situations where a study visit cannot be completed at the study center or offsite by a home healthcare professional visit, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events, concomitant medications (including hemin use), hospitalizations/procedures, and porphyria attacks.

[a] This visit is only applicable to patients who discontinue the study early (prior to study completion). Patients who discontinue treatment will be asked to complete their next clinic visit as well as a safety follow-up at 3 months (84 [± 14] days) after their last dose of givosiran. The safety follow-up visit (3 months following the last dose of study treatment) is only required for patients who discontinue prior to study completion.

[b] A complete physical examination will be performed at the EOS visit. At all other visits, a targeted physical examination will be performed. The physical examination will be performed prior to dosing. Targeted physical examinations/body system assessments may be conducted offsite by a home healthcare professional at all time points, where applicable country and local regulations and infrastructure allow.

[c] Dosing weight (in kilograms) will be collected during the clinical study center visits. Weight obtained within 6 months during a clinical study center visit or offsite may be used for dose calculations. Height (in centimeters) will be measured and BMI calculated at clinic visits every 6 months. BMI will be automatically calculated within the database. Upon implementation of Amendment 6, measurement of height and calculation of BMI is no longer required at Months 24, 30, and 36.

[d] Vital signs include blood pressure, heart rate, body temperature, and respiratory rate and will be collected predose. Vital signs will be measured in the seated or supine position (should be consistent across study visits for each patient), after the patient has rested comfortably for 10 minutes. Vital sign measurements may be conducted offsite at all time points, where applicable country and local regulations and infrastructure allow.

[e] Single 12-lead ECG will be performed in the supine position after the patient has rested comfortably for 5 minutes. ECGs will be collected predose and prior to any blood draws. When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECG assessments should be performed before blood samples are drawn. Upon implementation of Amendment 6, ECGs are no longer required at the Month 24 and 36 visits.

[f] Clinical laboratory parameters will include: serum chemistry including LFTs, lipase, amylase, hematology, coagulation, and urinalysis. Blood and urine samples for clinical laboratory evaluations will be collected predose. Blood and urine samples for clinical laboratory assessments may be collected offsite by a home healthcare professional at all time points, where applicable country and local regulations and infrastructure allow. Results from ALT and TBL tests collected within 6 weeks prior to dosing must be reviewed by the Investigator before study drug administration. Either centrally or locally analyzed ALT and TBL results may be reviewed to allow study drug administration. In the event that givosiran is administered offsite by the patient or caregiver, safety laboratory assessments other than ALT and TBL must be obtained from a central or local laboratory within 3 months prior to dosing. Serum ferritin assessments will be collected at the Month 24, Month 30 and Month 36 visits.

[g] Serum or urine pregnancy tests will be performed for females of child-bearing potential. Results must be available before dosing.

[h] Patients who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving 2.5 mg/kg once monthly will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran. Starting at Month 13, a dose increase to 2.5 mg/kg once monthly may be permitted based on Investigator judgment in consideration of dosing criteria described in Section 6.2.3.4. Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly. See Section 6.2.3.4 for further information on dose escalation.

[I] Spot urine samples for ALA, PBG, and ALAS1 mRNA measurement during the study should be collected predose; however, if hemin is used for an attack, scheduled urinary ALA, PBG and ALAS1 mRNA will be collected 4 days (+4 days) after the patient's last hemin dose. Where applicable country and local regulations and infrastructure allow, urine samples for ALA, PBG, and ALAS1 mRNA assessments may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit.

[j] Where allowed per local regulations and IRB/EC approval, serum, plasma, and urine samples for exploratory biomarker testing, and measuring homocysteine levels, will be collected prior to dosing.

[k] Blood samples for PK analysis will be collected prior to dosing at the time points listed in Table 8 or Table 9. PK assessments that cannot be collected in the intended visit window may be completed within 6 months at the next study center visit.

[l] Samples will be collected predose. ADA assessments that cannot be collected in the intended visit window may be completed within 6 months at the next study center visit.

[m] QOL questionnaires to be completed include SF-12, EQ-5D-5L, and missed days of work/school. In situations where a planned study visit cannot be completed at the study center, the patient will complete the QoL questionnaires at home.

[n] The PPEQ is a set of questions to assess treatment experience and impacts to the patient's life not collected by the other QOL assessments. In situations where a planned study visit cannot be completed at the study center, the patient will complete the PPEQ questionnaire at home.

[o] Potential porphyria attacks will be reported in the eDiary when they occur throughout the duration of the study (from screening through the EOS visit).

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AAR	Annualized attack rate
AE	Adverse event
AIP	Acute intermittent porphyria
ADA	Anti-drug antibody
ADP	ALAD deficient porphyria
AHP	Acute hepatic porphyria
ALA	Aminolevulinic acid
ALAD	ALA dehydratase
ALAS1	Aminolevulinic acid synthase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASGPR	Asialoglycoprotein receptor
ASHE	Asymptomatic high excreter
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CHE	Chronic high excreters
CHMP	Committee for Medicinal Products for Human Use
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DRF	Dose-range finding
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EQ-5D-5L	Euro Quality of Life Health State Profile Questionnaire
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GalNAc	N-acetylgalactosamine
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice

GnRH	Gonadotropin-releasing hormone
HBMS	Hydroxymethylbilane Synthase
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Hereditary Coproporphyria
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR (equivalent to PT/INR)	International normalized ratio (equivalent to prothrombin time/international normalized ratio)
IRB	Institutional Review Board
IRS	Interactive response system
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function tests
MAD	Multiple ascending dose
MDRD	Modification of diet in renal disease
MMRM	mixed-effects model repeated measures
mRNA	Messenger RNA
NOAEL	No observed adverse effect level
NOEL	No observed-effect level
NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OLE	Open-label extension
OTC	Over the counter
PBG	Porphobilinogen
PBGD	Porphobilinogen Deaminase
PCS	Physical Component Summary
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PPEQ	Porphyria Patient Experience Questionnaire
PT	Prothrombin time
QOL	Quality of life
RBC	Red blood cells
RNA	Ribonucleic acid
RNAi	RNA interference

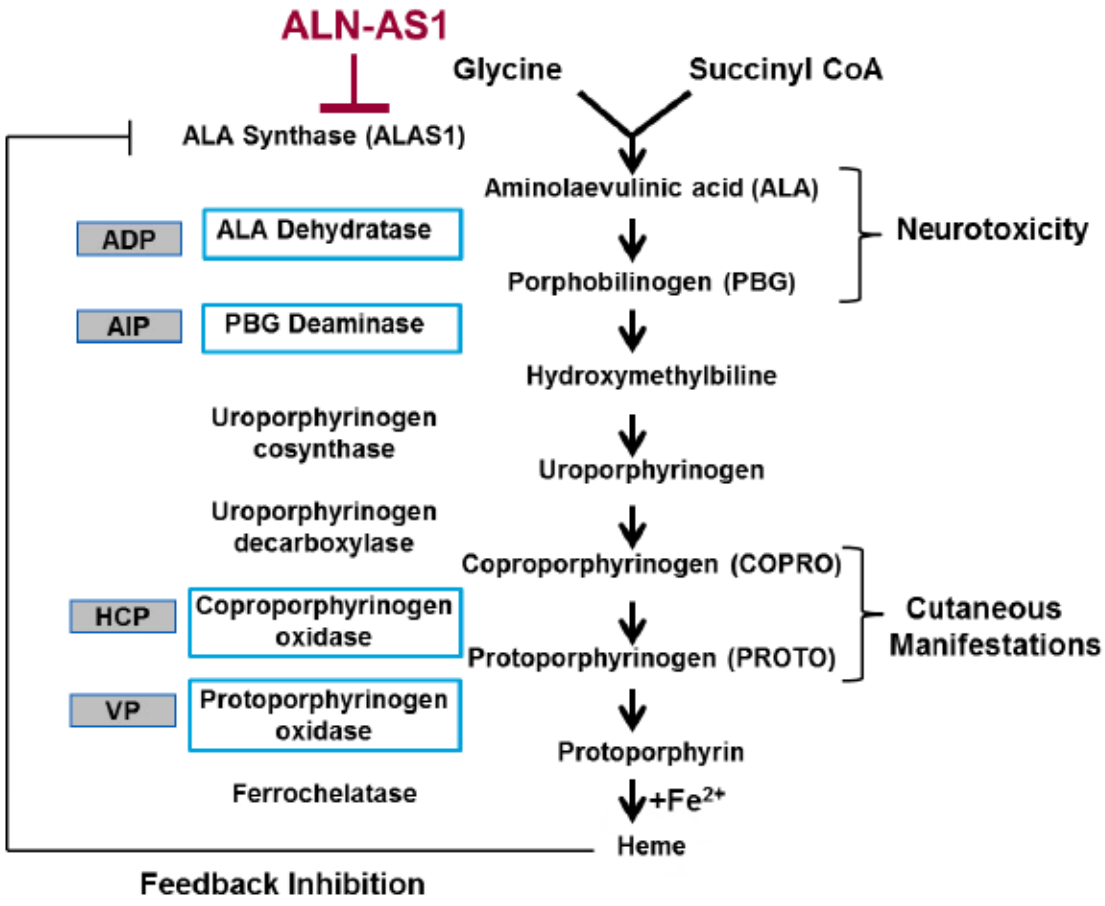
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SF-12	12-item Short-Form Health Survey
SiRNA	Small interfering RNAs
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin
T_{max}	Time to maximum plasma concentration
$t_{½\beta}$	Elimination half-life
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
V/F	Apparent volume of distribution
VP	Variegate porphyria
WHO	World Health Organization

1. INTRODUCTION

1.1. Disease Overview

The acute hepatic porphyrias (AHPs) are a family of rare, serious and life-threatening metabolic disorders predominantly caused by a genetic mutation in 1 of the 8 enzymes responsible for heme synthesis (Figure 1). The AHPs include Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), or ALA dehydratase deficient porphyria (ADP) (1); AIP is the most common AHP type. All AHP are due to autosomal dominant loss-of-function mutations in enzymes in the heme biosynthetic pathway, with the exception of ADP, which is the result of autosomal recessive mutations (2, 3).

Figure 1: Heme Biosynthetic Pathway and Enzyme Deficiency Resulting in Acute Hepatic Porphyria



Reference: James, et al 2000 (4)

Acute attacks are triggered by stress factors that induce the expression of aminolevulinic acid synthase 1 (ALAS1), which is the rate limiting step in heme synthesis. In women, attacks often occur around the menstrual cycle due to changes in ALAS1 expression from hormonal fluctuations. The induction of ALAS1, upstream of heme synthesis enzyme deficiencies, results in increased flux through the heme synthesis pathway and marked accumulation of the neurotoxic

porphyrin precursors, aminolevulinic acid (ALA) and/or porphobilinogen (PBG), the causal factors driving clinical manifestations of disease.

Disease symptom onset in AHP patients typically occurs after puberty, with women (~80%) more commonly affected than men (5). Patients experiencing acute attacks present with highly morbid and potentially life-threatening symptoms that relate to widespread dysfunction across the central, peripheral, and autonomic nervous system. The most debilitating and frequent symptom during acute attacks is diffuse, severe neurovisceral pain, most often in the abdomen, back, or limbs. Other common attack signs and symptoms include nausea and vomiting, fatigue, hypertension, tachycardia, motor weakness, hyponatremia, and mental status changes (3, 6). The attack manifestations and pain are often so severe that they require hospitalization, supportive care and the use of high-dose intravenous opioids (7). Limb numbness, weakness or paresis due to a sensory or motor neuropathy, respectively, can also occur, with progression to paralysis, respiratory failure and death (1, 8, 9).

Diagnosis of AHP is made with the combination of typical clinical presentation and symptoms as described above, along with biochemical testing for elevated urine ALA and/or PBG, and genetic testing to identify a mutation in the respective causative gene (Figure 1). In rare instances, AHP can be diagnosed in the absence of an identified mutation in a porphyria-related gene, in which case additional biochemical testing of plasma and stool porphyrins can distinguish AIP from the other AHPs (HCP, VP, and ADP) (1, 5).

There has been increasing recognition that AHP patients have significant chronic disease manifestations beyond attacks. Data from Study ALN-AS1-NT-001 (EXPLORE, an observational natural history study), conducted in a severely affected AHP patient population with recurrent attacks, determined that 64% of patients have chronic symptoms, with almost 50% experiencing symptoms on a daily basis, most commonly pain, followed by nausea and fatigue (10).

Furthermore, natural history studies done both in the US and in Sweden in AIP patients determined that 18 to 22% of AIP patients experience chronic symptoms, most commonly pain (in the abdomen, back or limbs) and fatigue (3, 11).

Over 75% of acute porphyria attacks require urgent medical care and/or hospitalization or intravenous hemin (10). Patients are initially treated with supportive care and intravenous (IV) glucose (10% dextrose), analgesics and antiemetics, along with the removal of known precipitating triggers, such as certain medications or dieting (12). Pain relief typically requires opioids until porphyria-specific therapy takes effect. In patients with moderate to severe attacks, or who fail to respond to supportive measures, treatment with IV hemin is used. After 2 to 5 days of hemin treatment, urinary ALA and PBG levels approach normalization accompanied by improvement in attack symptoms. However, in some patients attacks can last several weeks, requiring prolonged hemin use and hospitalization (13). Hemin administration can result in significant acute side effects such as severe headache, nausea, flu-like symptoms, fatigue and thrombophlebitis.

There are no approved treatments for the prevention of acute attacks of hepatic porphyria, and there is little evidence published on how best to manage AHP patients with recurrent attacks. Initial prevention steps include avoidance of potential triggers including harmful medications, smoking and alcohol use, and consumption of a low-calorie diet (13). The 3 therapeutic options

most commonly employed to prevent attacks are hormonal suppression therapy, the off-label use of prophylactic IV hemin infusions, and in extremely rare cases, liver transplantation (13, 14). Hormonal suppression therapy using a gonadotropin-releasing hormone (GnRH) analogue may have a beneficial effect in some women. However, the side effect of induction of menopause in a relatively young patient population makes the treatment difficult to tolerate (1, 15). Some porphyria specialists have resorted to the off-label prophylactic use of hemin to prevent attacks despite unfavorable characteristics for chronic therapy. Given the short half-life of hemin (10.8 hours), its beneficial effect on the toxic precursors ALA and PBG is short-lived, with their levels starting to rise within 48 hours of the infusion (16, 17). In most cases, patients receive hemin infusions through an indwelling IV catheter at a clinic or infusion center, on a scheduled basis. Chronic hemin administration can result in venous damage, iron overload and problems related to having an indwelling IV catheter (infection or thrombosis). Due to these described limitations and lack of strong efficacy data, off-label prophylactic hemin is not uniformly considered standard of care among porphyria specialists for chronic treatment or prevention of porphyria attacks.

In patients who are refractory to hemin or who no longer have adequate venous access, liver transplantation has occasionally been performed. After liver transplantation, the ALA and PBG levels normalize in 24 hours and acute attacks cease. In addition, patient quality of life has been shown to significantly improve (18). However, given the invasive and high-risk nature of transplantation and limited availability of organs, it is rarely performed (5, 19).

AHP is associated with significant morbidity and mortality, and negatively affects activities of daily living as well as the quality of life of patients. There is a clear unmet need for novel therapeutics with favorable safety profiles that effectively and durably decrease the frequency of debilitating attacks, diminish the chronic symptoms in between attacks, and improve patients' quality of life. In addition, therapeutics that do not require chronic indwelling catheters for intravenous administration would reduce complications associated with administration, including infection, deep vein thrombosis and in extreme cases the need for liver transplantation due to loss of venous access.

1.2. Givosiran

Givosiran is a synthetic chemically modified small interfering RNA (siRNA) targeting ALAS1 mRNA that is covalently linked to a triantennary N-acetyl galactosamine (GalNAc) ligand (ALN-60519) to facilitate delivery to of the siRNA to the liver (which is the primary site of ALAS1 synthesis). Givosiran acts via RNA interference (RNAi) to inhibit synthesis of liver ALAS1 and is formulated for administration via subcutaneous (SC) injection.

Givosiran is currently in development for treatment of acute hepatic porphyrias (AHPs) in adult and adolescent patients.

1.2.1. Summary of Nonclinical Data with Givosiran

The pharmacology, safety pharmacology, drug metabolism and pharmacokinetics and toxicology of givosiran were evaluated in a series of in vitro and in vivo nonclinical studies.

Givosiran is pharmacologically active in rodents, monkeys, and humans due to conservation within the siRNA target sequence. Transfection assays in human liver carcinoma cell line-G2

(HepG2) cells showed dose-dependent inhibition of endogenous ALAS1 messenger RNA (mRNA) levels with a half-maximal inhibitory concentration (IC_{50}) of approximately 26 pM givosiran. In multiple studies with mice, rats and monkeys, givosiran has demonstrated potent and dose-dependent pharmacologic activity when administered subcutaneously, resulting in consistent reduction of ALAS1 mRNA in the liver. After single dose administration, ALAS1 mRNA suppression in liver is durable (1-4 weeks) depending on the dose administered and correlates with the extent of ALAS1 mRNA suppression observed in serum or urine. Dose dependent, steady-state ALAS1 suppression has also been demonstrated with repeat-dose regimens. Studies in rodent AIP models have confirmed that ALAS1 mRNA suppression with givosiran treatment correlates with decreases in ALA and PBG heme intermediates.

A Good Laboratory Practice (GLP)-compliant safety pharmacology study conducted in monkeys showed no functional cardiovascular or respiratory effects, with a no observed-effect level (NOEL) of 150 mg/kg. Neurological assessments were conducted as part of a 13-week and a 39-week repeat dose GLP toxicity study in monkeys (once weekly dosing); no givosiran-related neurobehavioral observations occurred in either study. The NOEL for neurological effects was 150 mg/kg and 100 mg/kg in the 13-week and 39-week repeat-dose GLP toxicology studies, respectively, the highest doses evaluated. Genetic toxicity studies (bacterial reverse mutation, human peripheral blood lymphocyte chromosomal aberrations, and rat bone marrow micronucleus) assays were all negative at International Conference on Harmonization (ICH) S2 (R1) limit doses.

Two to 4-week exploratory (non-GLP) dose-range finding (DRF) toxicology studies were conducted with givosiran in mice, rats, and monkeys. In all 3 species, no dose-limiting toxicity (DLT) was observed up to the highest dose evaluated (300 mg/kg weekly SC dose), with the rat appearing to be the most sensitive species. The DRF studies were followed by 13-week GLP toxicology studies in rats and monkeys where givosiran was administered once (100 mg/kg) and once weekly at dose levels of 0, 3, 10, and 30 mg/kg in the rat and once weekly at dose levels of 0, 15, 50, or 150 mg/kg in the monkey. The no observed adverse effect levels (NOAELs) were 30 mg/kg in the rat and 150 mg/kg in the monkey (highest dose tested in each species).

In the chronic rat GLP toxicology study, givosiran was administered once weekly at dose levels of 0, 3, 10, and 30 mg/kg. The chronic rat study NOAEL was 10 mg/kg, based upon findings at 30 mg/kg, including hepatocellular single cell necrosis and vacuolation in the liver with correlating clinical pathology changes of increased aspartate aminotransferase and alkaline phosphatase. Additionally, angiectasis in islets of Langerhans (the endocrine and not the exocrine regions of the pancreas) was observed in a dose-dependent manner and thought to be possibly secondary to the liver findings at 30 mg/kg. In the chronic monkey GLP toxicology study, givosiran was administered once weekly at dose levels of 0, 10, 30, and 100 mg/kg. At initiation of the treatment, the monkeys were 13 to 17 months old. Monkeys at 24-36 months of age are generally considered to correspond with the development age of human adolescents >12 years of age. The chronic monkey study NOAEL was 30 mg/kg based upon findings at 100 mg/kg, including hepatocellular single cell necrosis that correlated with increased alanine aminotransferase, gamma glutamyl transferase, aspartate aminotransferase, and cholesterol. Angiectasis in the pancreas was not observed in the monkey study.

In the definitive rat fertility and embryofetal development study, administration of givosiran did not result in any effects on estrous cycling, mating, or fertility. The maternal NOAEL was

determined to be 3 (prior cohabitation)/0.5 (Gestation Day 6 – 17 [GD6-17]) mg/kg based upon maternal clinical pathology changes at ≥10 (prior cohabitation) /1.5 (GD 6 – 17) mg/kg. The developmental NOAEL was determined to be 30 (prior cohabitation)/5 (GD6-17) mg/kg based upon no givosiran-related effects on embryo-fetal survival, fetal body weights or fetal malformations.

In the definitive rabbit embryofetal development study, the maternal NOAEL could not be determined based upon maternal effects, which included reduced maternal body weight gains and food consumption at all doses, gross pathology signs in the liver at ≥1.5 mg/kg/day, clinical pathology changes at ≥0.5 mg/kg/day, one abortion at 5 mg/kg/day and 2 abortions at 20 mg/kg, and increased post-implantation loss because of increased early resorptions at ≥0.5 mg/kg/day. The developmental NOAEL was determined to be 0.5 mg/kg/day based upon the increased post-implantation loss at ≥1.5 mg/kg/day.

Further information on nonclinical safety, pharmacology, drug metabolism, PK, and toxicology of givosiran can be found in the current version of the Investigator's Brochure.

1.2.2. Summary of Clinical Data with Givosiran

In the givosiran clinical program as of 05 May 2017, a total of 40 unique patients have received givosiran; doses administered ranged from 0.35 mg/kg to 5.0 mg/kg. Data are available from 2 currently ongoing studies.

1.2.2.1. Phase 1 Study ALN-AS1-001

Study ALN-AS1-001 is a Phase 1 study to evaluate the safety, tolerability, PK, and PD of givosiran in adult patients with AIP. Parts A and B of this study are randomized single-blinded single ascending dose (SAD) and multiple ascending dose (MAD) evaluations in AIP patients who are asymptomatic high excreters (ASHE; also known as chronic high excreters [CHE]); these are patients who do not experience acute porphyria attacks but have biochemically active disease (ie, excrete approximately 2-3-fold higher levels of urinary ALA and PBG, relative to healthy volunteers). Part C is a randomized double-blind MAD design; all Part C patients are required to have AIP with recurrent attacks and have experienced at least 2 attacks during the 6 months prior to the study or to be on a treatment regimen of prophylactic hemin to prevent porphyria attacks. Patients on a prophylactic hemin regimen must be willing to cease prophylactic hemin dosing during the run-in and treatment periods, although all patients on the study are permitted to receive hemin as therapy for acute attacks post randomization. The doses in Study ALN-AS1-001 ranged from 0.035 mg/kg to 5.0 mg/kg of givosiran.

The primary objective of ALN-AS1-001 is to evaluate the safety and tolerability of givosiran when administered subcutaneously as a single dose or multiple doses to AIP patients who are CHE or who experience recurrent porphyria attacks. Additional objectives include assessment of PK, PD (ALA and PBG lowering), and clinical activity (annualized porphyria attack rate, annualized hemin usage, attack-free interval, levels of circulating ALAS1 mRNA, and patient quality of life) of givosiran. All interim preliminary data provided below are as of 05 May 2017.

In all parts (A, B, and C) of the Phase 1 study (ALN-AS1-001; n=40 patients), givosiran has been generally well tolerated in patients at doses of up to 5.0 mg/kg. The most common AEs (occurring in at least 2 patients) reported were nasopharyngitis (Parts A, B, and C), abdominal pain (Parts A and C), diarrhea, hypoesthesia (Part A), pruritus, rash (Part B), nausea, abdominal

distention, vomiting, headache, pyrexia, back pain, dizziness, migraine, cough, and oropharyngeal pain (Part C). There were no dose-dependent AEs or clinically significant changes in vital signs, ECG, laboratory values, or physical examination findings and no drug-related serious adverse events (SAEs) or discontinuations due to AEs were reported. Three patients in Part C have experienced a total of 5 SAEs, none of which were considered by the Investigator to be related to study drug. One fatal SAE of pancreatitis occurred in a patient with recurrent porphyria (Part C) receiving a dose of 5 mg/kg monthly that was considered by the Investigator to be unrelated to the study drug due to the presence of gallbladder sludge.

Parts A and B of Study ALN-AS1-001 (n=23 patients) demonstrated dose dependent and durable reductions in ALAS1 mRNA and urinary ALA and PBG with single and multiple givosiran doses. A single 2.5 mg/kg dose of givosiran resulted in a 64% reduction in ALAS1 mRNA, an 86% reduction in ALA levels, and a 95% reduction in PBG levels in CHE patients. In CHE patients who received 2 givosiran doses of 1.0 mg/kg administered 28 days apart, reduction in ALAS1 mRNA, ALA, and PBG of 54%, 84%, and 89%, respectively, was observed.

In Part C of Study ALN-AS1-001 (n=17 patients), available data demonstrated mean maximal reductions in ALAS1 mRNA relative to baseline in givosiran-treated patients of 39% in patients treated with 2.5 mg/kg every 3 months, 66% in patients treated with 2.5 mg/kg monthly, and 70% in patients treated with 5 mg/kg monthly. These reductions in ALAS1 were accompanied by rapid, dose-dependent and durable lowering of urine ALA and PBG to near normal levels (ie, similar to those seen in healthy volunteers) after dosing with givosiran at either 2.5 mg/kg or 5 mg/kg monthly doses for 3 months (4 doses). Moreover, the near-normalization of ALA and PBG levels was accompanied by improvement in attack symptoms.

Patients demonstrated a 63% mean decrease in their annualized porphyria attack rate (all attacks) and a 73% mean decrease in their annualized hemin doses in the givosiran treatment period compared to their 6-month pre-treatment run-in phase. In addition, compared to patients receiving placebo during the treatment period, those receiving givosiran experienced a 73% reduction in their annualized rate of attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

1.2.2.2. Phase 1/2 Open-label Extension Study ALN-AS1-002

Study ALN-AS1-002 is a Phase 1/2 open-label extension study to evaluate the long-term safety and clinical activity of givosiran in patients with AIP and recurrent porphyria attacks who have completed Study ALN-AS1-001 (Part C).

As of 05 May 2017, a total of 10 patients from Part C of Study ALN-AS1-001 are receiving ongoing open-label treatment with givosiran in the Phase 1/2 extension study (ALN-AS1-002) and have been dosed with givosiran at 2.5 or 5.0 mg/kg monthly or every 3 months; 4 patients are receiving a 5 mg/kg dose of givosiran every 3 months, 2 patients are receiving monthly doses of 5 mg/kg, and 4 patients are receiving monthly doses of 2.5 mg/kg. Preliminary results from the extension study (ALN-AS1-002) demonstrate continued safety and tolerability with longer-term givosiran dosing; as of the 05 May 2017 cutoff, no SAEs or discontinuations due to AEs have been observed. In addition, decreases in porphyria attack rates and hemin use suggest continued efficacy with extended dosing.

After the data cutoff of 05 May 2017, one patient in the 5 mg/kg every 3 months dose group experienced an SAE of upper extremity deep vein thrombosis that was determined by the Investigator to be unlikely related to study drug due to little temporal relationship to study drug administration, chronic venous damage from hemin prophylaxis, and the presence of an indwelling central venous catheter. In addition, one patient in the 2.5 mg/kg monthly dose group with a history of asthma and multiple allergies experienced an SAE of anaphylactic reaction that was determined by the Investigator to be definitely related to study drug given the temporal relationship of givosiran treatment to the onset of the reaction (within minutes). The patient was treated and recovered and was discontinued from the study.

Further information on the safety, efficacy, PK and PD of givosiran are available in the Investigator's Brochure.

1.2.2.3. Drug-drug Interaction Study ALN-AS1-004

An open-label drug-drug interaction (DDI) study (ALN-AS1-004) was conducted in AIP patients who are CHE to evaluate the effect of a single dose of 2.5 mg/kg givosiran administered SC on the pharmacokinetics of probe substrates for 5 major cytochrome P450 (CYP) enzymes that account for the metabolism of approximately 80% of prescribed drugs (20, 21). Results from this study demonstrated that givosiran treatment resulted in weak to moderate reduction in the metabolic activity of some of the 5 CYP enzymes studied, thereby leading to higher concentrations of some substrates and their metabolites. Treatment with givosiran resulted in an approximately 3-fold increase in exposure (as measured by AUC) to caffeine (a sensitive substrate for CYP1A2) and an approximately 2-fold increase in exposure to dextromethorphan (a sensitive substrate for CYP2D6). Exposure of midazolam (a sensitive substrate for CYP3A4) and omeprazole (a sensitive substrate for CYP2C19) increased less than 2-fold after treatment with givosiran. There was no effect of givosiran treatment on losartan (a sensitive substrate for CYP2C9).

1.3. Study Design Rationale

Data from the Phase 1 Study ALN-AS1-001 in CHE and AIP patients has demonstrated that administration of givosiran resulted in reduction in serum ALAS1 levels, leading to dose-dependent and durable reductions in urinary ALA and PBG. Furthermore, in patients with recurrent attacks (Part C), the reduction in ALA and PBG was associated with significant reductions in porphyria disease activity as indicated in Section 1.2.2.1. Phase 1 (ALN-AS1-001) and Phase 2 (ALN-AS1-002) data have also demonstrated evidence of clinically relevant reduction in the number and severity of porphyria attacks and meaningful improvement in other clinical outcomes in patients with porphyria. Further details of Studies ALN-AS1-001 and ALN-AS1-002 are summarized in the givosiran Investigator's Brochure.

The ENVISION Study (ALN-AS1-003) is a multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of SC-administered givosiran in patients with AHPs (n=74); the study is comprised of a 1:1 randomized, placebo-controlled double-blind treatment period of 6 months, followed by an OLE period of up to 30 months to evaluate the long-term safety and efficacy of givosiran.

During the 6-month placebo-controlled double-blind treatment period, all patients will receive SC doses of 2.5 mg/kg givosiran or placebo once monthly.

Patients crossing over to the OLE period will receive a dose based on the protocol version upon which they entered the OLE. Patients who crossed over to the OLE period prior to the implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving a 2.5 mg/kg once monthly givosiran dose will remain on that dose. Upon entry to the OLE period under amendment 3, patients will cross over to receive the 1.25 mg/kg once monthly dose of givosiran, enabling data on this additional dose of givosiran to be generated.

After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group who experience inadequate disease control may be allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg) based on discussion and agreement by the Investigator and medical monitor, demonstration of tolerability to givosiran, and fulfillment of ALA and clinical activity criteria.

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity to ensure that patients are receiving the recommended dose which was approved by the United States Food and Drug Administration (FDA) in November 2019 and received a Committee for Medicinal Products for Human Use (CHMP) positive opinion in January 2020. See Section 6.2.3.4 for further information on dose escalation.

The primary composite endpoint is the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visits, or IV hemin administration at home over the 6-month treatment period. Acute porphyria attacks are clinically meaningful and potentially life-threatening events that are the major contributors to disease burden in patients with AHPs. The proposed composite primary endpoint of attacks requiring hospitalizations, urgent healthcare visits (clinic, emergency department or infusion center), or intravenous hemin administration at home are clinical events requiring major specific intervention and can be objectively measured; based on results from Study ALN-AS1-NT-001 [EXPLORE], an observational natural history study (10), these characteristics comprise approximately 76% of all attacks in the intended patient population. The EXPLORE study population consisted of approximately 93% patients with AIP, 4% with VP, and 3% with HCP; this distribution is approximately similar to the population expected for enrollment in the Phase 3 study (ALN-AS1-003).

Secondary endpoints in the Phase 3 study (ALN-AS1-003) include the urinary porphyrin precursor levels of ALA and PBG at 3 months and 6 months. The accumulation of these precursors upstream of the PBGD enzyme defect is a causal factor of neurotoxicity and clinical manifestations of disease, such as porphyria attacks and chronic symptoms between attacks; evidence from Phase 1 (ALN-AS1-001) suggests a graded relationship between reduction in ALA/PBG and attack reduction. The impact of givosiran treatment on hemin use, nausea, fatigue and quality of life will also be assessed.

The endpoints will be evaluated against a placebo comparator for the first 6 months of the study (the double-blind treatment period); after this, all patients will receive open-label givosiran for up to an additional 29 months in the extension portion of the study. The placebo comparator was selected based on the lack of consensus guidance on the standard of care for preventative therapies for patients with recurrent attacks. No therapies are currently approved for the prevention of future attacks. The three options most commonly employed to prevent attacks are

hormonal suppression therapy, the off-label use of IV hemin as scheduled or prophylactic infusions, and in extremely rare cases, liver transplantation (13, 14, 22). The evidence supporting the safety and efficacy of each of these options is limited to case reports or small-uncontrolled studies. Thus, there are no consensus guidelines for the use of any of these treatments as a prophylactic regimen to prevent porphyria attacks. Moreover, each of these options has significant limitations.

Hemin is the only licensed medicinal product for the treatment of porphyria and it is only approved for use in treating acute attacks after they occur. Patients are permitted to continue to receive standard of care treatment, including hemin, for any acute attacks they experience while participating in the Phase 3 study, but they will not be permitted to use hemin prophylactically because givosiran is intended as monotherapy to prevent attacks and the regular co-administration of hemin could confound efficacy and safety signals related to givosiran.

The study population will be comprised of adults and adolescents (≥12 years of age) with a documented diagnosis of AHP.

Overall, based on the totality of safety, tolerability and efficacy data available from the Phase 1 placebo-controlled study (ALN-AS1-001) and the Phase 1/2 OLE study (ALN-AS1-002), givosiran is an appropriate candidate to be further studied in patients within a Phase 3 setting, given the high unmet medical need in this population.

1.4. Dose Rationale

Dose selection was guided by the principle of identifying an optimal dose that is both well-tolerated and efficacious. The proposed Phase 3 givosiran dose of 2.5 mg/kg administered monthly was selected based on observed data from ongoing clinical studies, and population pharmacokinetic-pharmacodynamic modeling. The key PD and clinical parameters used to support the dose selection include decreases in urinary ALA levels, the most proximate and direct PD effect of givosiran, as well as reductions in porphyria attacks, hemin usage and porphyria attack-free intervals.

In the Phase 1 placebo controlled-study (Study ALN-AS1-001) and the Phase 1/2 OLE study (Study ALN-AS1-002) a clear dose response with respect to reduction of elevated urinary ALA was observed, with monthly dosing yielding higher and sustained reductions compared to dosing every 3 months. From the dosing regimens evaluated, givosiran dose of 2.5 mg/kg administered monthly lowered urinary ALA in AIP patients by about 95% to levels that were close to those observed in normal healthy volunteers; these reductions in urinary ALA levels were associated with marked reductions in porphyria attacks, hemin usage and attack-free intervals.

In light of LFT elevations observed in the study, a lower givosiran dose of 1.25 mg/kg once monthly has been introduced as a down-titration dose, as detailed in Section 6.2.3.1.

Under amendment 3, patients entering the OLE period will be assigned to receive 1.25 mg/kg givosiran once monthly in order to generate additional data at this dose level. While the 2.5 mg/kg once monthly dose has been demonstrated to provide near-normalization of ALA levels in the majority of AIP patients with recurrent attacks in the completed Phase 1 ALN-AS1-001 study (Part C) and the ongoing Phase 1/2 ALN-AS1-002 open-label extension study, preliminary analyses of PK and PD data suggest that a givosiran dose of 1.25 mg/kg once monthly would reduce ALA levels in a substantial number of patients. The proposed study design will enable the

evaluation of the PD, efficacy, and safety of the 1.25 mg/kg monthly dose of givosiran, while continuing to provide data on the 2.5 mg/kg monthly dose. Based on the first 6 months of treatment during the OLE period in patients who received placebo in the double-blind period, a trend toward increased benefit, as indicated by greater reductions in composite attacks, hemin use, and ALA and PBG levels, was observed with the 2.5-mg/kg once monthly dose compared to the 1.25-mg/kg once monthly dose. Given the trend toward increased benefit with the 2.5-mg/kg dose of givosiran compared to the 1.25-mg/kg dose and considering that AHP is a disease in which each attack is serious, highly morbid, and carries potential for irreversible neurologic damage, implementation of amendment 5 increases the dose for all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations to the recommended dose of 2.5 mg/kg givosiran SC once monthly, which was approved by the United States FDA in November 2019 and received a CHMP positive opinion in January 2020.

The concentration of givosiran in the liver is the primary driver for its pharmacodynamic effects, which is primarily affected by body weight. Population pharmacokinetic-pharmacodynamic modeling and simulation across different body weights show similar liver exposures of givosiran in adolescents and adults following monthly dosing and consequently similar extent and duration of urinary ALA suppression. Therefore, the same doses are proposed to be administered to both adults and adolescents in this study.

1.5. Benefit-Risk Assessment

Based on the available nonclinical and clinical data (see Section 1.2.2), givosiran administered subcutaneously as a once-monthly dose regimen, may be able to offer dose-dependent, potent and sustained suppression of ALAS1, thereby decreasing the accumulation of the neurotoxic heme intermediates ALA and PBG. This may, in turn, potentially prevent the occurrence of acute porphyria attacks, as well as potentially ameliorate chronic porphyria symptoms that patients experience between attacks, including pain, nausea, and fatigue.

The givosiran nonclinical toxicology program, including dose-ranging studies in the mouse, rat, and monkeys, followed by clinical trial application-enabling, as well as chronic GLP toxicology studies in the rat up to 26 weeks and monkey (juvenile monkeys at initiation of the study) up to 39 weeks, demonstrated an adequate safety margin for clinical dosing of givosiran at 2.5 mg/kg per month. Givosiran was administered via SC injection in all toxicology studies, consistent with the intended clinical route of administration. All in vitro and in vivo genetic toxicity studies were negative at ICH S2 (R1) limit doses. In the rat and rabbit embryofetal developmental toxicity studies, givosiran-related increased post-implantation loss/early absorption (rabbits) and fetal skeletal variation (rats and rabbits) were observed. The observed maternal toxicity may have caused or contributed to the observed embryofetal effects, while there was no detectable level of givosiran via fetal transfer at any dose. To minimize any potential risk of embryofetal toxicity (teratogenicity), women of child-bearing potential must have a negative pregnancy test, cannot be breastfeeding, and must be willing to use an acceptable method of contraception during studies with givosiran. Contraception requirements and guidelines are provided in the clinical study protocols.

The clinical experience from Phase 1 Study ALN-AS1-001 (Part C) suggests that in patients with AIP and recurrent attacks, givosiran treatment is associated with sustained reductions in ALA/PBG levels, decreased attack frequency (ranging from 63 to 75%), and reduced hemin usage

in the 24-week treatment period, compared to the 12-week run-in period. In addition, interim safety results from the ongoing Phase 1 study and Phase 1/2 OLE study indicate that givosiran has an acceptable safety profile and is generally well-tolerated.

Further details on the nonclinical results and safety results for Study ALN-AS1-001 can be found in the givosiran IB. Given the biological target of givosiran, the available nonclinical and clinical data, and the mode of administration, other potential safety concerns include injection site reactions (ISRs), elevation of liver transaminases, increased serum creatinine/decreased estimated glomerular filtration rate (eGFR), pancreatitis, and anaphylactic reaction. A summary of preliminary clinical data from ongoing Phase 1 and Phase 1/2 studies of givosiran can be found in Section 1.2.2 and in the givosiran IB.

This clinical protocol includes exclusion criteria intended to minimize the risk of transaminitis, ISR and pancreatitis, and incorporates ongoing monitoring for elevated transaminases, serum lipase, and anaphylactic reactions (Section 6.2.3). Specific rules for dose withholding and stopping have been incorporated in the protocol for abnormalities in liver function tests, and serum amylase and lipase levels.

Blood homocysteine levels may be increased in patients with AHP, vitamin deficiencies, or chronic kidney disease. (23-25) During treatment with givosiran, increases in blood homocysteine levels have been observed compared to levels before treatment. The clinical relevance of the elevations in blood homocysteine during givosiran treatment is unknown. The protocol includes monitoring for changes in blood homocysteine levels during treatment with givosiran. It is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6 (see Section 6.3.4).

An Independent Data Monitoring Committee (DMC) will monitor safety over the course of the double-blind treatment period and until all patients have been in the OLE period for at least 6 months (Section 4.7).

Based on the emerging efficacy and safety data from the ongoing clinical studies (ALN-AS1-001 and ALN-AS1-002) and the observed preclinical margins, the benefit-risk assessment supports evaluation of givosiran in a phase 3 Study in AHP patients.

2. OBJECTIVES

2.1. Primary Objective

- Evaluate the effect of SC givosiran, compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with AIP

2.2. Secondary Objectives

- Evaluate the effects of givosiran, compared to placebo, on urinary ALA levels in patients with AIP
- Evaluate the effects of givosiran, compared to placebo, on urinary PBG levels in patients with AIP

- Evaluate the effects of givosiran, compared to placebo, on hemin usage in patients with AIP
- Evaluate the effects of givosiran, compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP
- Evaluate the effects of givosiran compared to placebo in patients with AIP on the symptoms of pain, nausea, and fatigue
- Evaluate the effects of givosiran, compared to placebo, in patients with AIP on the Physical Component Summary (PCS) of the 12-item Short-Form Health Survey (SF-12) (26)
- Evaluate the safety and tolerability of givosiran in patients with any AHP

2.3. Exploratory Objectives

- Evaluate the effects of givosiran, compared to placebo, in patients with AIP and in patients with any AHP over the 6-month treatment period on:
  - Rate of all porphyria attacks (requiring hospitalization, urgent healthcare visit, IV hemin administration at home, or treated at home without IV hemin)
  - Urinary ALAS1 mRNA levels
  - Analgesic usage (opioid and non-opioid)
  - Additional quality of life (QOL) measures, including missed days of work/school
  - Patient experience questionnaire and patient's impression of health status change
- Assess the treatment effect of givosiran at evaluated doses over the OLE period in patients with AIP and in patients with any AHP who had previously been randomized to placebo treatment
- Assess the long-term treatment effect of givosiran in patients with AIP and in patients with any AHP
- Characterize the PK of and assess the antidrug antibodies (ADA) of givosiran in patients with any AHP

3. ENDPOINTS

3.1. Primary Endpoint

- Annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with AIP over the 6-month treatment period. See Section 3.5 for the definition of porphyria attacks and associated terms.

3.2. Secondary Endpoints

- Urinary ALA levels in patients with AIP at 3 months

- Urinary ALA levels in patients with AIP at 6 months
- Urinary PBG levels in patients with AIP at 6 months
- Annualized rate of administered hemin doses in patients with AIP over the 6-month treatment period
- Annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP over the 6-month treatment period (Section 3.5)
- Daily worst pain score as measured by Brief Pain Inventory-Short Form (BPI-SF) numeric rating scale (NRS) in patients with AIP over the 6-month treatment period
- Daily worst nausea score as measured by NRS in patients with AIP over the 6-month treatment period
- Daily worst fatigue score as measured by Brief Fatigue Inventory-Short Form (BFI-SF) NRS in patients with AIP over the 6-month treatment period
- Change from baseline in the Physical Component Summary (PCS) of the 12-item Short-Form Health Survey (SF-12) (26) in patients with AIP at 6 months

3.3. Exploratory Endpoints

Exploratory endpoints will be measured in patients with AIP and in patients with any AHP over the 6-month treatment period or over the OLE period at doses evaluated:

- Rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home (Section 3.5)
- Rate of all porphyria attacks (Section 3.5)
- Rate of administered hemin doses
- Urinary ALA and PBG levels
- Urinary ALAS1 mRNA levels
- Daily worst pain, daily worst nausea, and daily worst fatigue scores over 12 months
- PCS of the SF-12 (26)
- EQ-5D-5L index score (27)
- Patient Global Impression of Change (PGIC)
- Porphyria Patient Experience Questionnaire (PPEQ)
- Analgesic usage (opioid and non-opioid)
- PK profile of givosiran
- Incidence and titer of ADAs

3.4. Safety Endpoints

- Incidence, severity, seriousness, and relatedness of adverse events over the 6-month treatment period and in the OLE period in patients with any AHP. Since porphyria attacks will be recorded for efficacy assessment of givosiran, they will not be treated as AEs or SAEs as described in Section 7.5.6.

3.5. Definition of Porphyria Attacks

Porphyria attacks are defined as meeting all the criteria below:

- an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs
- no other medically determined cause other than a porphyria attack
- requires treatment with IV dextrose or hemin, carbohydrates, or analgesics (opioid [synthetic and non-synthetic substances] or non-opioid), or other medications such as antiemetics, at a dose or frequency beyond the patient's usual daily porphyria management.

For the purposes of this study, the following definitions will be used to identify each non-overlapping sub-type of porphyria attack events:

- **Porphyria attacks requiring hospitalization:** porphyria attacks that prompt a hospitalization. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in an at least 24-hour stay (or a change in calendar date if the hospital admission or discharge times are not available).
- **Porphyria attacks requiring urgent healthcare visit:** Porphyria attacks that prompt urgent healthcare visits. An urgent healthcare visit is defined as an urgent, unscheduled office/practice, infusion center, or an emergency department visit that does not meet the criteria for a hospitalization. This endpoint includes presentation with a porphyria attack on a protocol-scheduled clinic visit if the patient would have sought an urgent healthcare visit in the absence of the protocol-scheduled clinic visit.
- **Porphyria attacks requiring IV hemin at home:** Porphyria attacks at home requiring IV hemin. "Home" is defined as any location that does not meet the criteria for a hospitalization or urgent healthcare visit.
- **Porphyria attacks at home not requiring IV hemin:** Porphyria attacks at home that do not require IV hemin but are treated with carbohydrates or analgesics (opioid or non-opioid) at a dose or frequency beyond the patient's usual daily porphyria management. "Home" is defined as any location that does not meet the criteria for a hospitalization or urgent healthcare visit.

The start of porphyria attacks is characterized by acute and sustained worsening of the patient's porphyria manifestations beyond normal day-to-day variability. The end of porphyria attacks is characterized by recovery from porphyria manifestations back to within a patient's normal day-to-day variability. Symptoms during an attack may be similar in nature in a given patient, but not necessarily in degree or severity. Since porphyria attacks will be recorded for efficacy assessment of givosiran, they will not be treated as AEs or SAEs as described in Section 7.5.6.

4. INVESTIGATIONAL PLAN

4.1. Summary of Study Design

This is a 2-part multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of givosiran in adults and adolescents (≥12 years of age) with a documented diagnosis of AIP. The efficacy and safety of givosiran will also be investigated in the other AHPs, including HCP, VP, or ADP. A schematic of the study design is shown in Figure 2.

Patients who were on hemin prophylaxis prior to enrollment will be eligible to participate if they meet the attack entry criteria. In this study, patients may be given hemin for the treatment of acute attacks if clinically indicated but may not use hemin prophylactically. Hemin prophylaxis is not permitted in this study because givosiran is intended as monotherapy to prevent attacks and the regular co-administration of hemin could confound efficacy and safety signals related to givosiran.

In the first part of the study, consenting (and assenting, where applicable) patients who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 2.5 mg/kg givosiran or placebo monthly for a 6-month treatment period; both givosiran and placebo will be administered subcutaneously. Treatment groups will be stratified at study entry by AHP type (AIP [with genetic evidence of mutation in the *HMBS* gene] vs HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene); all patients with AIP \will be further stratified by each patient's use of hemin prophylaxis regimen at the time of screening and by each patient's historical annualized attack rate. AIP patients on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <7 attacks vs ≥7 attacks in the past 12 months. Patients who were not on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <12 attacks vs ≥12 attacks in the past 12 months.

During the 6-month treatment period, patients will undergo efficacy and safety assessments every 2 weeks for the first month and monthly thereafter. Following the completion of 6 months of double-blinded study treatment, as well as all Month-6 visit assessments, patients from both the givosiran and placebo arms will begin the second part of the study, the OLE period in which they will be treated with givosiran for up to 29 months. Patients who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving a 2.5 mg/kg once monthly givosiran dose will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran.

After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group who experience inadequate disease control may be allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg) based on discussion and agreement by the Investigator and medical monitor, demonstration of tolerability to givosiran, and fulfillment of ALA and clinical activity criteria.

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose

increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. For further details, see Section 6.2.3.4.

Patients will undergo efficacy and safety assessments every 2 weeks for the first month of the OLE period and then monthly through Month 18, and every 3 months thereafter.

If hemin is used for porphyria attacks, the scheduled urine sample for ALA, PBG, and ALAS1 mRNA assessments will be collected 4 days (+4 days) after the patient's last hemin dose.

For particular visits, as specified in the Schedule of Assessments (Table 2 and Table 3), and where applicable country and local regulations and infrastructure allow, study procedures may be conducted by a home healthcare professional. Study drug administration may be conducted by a home healthcare professional for patients that have demonstrated the ability to tolerate the study drug at the study center. If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, givosiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on givosiran administration and the use of epinephrine (epi pen or equivalent) prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

Patients or caregivers will be provided with an electronic diary (eDiary) to record severity of daily pain, nausea, and fatigue, as well as analgesic use. Potential porphyria attacks will also be recorded in the eDiary by patients and caregivers when they occur; study centers will be notified when potential porphyria attacks are reported in the eDiary. In instances when the eDiary is not used to report potential porphyria attacks, study centers may be notified by telephone by patients, caregivers, or other healthcare providers. All potential porphyria attacks will be confirmed by the Investigator.

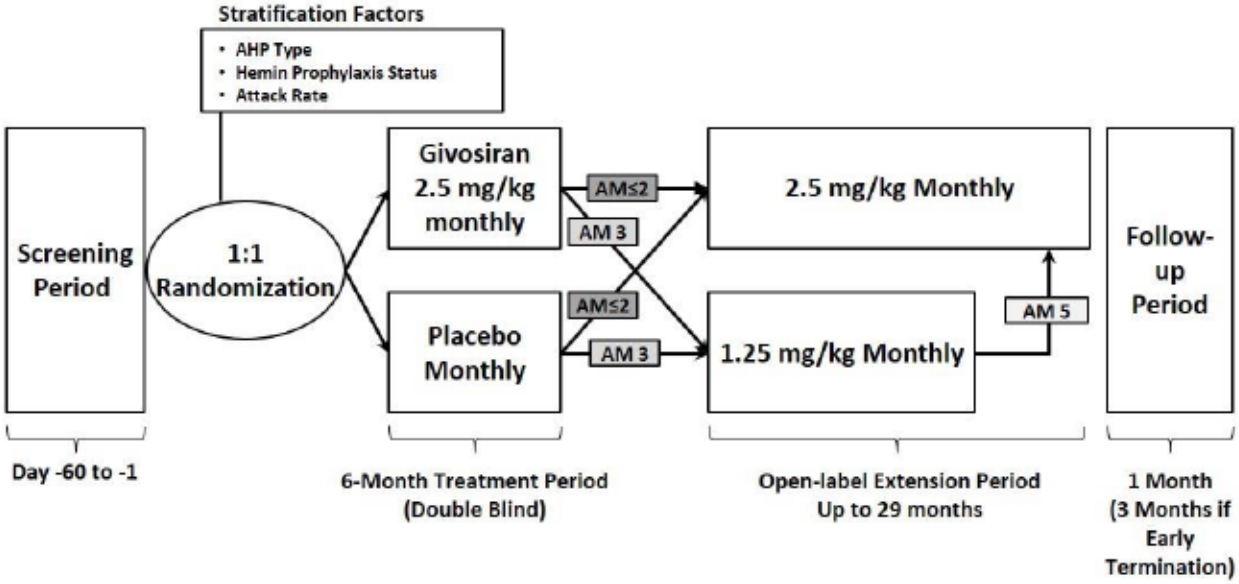
An external independent Data Monitoring Committee (DMC; Section 4.7) will monitor safety over the course of the double-blind treatment period and until all patients have been in the OLE period for at least 6 months. Details for the committee will be provided in committee charter.

During the OLE Period, patients may receive givosiran as long as they do not fulfill any of the study discontinuation criteria (see Section 5.3) or until givosiran is commercially available in the patient's territory or the givosiran development program is discontinued (whichever comes first).

All patients are asked to participate in the Safety Follow-up visit after they have received their last dose of givosiran.

Where required by local regulations, this trial may be replaced with a post-marketing clinical trial once marketing authorization for givosiran is received.

Figure 2: Study Design



Abbreviations: AM ≤2=original protocol (06 Sept 2017), protocol amendment 1 (04 May 2018), and protocol amendment 2.0 (26 July 2018); AM 3=protocol amendment 3 (21 Sept 2018); AM 5=protocol amendment 5 (12 February 2020)

4.2. Duration of Treatment

The estimated total time on study for each patient is approximately 38 months, including up to 2 months of screening, up to 35 months of treatment (double-blind treatment period of 6 months and up to 29-month open-label extension period), and a 1-month follow-up period.

The primary endpoint will be analyzed at the completion of the 6-month treatment period.

A patient will be considered to have completed the primary outcome measure at the time of completion of the Month-6 treatment assessments.

4.3. Number of Patients

The planned total enrollment in the study is approximately 74 AHP patients, including approximately 70 AIP patients.

4.4. Method of Assigning Patients to Treatment Groups

Patients will be randomized 1:1 to study drug or placebo in a double-blind manner. Treatment groups will be stratified at study entry by AHP type (AIP [with genetic evidence of mutation in the *HMBS* gene] vs HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene).

Randomization for AIP patients will be further stratified by each patient's use of hemin prophylaxis regimen at the time of screening and by each patient's historical annualized attack rate. Patients on a hemin prophylaxis regimen prior to study entry will be stratified by their historical annualized attack rate: <7 attacks vs ≥7 attacks in the past 12 months. Patients who were not on a hemin prophylaxis regimen prior to study entry will be stratified by their historical

annualized attack rate: <12 attacks vs ≥12 attacks in the past 12 months. These stratification cutoffs are based on the average annualized attack rates observed in the Study ALN-AS1-NT-001 (EXPLORE, an observational natural history study).

As very few non-AIP patients are anticipated to be enrolled in the study, no additional stratification factors will be considered for these patients.

Each patient will be uniquely identified in the study by a combination of the study center number and patient identification number. Upon completion of the informed consent form (ICF; and assent, if applicable) by the patient/parent or guardian, the patient will be assigned a patient identification number by the interactive response system (IRS). The Investigator or his/her delegate will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria and a blinded treatment will be assigned.

4.5. Blinding

Individual subject treatment assignments will be maintained by the IRS. Members of the study team will not have access to unblinded data until the 6-month treatment period data is unblinded for its final analysis. Any unplanned unblinding occurring during the study period will be documented and reported in the clinical study report.

The independent DMC and an independent biostatistics group will have access to subject level treatment assignments. In addition to periodic safety monitoring by the DMC, an interim analysis based on accumulating efficacy and safety data may be performed by an unblinded group. Members in the designated unblinded group will not have direct roles or responsibilities in conducting this study. Alnylam staff members who are involved in randomization and analysis of PK, urinary ALAS1, urinary ALA, and PBG, and anti-drug antibody (ADA) may have treatment assignment information but will not have access to subject level data from the clinical trial databases.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further clinical management of the patient. The principal investigator is strongly encouraged to contact the medical monitor before unblinding any patient's treatment assignment but must do so within 1 working day after the event. A record of when the blind was broken, who broke the blind, and why it was broken, will be maintained in the trial master file (TMF).

Refer to the IRS instructions for details on unblinding.

Laboratory results of urinary ALA, PBG, (performed at a central laboratory) or ALAS1 mRNA (performed at Alnylam) will be blinded from after the time of the first dose until unblinding of the clinical database and will not be reported to the investigator post-screening. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining local ALA or PBG measurements until at least 12 weeks after the Month 6 visit (to avoid potential unblinding). If ALA or PBG is measured during this period, all reasonable steps must be undertaken to avoid informing the patient and study personnel of the results.

A list of all Alnylam personnel or personnel working on behalf of Alnylam who are unblinded to study data will be maintained in the TMF.

4.6. Patient Electronic Diary (eDiary)

Patients or caregivers will be provided with an electronic diary (eDiary) at screening and trained on its use. Daily entries into the eDiary will include pain, nausea, and fatigue severity, as well as analgesic use. For further details, see Section 7.2.2.

Patients or caregivers will report potential porphyria attacks in the eDiary when they occur from screening throughout the duration of the study. For additional details, see Section 7.2.1.

Complete instructions on electronic diary use will be provided in the Study Manual.

4.7. Independent Data Monitoring Committee

An external independent DMC will monitor safety over the course of the double-blind treatment period and until all patients have been in the OLE period for at least 6 months. Analyses for the DMC are provided by an independent biostatistics group. Details are provided in the DMC Charter.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Age ≥12 years
2. Documented diagnosis of AIP, HCP, VP, or ADP based on clinical features (eg, acute attacks of abdominal, back, chest, extremities, and/or limb pain), at least one documented urinary or plasma PBG or ALA value ≥4× upper limit of normal (ULN) within the past year prior to or during Screening, AND one of the following:
   - Documented genetic evidence of mutation in a porphyria-related gene, defined as ANY of the following:
     - AIP: mutation in the hydroxymethylbilane synthase gene (*HMBS*; also referred to as the porphobilinogen deaminase [*PBGD*] gene)
     - HCP: mutation in the coproporphyrinogen oxidase (*CPOX*) gene
     - VP: mutation in the protoporphyrinogen oxidase (*PPOX*) gene
     - ADP: mutation in the aminolevulinic acid dehydratase (*ALAD)* homozygous or compound heterozygous genes
   - OR if the results of a patient's genetic testing do not identify a mutation in a porphyria-related gene (<5% of cases), a patient may be eligible for the study if they have both clinical features and diagnostic biochemical criteria consistent with AHP (Table 11)

3. Have active disease, with at least 2 porphyria attacks requiring hospitalization, urgent healthcare visit or treatment with IV hemin at home within the 6 months prior to Screening
4. Willing to discontinue and/or not initiate use of prophylactic hemin at the time of Screening and for the duration of the study
5. Have adequate venous access for study sample collection as judged by the investigator
6. Be willing to comply with the contraceptive requirements during the study period, as described in Section 6.4.
7. Be willing and able to comply with the study requirements and to provide written informed consent per local and national requirements. In the case of patients under the age of legal consent, legal guardian(s) must provide written informed consent and the patient should provide assent per local and national requirements and institutional standards.

5.2. Exclusion Criteria

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Any of the following laboratory parameter assessments at Screening:
   a. Alanine aminotransferase (ALT) >2×ULN
   b. Total bilirubin >1.5× ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2×ULN
   c. International normalized ratio (INR) > 1.5 (patients on an anticoagulant [eg, warfarin] with an INR< 3.5 will be allowed)
2. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula
3. On an active liver transplantation waiting list, or anticipated to undergo liver transplantation during the blinded study treatment period
4. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or to N-acetylgalactosamine (GalNAc)
5. History of intolerance to subcutaneous injection(s)
6. Known active HIV infection; or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
7. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer) since ending another investigational device or drug study(s), or receiving other investigational agent(s)
8. Females who are pregnant, breast-feeding, or planning to become pregnant during the study

9. Any condition (eg, medical concern or alcohol or substance abuse), which in the opinion of the Investigator, would make the patient unsuitable for dosing or which could interfere with the study compliance, the patient's safety and/or the patient's participation in the 6-month treatment period of the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to porphyria identified by key laboratory abnormalities or medical history.
10. History of recurrent pancreatitis, or acute pancreatitis with disease activity within the past 12 months prior to Screening
11. Has a major surgery planned during the first 6 months of the study
12. History of serious infection within one month prior to Screening
13. Had a malignancy within 5 years prior to Screening, except for basal or squamous cell carcinoma of the skin, cervical in-situ carcinoma, or breast ductal carcinoma, that has been successfully treated

5.3. Discontinuation of Study Drug and/or Study

Patients or their legal guardians (in the case that the patient is a minor) are free to discontinue treatment and/or study or withdraw their consent at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or of the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator. The Investigator may withdraw a patient from the study at any time if this is considered in the patient's best interest.

Discontinuation of study drug and withdrawal from the study are described in Section 5.3.1 and Section 5.3.2 , respectively. If a patient stops participation from the study or withdraws consent from the study, he/she will not be able to re-enroll in the study

5.3.1. Discontinuation of Study Drug

The Investigator or designee may discontinue dosing in a patient if the patient:

- Is in significant violation of the protocol
- Experiences a SAE considered to be related to the study drug or an intolerable AE
- Becomes pregnant
- Is non-adherent to the treatment regimen

The Investigator will confer with the Sponsor or medical monitor before discontinuing dosing in the patient.

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 7.5.6.6 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

If a patient discontinues dosing due to a serious adverse event (SAE), the SAE should be followed as described in Section 7.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the electronic case report form (eCRF). Patients who discontinue study drug

and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study treatment during the 6-month treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month-6 assessments) will be encouraged to remain on the study and complete assessments through Month 6 and continue to report potential porphyria attacks as they occur; they will also be asked to complete a safety follow-up 3 months (84±14 days) after their last dose of study drug (see Table 3).

Patients who discontinue study treatment during the OLE period will be asked to return for their next scheduled visit to complete EOS/ET assessments; they will also be asked to complete a safety follow-up visit 3 months (84±14 days) after their last dose of study drug (see Table 3).

5.3.2. Discontinuation from the Study

A patient or their legal guardian may decide to stop the patient's participation in the study at any time. Patients considering stopping the study should be informed that they can discontinue treatment and complete study assessments including follow-up, as per the SOA, or alternatively may complete any minimal assessments for which the patient consents. The Investigator may withdraw a patient at any time if this is considered in the patient's best interest.

However, study integrity and interpretation are best maintained if all randomized patients continue study assessments and follow-up. Stopping study participation could mean:

- If a patient stops participation during the 6-month treatment period, they should be informed that they can discontinue treatment, but continue to complete their study assessments through the 6-month visit, including follow-up.
- If a patient stops participation during the open-label extension period, they should be asked to return for an Early Termination Visit as well as a Safety Follow-Up Visit 3 months after their last dose of study drug.
- A patient can stop taking the study drug and stop study-related visits, but allow the investigator and study team to review the patient's medical records, public records or be contacted to receive information about the patient's health

When a patient stops the study, the discontinuation and reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient stops the study due to an adverse event (AE), including an SAE, the AE should be followed as described in Section 7.5.6.

If the patient wants to stop participation in the study, he/she should notify the study doctor in writing or in any other form that may be locally required. The personal data already collected during the study, including patient's biological samples, will still be used together with the data collected on other patients in the study according to the informed consent and applicable laws.

In addition to stopping participation in the study, the patient could decide to withdraw his/her consent as explained in Section 5.3.3

5.3.3. Withdrawal of Consent to Collect and Process the Patient's Personal Data

The patient may decide to withdraw his/her consent informing the study doctor at any time in writing, or in any other form that may be locally required. This means that the patient wants to stop participation in the study and any further collection of his/her personal data.

- The sponsor will continue to keep and use a patient's study information (including any data resulting from the analysis of the patient's biological samples until time of withdrawal) according to applicable law. This is done to guarantee the validity of the study, determine the effects of the study treatment, and ensure completeness of study documentation.
- The patient can also request that collected samples be destroyed or returned (to the extent it is permitted by applicable law) at any time.
- Patients who withdraw their consent to collect and use personal data should understand that public records may be reviewed to determine the patient's survival status as allowed per local and national regulations.

In US and Japan, otherwise, samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of the protocol and of the informed consent form.

In EU and rest of world, in any event, samples not yet analyzed at the time of withdrawal will not be used any longer, unless permitted by applicable law. They will be stored or destroyed according to applicable legal requirements.

5.3.4. Replacement of Patients

Patients discontinuing from study drug or withdrawing from the study will not be replaced.

6. TREATMENTS

6.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

6.2. Investigational Study Drug

Detailed information describing the preparation, administration, and storage of givosiran and placebo is provided in the Pharmacy Manual.

6.2.1. Description

The givosiran drug product (ALN-AS1) will be supplied as a sterile solution in water for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to givosiran and an identical volume will be administered.

6.2.2. Dose and Administration

The study drug should be injected into the abdomen or upper arms or thighs. Detailed instructions for study drug administration are presented in the Pharmacy Manual. As is consistent with good medical practice for subcutaneous drug administration, patients will be observed for a minimum of 20 minutes after each injection. Treatment for anaphylactic reactions should be readily available where patients are being dosed, and follow country and/or local hospital treatment guidelines (28).

Givosiran will be administered by a qualified and authorized health care professional trained in the recognition and management of anaphylactic reactions, whenever possible. Study drug administration may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor, during particular study visits, as specified in the Schedules of Assessments (Table 2 and Table 3). If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, givosiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on givosiran administration and the use of epinephrine (epi pen or equivalent) prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing. However, study drug administration at the study center should be considered for patients who have ongoing study drug-related AEs or known risk factors for developing anaphylactic reactions, including but not limited to: prior history of an anaphylactic reaction to food, medications or due to unknown etiology, worsening injection site reactions with repeat dosing, or anyone in the opinion of the investigator that would benefit from clinical observation following dosing.

ALT and total bilirubin (TBL) results collected within 6 weeks of study drug administration must be reviewed prior to dosing. In the event that givosiran is administered offsite by the patient or caregiver, safety laboratory assessments other than ALT and TBL must be obtained from a central or local laboratory within 3 months prior to dosing. For patients with new signs or symptoms, appropriate evaluation, including laboratory assessments, should be performed based on investigator judgment prior to study drug administration.

If a patient does not receive a dose of study treatment within the specified dosing window, the Investigator should contact the medical monitor. After such consultation, the dose may be administered or will be considered missed and not administered.

Patients will be permitted to miss one dose of study drug during the 6-month treatment period and one dose within each 6-month interval of the OLE period. However, if a patient misses multiple doses, the Investigator, in consultation with the medical monitor, will discuss whether the patient will be able to continue receiving study drug while on the study.

Detailed instructions for study drug administration are presented in the Pharmacy Manual. In addition, instructions and procedures related to administration of givosiran by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

6.2.2.1. During the 6-Month Treatment Period (Day 1 to Month 6)

Patients will be administered givosiran 2.5 mg/kg or placebo as an SC injection once a month.

To maintain the blind, the syringes are to be masked prior to study drug withdrawal from the masked vial. At the Month 6 study visit, following the completion of all Month 6 assessments, including the urine sample for ALA and PBG levels (to end the double-blind period), patients will be administered their first open-label (unmasked) dose of givosiran to begin their participation in the open-label extension portion of the study.

6.2.2.2. During the Open-Label Extension Period (After Month 6 through End of Treatment)

Patients who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving 2.5 mg/kg once monthly will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran. After implementation of amendment 3 and until implementation of amendment 5, a dose increase to 2.5 mg/kg once monthly may be permitted starting at Month 13 for patients receiving 1.25 mg/kg once monthly (see Section 6.2.3.4).

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly per guidance in Section 6.2.3.4.

6.2.3. Dose Modifications

During the 6-month double-blind treatment period, no study drug dose modifications will be allowed, except in response to LFT elevations as described in Section 6.2.3.1.

During the open-label extension period, dosing modifications will be allowed under the following circumstances:

- In response to LFT elevations as described in Section 6.2.3.1
- After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group who experience inadequate disease control may be allowed to have their monthly dose increased to 2.5 mg/kg starting at Month 13 (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg) based on discussion and agreement by the Investigator and medical monitor, demonstration of tolerability givosiran, and fulfillment of ALA and clinical activity criteria as described in Section 6.2.3.4.
- Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. See Section 6.2.3.4 for further information on dose escalation.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the medical monitor should be contacted.

6.2.3.1. Monitoring and Dosing Rules Based on Liver Function Test Results

ALT and TBL results should be reviewed within 6 weeks prior to dosing.

For any ALT elevation >3×ULN (or >3×baseline in patients with elevated baseline) or >300 U/L (whichever is lower), results should be confirmed by the central laboratory (within 2 to 3 days, but no greater than 7 days). If such ALT elevations are confirmed, the additional hepatic assessments shown in Table 5 should be obtained.

Subjects with abnormally elevated hepatic laboratory values (eg. ALT, AST, TBL, or INR) or signs/symptoms of hepatitis may meet criteria for withholding study drug. Criteria for withholding, monitoring and stopping study drug dosing are detailed in Table 4:

Table 4: Monitoring and Dosing Rules in Patients with Alanine Transaminase (ALT) Elevations

ALT Transaminase Level	Patients with Normal Baseline ALT	Patients with Elevated Baseline ALT[a]
>3× to 5× ULN or Baseline	• Discontinue dosing when ALT is >3×ULN and patient is symptomatic[b], or has TBL ≥2×ULN or INR >1.5 (for patients not on warfarin), and there is no alternative cause • Otherwise, dosing may continue with monitoring every 2 weeks (±7 days)[c] that includes LFTs per Table 7 and INR • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.	• Discontinue dosing when ALT is >3× baseline or >300 U/L (whichever is lower) and patient is symptomatic[b], or has TBL >2×ULN or INR >1.5 (for patients not on warfarin), and there is no alternative cause • Otherwise, dosing may continue with monitoring every 2 weeks (±7 days)[d] that includes LFTs per Table 7 and INR. • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.
>5× to 8× ULN or Baseline	• Discontinue dosing when ALT >5× to 8× ULN and patient is symptomatic[b], or has TBL ≥2×ULN or INR >1.5 (for patients not on warfarin) and there is no alternative cause • For patients who are asymptomatic and do not have INR >1.5 or TBL ≥2x ULN: – Hold dosing if ALT >5×ULN, until ALT recovers to ≤2×ULN – Dosing can be resumed when ALT recovers to ≤2 x ULN according to Section 6.2.3.1.1, and following discussion with the medical monitor • Perform weekly (±3 days) monitoring of LFTs per Table 7 and INR until ALT declines to	• Discontinue dosing when ALT >5× to 8× baseline or >300 U/L (whichever is lower) and patient is symptomatic[b], or has TBL ≥2×ULN or INR >1.5 (for patients not on warfarin) and there is no alternative cause • For patients who are asymptomatic and do not have INR >1.5 or TBL ≥2x ULN: – Hold dosing if ALT >5×baseline or >300 U/L (whichever is lower), until ALT recovers to ≤2×baseline – Dosing can be resumed when ALT recovers to ≤2 x baseline according to Section 6.2.3.1.1, and following discussion with the medical monitor

ALT Transaminase Level	Patients with Normal Baseline ALT	Patients with Elevated Baseline ALT[a]
	≤3×ULN; then monitor every 2 weeks (±7 days) until ALT level reaches 2×ULN[c] • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.	• Perform weekly (±3 days) monitoring of LFTs per Table 7 and INR until ALT declines to ≤3×baseline; then monitor every 2 weeks (±7 days) until ALT level reaches 2× baseline[d] • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.
>8× ULN or Baseline	Discontinue dosing after confirmation if ALT >8×ULN	Discontinue dosing after confirmation if ALT >8×baseline or >500 U/L (whichever is lower)

Abbreviations: ALT=alanine aminotransferase; INR=international normalized ratio; LFT=liver function test(s); TBL=total bilirubin; U/L=units per liter; ULN=upper limit of normal

Note: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

[a] If multiple baseline ALT measurements are available, baseline ALT will be defined as the average of the 2 most recent ALT measurements prior to the first dose administered.

[b] Symptoms may include nausea, right upper quadrant pain, jaundice, with no known alternative causes identified but possibly associated with (but not limited to) such causes as hepatobiliary tract disease, viral hepatitis, alcoholic hepatitis, or non-alcoholic steatohepatitis (NASH). A clinical picture consistent with drug-induced autoimmune hepatitis, including but not limited to the presence of rash, fever, lymphadenopathy and eosinophilia in addition to elevated transaminases may also be a cause for considering dosing discontinuation.

[c] The frequency of laboratory monitoring should be decreased from every 2 weeks (±7 days) to monthly (±7 days or during scheduled study visits) once ALT has decreased to ≤2× ULN.

[d] The frequency of laboratory monitoring should be decreased from every 2 weeks (±7 days) to monthly (±7 days or during scheduled study visits) once ALT has decreased to ≤2× baseline.

For ALT, TBL, and INR testing, local laboratory results may be used to inform dosing decisions; however, parallel samples should be collected for analysis at the central laboratory.

Table 5: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Hematology	
CBC with differential	
Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2[a]	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
CPK	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: AAT=alpha-1 antitrypsin; anti-LKM=anti-liver-kidney microsomal antibodies; CBC=complete blood count; CPK=creatine phosphokinase; CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA=soluble liver antigen; TSH=thyroid-stimulating hormone
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.
- Additional samples may be collected for assessment of potential alternative causes of liver injury, which may include AAT, ceruloplasmin, acetaminophen/paracetamol levels, anti-LKM antibodies, toxicology screen, ferritin, parvovirus B19, anti-SLA antibodies, gamma-globulins (including IgE and IgG levels), and transferrin saturation, as clinically indicated.

[a] HIV testing will not be performed where prohibited by local regulations.

6.2.3.1.1. Criteria for Rechallenge of Givosiran After Being Withheld for ALT Elevation

For patients in whom givosiran dosing is withheld due to elevated ALT, resumption of dosing may be considered using the following guidelines:

- Patients who did not meet criteria for study drug discontinuation per Table 4 may be considered for rechallenge following consultation with the medical monitor and

resolution of ALT to ≤ 2× ULN or ≤ 2× baseline (for patients who had elevated baseline ALT)

- The decision to rechallenge the patient should be discussed and agreed upon by the patient, Investigator, and medical monitor
- The dose regimen for patients who meet rechallenge criteria, regardless of their dose at the time of the ALT elevation, is a dose of either 1.25 or 2.5 mg/kg monthly per Investigator judgement and after discussion with the medical monitor:
  - LFTs, INR and TBL will be monitored every 2 weeks (±7 days) for the first month, then monthly (±7 days or during the scheduled study visits) as per the Schedule of Assessments
  - Laboratory monitoring and dosing rules in response to LFT elevation will follow Table 4 guidelines
- If dose withholding rules per Table 4 are met on rechallenge with the 1.25-mg/kg dose, permanently discontinue dosing
- If a patient experiences a second dose hold due to LFT elevation while on 2.5 mg/kg monthly:
  - Follow Table 4 guidelines for monitoring and evaluations
  - If ALT resolves to ≤2×ULN, redosing with 1.25 mg/kg monthly may be considered after discussion with the Alnylam medical monitor. If dosing is resumed, follow the guidance above for rechallenge regimen regarding laboratory monitoring and dosing rules. No subsequent re-escalation to 2.5 mg/kg monthly will be allowed.

6.2.3.2. Monitoring and Dosing Rules Based on Lipase and Amylase Results

Lipase and amylase results should be reviewed prior to dosing.

The criteria for withholding, monitoring and stopping study drug dosing based on lipase and amylase results are detailed in Table 6.

Table 6: Monitoring and Dosing Rules in Patients with Lipase or Amylase Elevations

Hold Further Dosing	• If a lipase or amylase elevation >3×ULN (or 3× baseline in patients with elevated baseline value) occurs, with or without clinical symptoms, until confirmation from the central laboratory (within 2 to 3 days, but no greater than 7 days). • If the elevated lipase/amylase is accompanied by clinical symptoms consistent with pancreatitis (eg, epigastric pain, vomiting), dosing should be held until any additional work-up is complete.

Table 6:	Monitoring and Dosing Rules in Patients with Lipase or Amylase Elevations
	• If the elevation of either lipase or amylase is confirmed, an imaging evaluation should be obtained (eg, right upper quadrant ultrasound and/or other testing, based on Investigator judgment). • Monitor lipase/amylase every 2 weeks (±7 days) until the elevated lipase and/or amylase value declines to <3×ULN.
Dosing May Resume	• After consultation with the medical monitor and Investigator if the patient is asymptomatic and imaging studies do not reveal hepatobiliary or pancreatic abnormalities. • If an alternate etiology was identified for the elevations and the condition has resolved. • Monitor lipase/amylase every 2 weeks (±7 days) until the value declines to <3×ULN.
Permanently Discontinue Dosing	• If the patient is diagnosed with acute pancreatitis with no known alternate etiology (eg, acute gallstones) • If the patient experiences persistent lipase and amylase elevations >3×ULN for >2 months without periods of recovery to <3×ULN

Abbreviations: ULN=upper limit of normal

For lipase and amylase testing, local laboratory results may be used to inform dosing decisions; however, parallel samples should be collected for analysis at the central laboratory.

Lipase and amylase testing and imaging evaluations should also be considered at any point in the study if a patient experiences uncharacteristic signs and symptoms during porphyria attacks and there is clinical suspicion of pancreatitis.

6.2.3.3. Monitoring and Dosing Rules in Patients with Potential Cases of Anaphylactic Reaction

An anaphylactic reaction is a severe, potentially fatal, systemic allergic reaction with acute onset (minutes to hours). For reference see Section 11.2 (28).

Stop administering the study medication immediately if an anaphylactic reaction to the study medication is suspected. Study medication must be permanently discontinued in patients for whom an anaphylactic reaction is assessed as related to the study medication.

Laboratory testing: Obtain blood sample for tryptase, total IgE, and ADA antidrug antibodies (ADA) ideally within 15 minutes to 3 hours after the onset of a suspected anaphylactic reaction; however, up to 6 hours is acceptable. An additional blood sample to assess tryptase, total IgE, and ADA should be obtained between 1 to 2 weeks from onset of event. Local laboratory may be used to analyze samples; however, parallel samples should be sent to the central laboratory for analysis. Sample collection and shipping instructions are included in the Laboratory Manual.

Reporting: The PI or designee must notify the sponsor or designee within 24 hours of the occurrence of a suspected case of anaphylactic reaction or being informed of the case as required for AEs of Clinical Interest (AECI) and SAEs, per AE reporting requirements (Section 7.5.6.1 through Section 7.5.6.3).

6.2.3.4. Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period

After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group may be allowed to have their monthly dose increased to 2.5 mg/kg starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed at 1.25 mg/kg), based on discussion and agreement by the Investigator and medical monitor. Dose escalation may be considered if the following criteria are met:

- Tolerability to givosiran at 1.25 mg/kg once monthly has been demonstrated based on no dose interruptions due to LFT elevations at the 1.25 mg/kg once monthly dose level (see Section 6.2.3.1) and no significant safety concerns due to other AEs that would preclude a patient from receiving a higher dose of givosiran as judged by the Investigator and Sponsor.
- Urine ALA levels (mmol/mol Cr) are not stably maintained ≤ULN or are inducible
- Patient has inadequate clinical response (eg, breakthrough attacks or ongoing chronic symptoms), according to Investigator judgement.

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. Dose increases should take effect as of the date that sufficient study drug material can be made available for the patient.

6.2.4. Preparation, Handling, and Storage

Study drug will be stored upright and refrigerated at approximately 2 to 8°C.

Staff at each clinical study center, or the home healthcare professional, will be responsible for preparation of givosiran doses, according to procedures detailed in the Pharmacy Manual. In cases where givosiran is administered at home by a patient/caregiver, dosing may be prepared and administered by the patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage methods, dispensing procedures, and records.

Additional storage and preparation details are provided in the Pharmacy Manual and the Patient/Caregiver Storage and Administration Instructions.

6.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

6.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. All used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability are detailed in the Pharmacy Manual.

6.3. Concomitant Medications

Use of concomitant medications will be recorded on the patient's electronic case report form (eCRF) or electronic diary as indicated in the Schedules of Assessments (Table 1, Table 2, and Table 3). This includes all prescription medications, herbal preparations, over-the-counter (OTC) medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Patients should not start new medication regimens during the study, including regimens of vitamins or herbal medications, without consultation with the Investigator.

Porphyria attacks may be treated according to local standard of care which vary by region but can include, but not limited to, carbohydrate loading, oral or IV glucose, oral or IV analgesics, oral cimetidine, and IV hemin. Use of these medications is permitted at any point in the study (except regularly scheduled hemin for prophylaxis), based on clinical judgment. All treatments received for porphyria attacks including any hemin use will be captured in the concomitant medications eCRF.

Patients with porphyria could have altered hepatic heme synthesis, and treatment with givosiran could also modulate this pathway and secondarily impact CYP enzyme activity. Results from a DDI study in AIP patients who are CHE are presented in Section 1.2.2.3. The DDI study demonstrated that givosiran treatment resulted in weak to moderate reduction in activity of some of the CYP enzymes resulting in corresponding low to moderate increase in the plasma levels of drugs that are metabolized by these CYP enzymes. Based on the moderate decrease in CYP2D6 or CYP1A2 activity, investigators will review all concomitant medications that are primarily metabolized by these enzymes and monitor the patient's clinical response to these medications during the study. Medications metabolized primarily by CYP2D6 and CYP1A2 with a narrow therapeutic index (ie, that require regular laboratory monitoring) may need to be monitored more

frequently to determine if a dose adjustment of the concomitant medication is required. For patients who require new medications while on study, selection of medications that are not primarily metabolized by CYP2D6 or CYP1A2 should be considered. Refer to the individual product's prescription information to determine if there is a need to monitor concomitant medications for differences in safety or efficacy of the medication based on reported DDIs with CYP2D6 or CYP1A2. For more detailed and up-to-date information on CYP substrates, see: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Standard vitamins (including vitamin B6 supplementation, see Section 6.3.4) and topical medications are permitted; however, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

6.3.1. Hemin Prophylaxis

In patients who were on regularly scheduled hemin prophylaxis prior to the study, collection of urine samples for ALA, PBG, and ALAS1 mRNA assessments during Screening must occur ≥4 days after prophylactic hemin discontinuation.

Use of hemin for the treatment of acute or ongoing porphyria attacks is allowed during the study and should be recorded as a concomitant medication in the eCRF. If hemin is used for porphyria attacks, scheduled urine samples for ALA, PBG and ALAS1 mRNA assessments will be collected 4 days (with a window of up to 8 days [+4 days]) after the patient's last hemin dose.

Where applicable country and local regulations and infrastructure allow, Screening and on-study urine samples for ALA, PBG, and ALAS1 mRNA assessments may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit.

6.3.2. Gonadotropin-Releasing Hormone Analogue Treatment

If, at the time of Screening, patients are receiving treatment with a gonadotropin-releasing hormone (GnRH) analogue to prevent attacks, they may enroll in the study if they meet the inclusion criteria for porphyria attacks (Section 5.1) and agree to remain on GnRH treatment throughout the 6-month treatment period. At the discretion of the investigator, GnRH analogues may be discontinued after patients have completed the 6-month treatment period, if clinically indicated.

The initiation of treatment with GnRH analogues during the 6-month treatment period is discouraged.

6.3.3. Analgesic Usage

Analgesic medications, including opioids (synthetic and non-synthetic substances [narcotics]) or non-steroid anti-inflammatory medications (NSAIDs) are permitted for the management of porphyria and for porphyria attacks, based on clinical judgment. All analgesia usage as taken by the patient at home will be captured by the patient or caregiver via the eDiary using daily questions on the type, dose, and frequency of analgesic use through Month 12 of the study. Additional medications, including analgesics, taken at a healthcare facility (eg, during an attack) will be captured in concomitant medications eCRF.

After Month 12, usage of any analgesic medications will be recorded in the concomitant medications eCRF, along with all other medications used.

For patients being treated with regular opioid analgesics between attacks, if the Investigator (or a treating pain specialist) determines that a reduction of the opioid dose is clinically indicated, country specific guidance on opioid tapering should be followed and consultation with a pain specialist should be considered. A decrease of ≤10% per week is consistent with current guidance. Guidance on opioid tapering may be found at: https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf.

If patients use NSAIDs intermittently or chronically, they must be able to tolerate them and have had no previous side effects (eg, gastric distress or bleeding).

6.3.4. Vitamin B6 Supplementation

During treatment with givosiran, blood homocysteine levels may show an increase compared to levels before treatment. Blood homocysteine levels will be assessed as indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3). It is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6. All vitamin supplements should be recorded on the concomitant medications eCRF.

6.4. Contraceptive Requirements

No data are available on the use of givosiran in pregnancy; however, there is no suspicion of human teratogenicity based on class effects or genotoxic potential. Givosiran was neither genotoxic nor clastogenic in in vitro and in vivo studies.

Women of child-bearing potential must be willing to use acceptable methods of contraception from 14 days before the first dose, throughout study participation, including the 6-month double blind treatment period and extension period through the End of Study visit or Safety Follow-up visit, if the patient discontinues the study prior to its completion.

Birth control methods which are considered acceptable include:

- Placement of an intrauterine device
- Bilateral tubal occlusion
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral, implantable, injectable, transdermal hormonal, or intrauterine hormone-releasing system as methods of contraception: Women of child-bearing potential using hormonal methods of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]). See Section 6.3.
- If hormonal methods of contraception are medically contraindicated due to underlying disease, a double-barrier method (combination of male condom with cap, diaphragm, or sponge, in conjunction with spermicide) is also considered an acceptable method of contraception.

- Sexual abstinence, when this is in line with the preferred and usual lifestyle of the patient, is considered an acceptable method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug (defined above). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered sexual abstinence and do not meet criteria for an acceptable method of birth control. As determined by the investigator, the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Abstinent patients must agree to use 1 of the abovementioned contraceptive methods if they start a heterosexual relationship during the study and continue to do so for the entire period of risk associated with the study drug (defined above).
- Women of child-bearing potential include any female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by a follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study.

6.5. Treatment Compliance

Compliance with study drug administration will be monitored by study staff or trained home healthcare professionals.

7. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1 (Screening and 6-Month Treatment Period), Table 2 (Open-label Extension Study: After Month 6 through Month 18), and Table 3 (Open-label Extension Study: Month 19 through EOS).

Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study assessments including targeted physical exam/body system assessment, assessments for vital signs, and collection of blood and urine samples for safety laboratory assessments, and PD assessments, at all timepoints as specified in the Schedule of Assessments.

7.1. Screening Assessments

An informed consent form (ICF), and assent form if applicable, that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF and/or assent form.

Patient demographic and medical history/disease history will be obtained at Screening. Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria (Section 5.1 and Section 5.2, respectively). If required, ALA/PBG levels collected during the screening period for eligibility purposes should be analyzed locally. Medical history collected will incorporate the patient's porphyria history, including their typical attack characteristics, triggers, and treatment, as well as central venous access history, iron overload history, and prior liver disease history.

Any previous participation in a gene therapy study or other porphyria study should be noted in the eCRF.

In patients who were on hemin prophylaxis prior to the study, urinary samples for ALA, PBG, and ALAS1 mRNA must be collected when the patient is not having an attack and at least 4 days after prophylactic hemin discontinuation and after the patient's last hemin dose. Two Screening urine samples for ALA and PBG should be collected on any 2 different days (can be consecutive days) during the Screening period; one Screening urine sample should be collected for ALAS1 mRNA. Where applicable country and local regulations and infrastructure allow, these samples may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit. Patients will be trained on at-home sample collection, storage, and handling.

7.1.1. Retesting

If, in the Investigator's judgment, lab abnormalities are likely to be transient, laboratory tests can be repeated. INR and other laboratory values can be retested during Screening as long as the patient can be evaluated for eligibility and randomized within the allowed Screening period.

7.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued, variability in ALT measurements) will be allowed to return for rescreening.

A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

7.2. Efficacy Assessments

The clinical efficacy of givosiran will be assessed by the frequency and characteristics of porphyria attacks, as described in Sections 3.1 and 3.2.

7.2.1. Porphyria Attack Reporting

Porphyria attacks are defined in Section 3.5. Patients or caregivers will report potential porphyria attacks when they occur throughout the duration of the study (Screening through the EOS visit). If a patient experiences a potential porphyria attack, the patient or designated caregiver should notify the study staff via the eDiary (Section 4.6). Under circumstances in which the eDiary cannot be used to record a potential porphyria attack, patients, caregivers, or treating physicians should notify the study center directly. In some instances, the site may be notified of potential porphyria attacks by healthcare providers not participating in the study. The study center will contact the patient/caregiver or the treating physician to determine if a potential porphyria attack

has occurred; events that are not confirmed as porphyria attacks should be reported as AEs or SAEs, as defined in Section 7.5.6. All relevant clinical information pertaining to the event should be obtained, including laboratory values, medical records, discharge summaries and medical test results.

7.2.2. Pain and Pain-Related Assessments

Patients or caregivers will record analgesic usage and pain-related assessments in the patient's eDiary daily from Screening through Month 12, which includes the 6-month treatment period and first 6 months of the OLE. During the screening period, there should be a minimum of 4 entries completed on days when the patient is not having an attack.

Severity of pain will be captured via eDiary using question #3 (an NRS) from the BPI-SF, wherein the patient is asked to choose the rating that describes the worst level of pain experienced over the past 24 hours.

Analgesic usage as taken by the patients at home will be captured via the eDiary using daily questions on the type, dose, and frequency of analgesic use through Month 12 of the study. Additional medications, including analgesics, taken at a healthcare facility (eg, during an attack) will be captured in concomitant medications eCRF.

After Month 12, usage of any analgesic medications will be recorded in the concomitant medications eCRF, along with all other medications used.

7.2.3. Assessments of Nausea and Fatigue

Patients or caregivers will record the following nausea and fatigue assessments in the patient's eDiary daily from Study Day 1 through Month 12, which includes the 6-month treatment period and first 6 months of the OLE.

Severity of nausea will be captured via eDiary using an 11-point NRS, wherein the patient is asked to choose the rating that describes the worst level of nausea experienced over the past 24 hours.

Severity of fatigue will be captured via eDiary using question #3 (an 11-point NRS) from the Brief Fatigue Inventory-Short Form (BFI-SF), wherein the patient is asked to choose the rating that describes the worst level of fatigue experienced over the past 24 hours.

7.2.4. Quality of Life (QOL)

QOL questionnaires will be used to evaluate overall health status and quality of life. If QOL assessments are obtained during a porphyria attack, it should be documented in the patient's eCRF.

QOL assessments include the following:

- SF-12: a 12-question measure capturing global QOL and overall health status over the past 4 weeks that takes approximately 5 minutes to complete.(26)
- EQ-5D-5L: a 2-page scale that includes questions that capture health on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analog scale (VAS) capturing the patient's self-rated health (27). The EQ-5D-5L takes approximately 5 minutes to complete.

- PGIC: The Patient Global Impression of Change (PGIC) is one question answered according to a 7-point scale (ranging from very much improved to very much worse) for the assessment of a patient's perceived overall health status change since the beginning of the study. This questionnaire takes approximately 2 to 3 minutes to complete.
- PPEQ: The Porphyria Patient Experience Questionnaire (PPEQ) is a set of questions to assess treatment experience and impacts to the patient's life not collected by the other QOL assessments. This questionnaire takes approximately 5 minutes to complete.

Additionally, days of missed work or school due to porphyria symptoms/attacks will be assessed.

7.3. Pharmacodynamic Assessments

Urine samples will be collected for assessment of givosiran PD parameters prior to dosing. The PD effect of givosiran will be evaluated by spot urine ALA and PBG levels normalized to spot urine creatinine levels. Urine samples will be collected for assessment of circulating ALAS1 mRNA levels. Analysis of urine ALAS1 mRNA levels will be performed at Alnylam; all other urine PD analyses will take place at a central laboratory. Since Investigators are blinded to treatment assignments, they will also be blinded to ALA and PBG results analyzed at the central laboratory. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining local ALA or PBG measurements until at least 12 weeks after the month 6 visit (to avoid potential unblinding). If ALA or PBG is measured during this period, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Urine ALA analyses may be conducted at a local laboratory or ALA results from previous visits may be evaluated in patients on the 1.25 mg/kg monthly dose in whom dose escalation to 2.5 mg/kg once monthly is being considered due to inadequate clinical response and who have demonstrated tolerability to givosiran. Dose escalation in patients on the 1.25 mg/kg once monthly dose can occur starting at Month 13. See Section 6.2.3.4 for further information on dose escalation.

Details regarding the processing and aliquoting of samples for storage and analyses will be provided in the Laboratory Manual.

7.4. Pharmacokinetic Assessments

Blood and urine samples will be collected from all patients for assessment of the PK of givosiran and its major metabolite, 3'(N-1) givosiran, at the time points in Appendix Section 11, Table 8, Table 9, and Table 10.

At selected study visits, as noted in Table 8 and Table 9, a predose sample and a 2 hour postdose sample (±15 minutes) will be collected in all patients; these assessments will be paired with triplicate ECG measurements.

In addition, 24-hour (±2 hours) postdose PK samples will be collected in a subset of approximately 24 patients at preselected study centers (including all patients from East Asian study centers) (Table 8 and Table 9). Population PK analysis will be performed on the sparse PK samples from all patients.

Blood must be aliquoted and processed as plasma for PK analysis.

The concentration of givosiran will be determined using a validated assay. Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

7.4.1. Pharmacokinetic Assessments in Patients at East Asian Study Centers

A full 24-hour (±2 hours) PK evaluation will be performed following the first dose (Study Day 1) and Month 6 dose from all patients at East Asian study centers (Japan, Taiwan, or South Korea) at the time points specified in Table 9 (Appendix Section 11). Plasma PK parameters such as C_{max}, t_{max}, $t_{½\beta}$, AUC, CL/F, and V/F will be assessed for givosiran and its major metabolite, 3'(N-1) givosiran.

A PK analysis will also be performed from pooled urine samples collected over 24 hours from patients at East Asian study centers according to the schedule provided in Table 10 (Appendix Section 11).

7.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs) (Section 7.5.6), recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests.

Since porphyria attacks (as defined in Section 3.5) are recorded as an efficacy assessment of givosiran, these will not be treated as AEs or SAEs. However, if a patient experiences a non-porphyria AE during a porphyria attack, it should be reported.

Safety will be monitored over the course of the study by a DMC, as described in Section 4.7.

7.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1, Table 2, and Table 3) and will include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position (should be consistent throughout the study for each patient), after the patient has rested comfortably for 10 minutes.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital sign assessments may be added at the discretion of the Investigator.

7.5.2. Weight and Height

Height, body weight, and BMI measurements will be collected as specified in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Height will be measured in centimeters and body weight will be measured in kilograms. Body mass index will be calculated in the database.

Body weight obtained within 6 months during a clinical study center visit or offsite may be used for dosing calculations.

7.5.3. Physical Examination

Complete and targeted physical examinations will be conducted as specified in the Schedule of Assessments (Table 1, Table 2, and Table 3); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

Complete physical examinations will include the examination of the following: general appearance, head, eyes, ears, nose and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric.

Targeted physical examinations will include the examination of the following: general appearance, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, and neurological/psychiatric.

7.5.4. Electrocardiogram

A single standard 12-lead ECG will be recorded at Screening; all other ECGs will be performed in triplicate, using centralized ECG service equipment, with readings approximately 1 minute apart. Triplicate ECGs will be performed predose and at 2 hours postdose in all patients on Study Day 1 and at the Month 5, Month 6, and Month 12 visits (Table 8 and Table 9); these assessments will be paired with PK measurements.

In a subset of approximately 24 patients from prespecified study centers (including all patients at East Asian study centers), ECGs at 24-hours (±2 hours) postdose should be performed in triplicate (along with a 24-hour PK assessment) on Study Day 1 and at the Month 6 Visit (Table 8 and Table 9).

Patients should be supine for at least 5 minutes before each ECG is obtained. The electrophysiological parameters assessed will be rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, Bazett-corrected QT interval (QTcB), and Fridericia corrected QT interval (QTcF).

When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECGs should be performed before blood samples are drawn.

Single standard 12-ECGs can be performed on local ECG machines. For all triplicate ECGs, the ECGs must be acquired using centralized ECG service equipment and results should be interpreted at a central laboratory. The Investigator or qualified designee will review all ECGs to assess whether the results have changed since baseline and to determine the clinical significance of the results. Additional ECGs may be collected at the discretion of the Investigator. Recordings will be archived according to the Study Manual.

7.5.5. Clinical Laboratory Assessments

Clinical laboratory assessments are listed in Table 7 and will be evaluated at a central laboratory at time points specified in the Schedule of Assessments (Table 1, Table 2, and Table 3). If a

clinical laboratory assessment is scheduled for a dosing visit, the blood sample for the assessment should be collected prior to dosing.

ALT and TBL collected within 6 weeks prior to dosing must be reviewed by the Investigator before study drug administration. In the event that givosiran is administered offsite by patient or caregiver, safety laboratory assessments other than ALT and TBL must be obtained from a central or local laboratory within 3 months prior to dosing. Locally analyzed results may be reviewed to inform dosing decisions, but additional samples for central analysis must also be collected on the day of dosing prior to the dose administration.

Ferritin will be assessed at the central laboratory on Study Day 1 and at 6-month intervals, thereafter.

D-dimer assessments will be performed at the Screening, Day 1, Month 3, Month 6, Month 9, and Month 12 visits only; as a clinical research parameter only, d-dimer results will not be communicated to the study centers.

Specific dosing and monitoring instructions are provided for elevations in ALT transaminases (Section 6.2.3.1) and elevations in lipase and/or amylase (Section 6.2.3.2). For any other unexplained clinically relevant, abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality.

Additional safety laboratory assessments, imaging, and consultation may be performed, as indicated by the clinical situation, for evaluation and/or in consultation with the medical monitor; results may be collected and should be included in the clinical database.

Table 7: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Lipase	Ferritin
Amylase	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time (PT)	D-dimer[a]
Partial Thromboplastin Time (PTT)	International Normalized Ratio (INR)
Pregnancy Testing (Females of child-bearing potential only)	
β-human chorionic gonadotropin	

Abbreviations: AST=aspartate transaminase; ALP=alkaline phosphatase; ALT=alanine transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; GGT=gamma-glutamyltransferase; INR=international normalized ratio; PT=prothrombin time; RBC=red blood cells.

[a] D-dimer assessments will be performed at the Screening, Day 1, Month 3, Month 6, Month 9, and Month 12 visits only; as a clinical research parameter only, d-dimer results will not be communicated to the study centers.

7.5.5.1. Immunogenicity

Blood samples will be collected to evaluate the incidence and titer of antidrug antibodies (ADA) to givosiran. Blood samples for ADA testing must be collected before study drug administration at time points specified in the Schedule of Assessments (Table 1, Table 2, and Table 3); for further details, see Table 8 and Table 9.

Sample collection for patients who experience a potential anaphylactic reaction is discussed in Section 6.2.3.3.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

7.5.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential only. A serum pregnancy test will be performed at Screening and serum or urine pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1, Table 2, and Table 3) and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation.

Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 7.5.6.6 for follow-up instructions).

7.5.6. Adverse Events

7.5.6.1. Definitions

Adverse Event

According to the International Conference on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Since porphyria attacks (as defined in Section 3.5) are recorded as an efficacy assessment of givosiran, these will not be treated as AEs or SAEs. However, if a patient experiences a non-porphyria AE during a porphyria attack, it should be reported.

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Porphyria attacks (as defined in Section 3.5) will be recorded for efficacy assessment of givosiran and *will not* be treated as SAEs. However, if a patient experiences a non-porphyria-attack SAE (or SAEs) during a porphyria attack that meets SAE criteria, this non-porphyria-attack SAE(s) should be reported.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study treatment should be evaluated by the Investigator using the following criteria:

Definitely related:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Possibly related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.
Unlikely related:	A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
Not related:	A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.

Adverse Events of Clinical Interest

The following events are considered to be AEs of clinical interest:

- ALT elevations >3×ULN (or >3× the baseline ALT measurement if baseline is >ULN
- Lipase or amylase >3×ULN (or >3× the baseline lipase or amylase measurement if baseline is >ULN)
- Severe or serious ISRs, ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections) or, ISRs that lead to temporary dose interruption or permanent discontinuation of study drug
- Anaphylactic Reactions. Anaphylactic reaction is a severe, potentially fatal, systemic allergic reaction with acute onset (minutes to hours). Symptoms of an anaphylactic reaction may include skin or mucosal tissue (e.g. generalized hives, pruritus, angioedema), respiratory compromise (e.g. wheezing, bronchospasm, hypoxia), reduced blood pressure or associated symptoms (e.g. syncope, hypotonia). See Section 11.2 for guidance on diagnosing anaphylactic reactions (28).

7.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in his/her health since the last visit. The patient should also be asked if he/she has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and OTC). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether they are considered drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to investigational drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, the event(s) must be recorded in the eCRF. If the electronic data capture (EDC) is unavailable, a back-up SAE form should be completed.

For AEs that are considered AEs of clinical interest, the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of clinical interest (AECI) eCRF. Additional clinical and laboratory information may be collected based upon the severity or nature of the event; see Section 6.2.3 regarding monitoring for liver or pancreas abnormalities.

Refer to CRF completion guidelines for details on reporting events in the supplemental AECI eCRF.

Recording an ISR

For each ISR that meets AECI criteria (Section 7.5.6.1), the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, and event outcome). An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A reaction with onset and resolution within 4 hours of the injection (eg, transient pain/burning at injection site) does not meet the study definition of an ISR unless immediate treatment is required. A systemic reaction which includes the injection site, eg, generalized urticaria or other distinct entities or conditions like lymphadenopathy that may be near the injection site, is not considered an ISR.

7.5.6.3. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 7.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/study center information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should

be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

7.5.6.4. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

7.5.6.5. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

7.5.6.6. Pregnancy Reporting

If a female patient becomes pregnant during this study through 3 months following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 7.5.6.3.

7.5.6.7. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. It is up to the Investigator to decide whether a dose is to be considered an overdose, in consultation with the Sponsor. Overdose must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

7.6. Exploratory Assessments

7.6.1. Exploratory Biomarkers

Where allowed per local regulations and IRB/EC approval and patient consent (and assent, where applicable), serum, plasma, and urine samples will be collected and may be archived and used for analyses of exploratory biomarkers related to metabolic profiling or the effects of givosiran or

other proteins related to AHPs and their complications. Samples may also be used for testing homocysteine levels.

Where local regulations allow, these biologic samples for biomarker research can be retained on behalf of the Sponsor for a maximum of 15 years following the last patient's last visit in the study.

Details regarding the collection, processing, storage, and shipping of samples can be found in the Laboratory Manual.

7.6.2. DNA Samples

A blood or saliva sample for DNA will be collected at Screening for genetic testing of porphyria-related genes only in patients without prior documented genetic testing for porphyria.

In addition, where local regulations permit and subject to discretionary approval from each center's IRB/IEC as well as patient consent (and assent, where applicable), a voluntary blood sample may be collected as part of a later DNA analysis, which could include a determination of the spectrum of porphyria mutations in patients with AHPs and the relationship between porphyria mutations and the safety and efficacy of givosiran.

The Sponsor will analyze DNA sequences within genes relevant to the mode of action and response to givosiran. No additional testing will be performed on the samples collected in the study.

Details regarding the collection, processing, storage, and shipping of the samples can be found in the Laboratory Manual. The sample collected as part of a later analysis will be securely stored in a central biorepository for up to 15 years following the completion of this clinical study (ie, last patient, last visit), or as local regulations allow. After 15 years have elapsed, the samples will be destroyed.

7.7. COVID-19 Data Collection

Information on the coronavirus disease 2019 (COVID-19) infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

8. STATISTICS

A detailed Statistical Analysis Plan (SAP) will be finalized before any interim analysis or database lock, whichever occurs earlier. The plan will detail the implementation of statistical analyses in accordance with the principal features described in the protocol.

8.1. Determination of Sample Size

The planned total enrollment for the study is approximately 74 patients, including approximately 70 AIP patients.

In this study, 70 patients will have at least 90% power to detect a 45% reduction in the annualized attack rate at a 2-sided 5% significance level assuming a mean annualized attack rate of 8, a standard deviation (SD) of 5 in the control arm, and a mean annualized attack rate of 4.4 with SD

of 3 in the givosiran arm, using a negative binomial model. This study design will still have at least 80% power even if the dropout rate is as high as 15% under the same assumptions.

8.2. Statistical Methodology

8.2.1. Populations to be Analyzed

The population analysis sets for the 6-month treatment phase are defined as follows:

- Full Analysis Set (FAS): All randomized patients (AHP) who received at least one dose of study drug. Patients will be grouped by their randomly assigned treatment group (i.e. as randomized).
- Full Analysis Set in AIP patients (FAS_{AIP}): All randomized AIP patients (with mutation in the *HMBS* gene) who received at least one dose of study drug. Patients will be grouped by their randomly assigned treatment group (i.e. as randomized).
- Safety Analysis Set: All patients who received at least one dose of study drug, grouped according to the treatment actually received. Patients who received any amount of givosiran will be included in the givosiran arm.
- PK Analysis Set: All patients who received any amount of study drug and have at least one postdose blood sample for PK parameters and who have evaluable PK data.
- PD Analysis Set: All patients who received any amount of study drug and who have at least one postdose urine sample for the determination of ALA or PBG will be included in the PD analyses.

The primary population used to evaluate efficacy will be the FAS_{AIP} for the primary endpoint and secondary endpoints in AIP patients, and FAS for the secondary endpoint of annualized attack rate in AHP patients. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

8.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

8.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

8.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the FAS and Safety Analysis Set.

8.2.5. Efficacy Analyses

The analysis of the primary endpoint and the secondary endpoints that pertain to the AIP population will be based on the FAS_{AIP}. The analysis of the secondary endpoints that pertain to the AHP population will be based on the FAS.

The overall Type I error rate will be strongly controlled at a 2-sided 0.05 significance level for the primary and secondary endpoints using an alpha spending function for the interim analysis and a fixed sequential testing procedure at the final analysis. The primary endpoint will be compared between treatment arms at the final analysis significance level. If the primary analysis of the primary endpoint is statistically significant, then the secondary endpoints will each be tested in the order specified in the Secondary Endpoints section (Section 3.2).

If a test of the primary or a secondary endpoint is not statistically significant at the final analysis significance, the testing of remaining endpoints in the sequence will stop.

8.2.5.1. Primary Endpoint

The primary endpoint of the study is a composite of the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with AIP over the 6-month double-blind treatment period (Section 3.5). The annualized attack rate (AAR) will be calculated as the total number of porphyria attacks treated at urgent healthcare visit or with IV hemin at home, divided by the total number of days in the treatment period, multiplied by the number of days in a year,

$$\frac{\text{total number of qualifying porphyria attacks}}{\text{total number of days in the treatment period}} \times 365.25$$

The primary analysis is a test in which the null hypothesis is that the ratio of the mean annualized attack rate for the givosiran arm, relative to the mean annualized attack rate for the placebo arm, is equal to 1.0 and the alternative hypothesis is that the ratio is not equal to 1.0. The mean annualized attack rate for the placebo and active arms will be compared using a negative binomial regression model that will include fixed effects for the treatment arm and stratification factors (status of hemin prophylaxis use prior to study entry and historical attack rate).

The number of days patients spend in the 6-month double-blind treatment period will be included in the model as an offset variable. With the offset variable, the negative binomial regression model essentially models the annualized attack rate for each patient based on the length of time the patient is in the treatment period, and hence, will be able to account for the differing length of follow-up for patients in the treatment period.

Patients who discontinue the study treatment early (before the end of the 6-month treatment period) will still be followed for collection of attack data through the end of the 6-month treatment period and their data will be used in the primary analysis. For patients who discontinue study treatment and subsequently receive hemin prophylaxis, the primary analysis will include attack data collected up to the start of hemin prophylaxis.

In addition to the primary analysis p-value, an estimated ratio of mean annualized attack rates between treatment arms with its corresponding 95% confidence interval will be estimated from the negative binomial regression model. Descriptive statistics for the median and interquartile range of the annualized attack rate will also be presented for each treatment arm.

Sensitivity analyses will be detailed in the SAP.

8.2.5.2. Secondary Endpoints

Secondary endpoints are described in Section 3.2.

The analysis of the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in all AHP patients (the FAS) over the 6-month double-blind period and the annualized rate of hemin doses will be conducted using the same approach as the primary analysis.

For the analysis of urinary ALA-related endpoints, the ALA levels will be compared between treatment arms using a mixed-effects model repeated measures (MMRM) with baseline ALA as a continuous covariate and fixed effect terms including treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), visit and treatment by visit interaction. PBG-related endpoints will also be analyzed using this methodology.

Daily pain, nausea, and fatigue scores will be analyzed separately using the area under the curve (AUC) approach: the AUC over 6 months in the respective score will be calculated for each patient, and the mean AUC will be compared between treatment arms in an ANCOVA model. The change from baseline in PCS of SF-12 at 6 months will be analyzed use an MMRM model. Details will be described in the SAP.

8.2.5.3. Exploratory Endpoints

Descriptive statistics will be provided for the exploratory endpoints (Section 3.3). Details will be described in the SAP.

8.2.6. Pharmacodynamic Analysis

Analyses of ALA and PBG are described in Section 8.2.5.2. In addition, ALA and PBG levels will be summarized descriptively at each scheduled visit.

8.2.7. Pharmacokinetic Analysis

Population pharmacokinetic analysis will be performed to describe the plasma pharmacokinetics of givosiran and its major metabolite, 3'(N-1) givosiran. The impact of relevant covariates, such as, eg, demographics, renal function) on plasma PK will be evaluated.

In patients from East Asian centers with 24-hour PK collection, pharmacokinetic analyses of plasma and urine will be conducted using noncompartmental methods. Plasma pharmacokinetic parameters include but will not be limited to: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F). Other parameters may be calculated, if deemed necessary.

8.2.8. Safety Analyses

The primary safety parameter is the incidence of adverse events (AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized. The primary summaries of the safety of givosiran versus placebo will be based on safety parameters within the 6-month double-blind treatment period, using the Safety Analysis Set. Additional safety analyses will also be performed for the OLE period.

Adverse events will be classified according to the MedDRA System Organ Class and Preferred Term. AEs will be collected starting at the time the first dose of study drug is administered (Study

Day 1) through the duration of the study; SAEs will be collected starting at the time that informed consent is signed and through the duration of the study.

The number and percentage of patients experiencing AEs after the first dose of the study drug will be summarized for the following AE categories; additional categories may be specified in the SAP.

- Any AE
- Any AE that is assessed as related to study drug by the Investigator
- Any serious adverse event (SAE)
- Any AE leading to discontinuation of study drug
- Any AE leading to death

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation. Incidence of adverse events of clinical interest will also be summarized by treatment group, and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last predose observation on or before Day 1. Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing.

Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Details of any abnormalities will be included in patient listings.

Antidrug antibody results, including incidence and titer will be tabulated. A by-patient data listing will also be provided.

8.2.9. Other Analyses

The long-term efficacy and safety data of givosiran over the OLE period will be summarized descriptively. Patients who were randomized to placebo and received givosiran at a starting dose of 1.25 mg/kg once monthly during the OLE period (per amendment version 3) will be assessed to characterize the efficacy and safety for the lower dose 1.25 mg/kg once monthly.

Analyses for other exploratory endpoints such as exploratory biomarkers will be detailed in the SAP.

Additional data summaries to help understand any impact of the COVID-19 pandemic on efficacy and safety assessments will be performed, as appropriate.

8.2.10. Interim Analysis

An unblinded interim analysis will be conducted when approximately 30 AIP patients have completed at least 3 months of the treatment period. The endpoint for this interim analysis is the ALA level at 3 months. The ALA level at 3 months will be compared between treatment arms using an ANCOVA model with fixed effect of treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), and with baseline ALA as a

covariate. An alpha-spending function will be used to adjust the significance level to ensure the overall type I error rate is not inflated; the error spending function will be specified in the statistical analysis plan. The significance level for the comparison at the interim is 0.001 (2-sided). To assess durability of the study drug in lowering and maintaining ALA level over time, the overall treatment effect from Month 1 through Month 3 will be evaluated through a mixed effect model repeated measurement (MMRM).

Stopping for efficacy or futility is not planned in this study. To ensure that the study is adequately powered for the primary endpoint comparison at the final analysis, attack rates may also be evaluated in a blinded manner for sample size reassessment at the time of the interim analysis.

The interim analysis will be described in detail in the SAP.

9. STUDY ADMINISTRATION

9.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

9.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/Legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided. In the case of patients under the age of legal consent, legal guardian(s) must provide informed consent and the patient should provide assent per local regulations and institutional standards.

The patient's/legal guardian's signed and dated informed consent (and assent, if applicable) must be obtained before conducting any study procedures.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

The Investigator must maintain the original, signed Informed Consent Form (and assent, if applicable). A copy of the signed Informed Consent Form (and assent, if applicable) must be given to the patient/legal guardian.

9.1.2. Ethical Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent form (and assent form, if applicable) and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 7.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol.

9.1.3. Serious Breach of Protocol

Investigators must notify the medical monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

9.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for the period required by applicable local law. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the CRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number and initials. If patient names are included on copies of documents submitted to the Sponsor or designees, the names (except for initials) will be obliterated and the assigned patient number added to the document. Documents not for

submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

In compliance with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

9.1.5. End of Study

The End of Study is defined as last patient, last visit.

9.1.6. Discontinuation of the Clinical Study

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time. If the study center does not recruit at a reasonable rate, the study may be discontinued at that site. Should the study be terminated, and/or the study center closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IEC/IRB and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Patients should then be withdrawn from the study.

9.2. Data Quality Control and Quality Assurance

9.2.1. Data Handling

Study data must be recorded on case report forms (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained study center personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

9.2.2. Study Monitoring

The clinical monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the study center. The monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct study center visits to the investigation facilities for monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug

accountability records, patient charts and study source documents, and other records relative to study conduct.

9.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative centers as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the study center to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor, or its designee, immediately if contacted by a regulatory agency about an inspection.

9.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator can be submitted for publication after this primary manuscript is published or following the period of 18 months after completion of the study at all centers. A copy of any proposed manuscript must be provided and confirmed received at the Sponsor at least 30 days before its submission, and according to any additional publication details in the study center's Clinical Trial Agreement.

10. LIST OF REFERENCES

1. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-50.

2. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010;375(9718):924-37.

3. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014;127(12):1233-41.

4. James MF, Hift RJ. Porphyrias. Br J Anaesth. 2000;85(1):143-53.

5. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood. 2012;120(23):4496-504.

6. APF-Webcast. Patient Focused Drug Development (PFDD) meeting for the Acute Porphyrias. In: Foundation AP, editor. USA2017. p. 3:33:59.

7. Kadish K, Smith K, Guilard R. The Porphyrin Handbook. Kadish K, Smith K, Guilard R, editors2003.

8. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. Appl Clin Genet. 2015;8(8):201-14.

9. Jeans JB, Savik K, Gross CR, Weimer MK, Bossenmaier IC, Pierach CA, et al. Mortality in patients with acute intermittent porphyria requiring hospitalization: A United States case series. American Journal of Medical Genetics. 1996;65(4):269-73.

10. Gouya L, Bloomer JR, Balwani M, Bissell DM, Rees D, Stolzel U, et al., editors. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyrias (AHP) with Recurrent Attacks. International Congress on Porphyrins and Porphyrias; 2017; Bordeaux: ICPP.

11. Andersson C, Innala E, Backstrom T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. J Intern Med. 2003;254(2):176-83.

12. Chemmanur AT, Bonkovsky HL. Hepatic porphyrias: diagnosis and management. Clin Liver Dis. 2004;8(4):807-38, viii.

13. Stein P, Badminton M, Barth J, Rees D, Stewart MF, British, et al. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. Ann Clin Biochem. 2013;50(Pt 3):217-23.

14. Soonawalla ZF, Orug T, Badminton MN, Elder GH, Rhodes JM, Bramhall SR, et al. Liver transplantation as a cure for acute intermittent porphyria. The Lancet. 2004;363(9410):705-6.

15. Anderson KE. A gonadotropin releasing hormone analogue prevents cyclical attacks of porphyria. Arch Intern Med. 1990;**150**(7).

16. Herrick AL, McColl KE, Moore MR, Cook A, Goldberg A. Controlled trial of haem arginate in acute hepatic porphyria. Lancet. 1989;1(8650):1295-7.

17. Hift RJ, Meissner PN. An Analysis of 112 Acute Porphyric Attacks in Cape Town, South Africa. Medicine. 2005;84(1):48-60.

18. Dowman JK, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, Newsome PN. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. Liver Transplantation. 2012;18(2):195-200.

19. Yasuda M, Erwin AL, Liu LU, Balwani M, Chen B, Kadirvel S, et al. Liver Transplantation for Acute Intermittent Porphyria: Biochemical and Pathologic Studies of the Explanted Liver. Mol Med. 2015;21:487-95.

20. Ryu JY, Song IS, Sunwoo YE, Shon JH, Liu KH, Cha IJ, et al. Development of the "Inje cocktail" for high-throughput evaluation of five human cytochrome P450 isoforms in vivo. Clin Pharmacol Ther. 2007;82(5):531-40.

21. Williams D, Tao X, Zhu L, Stonier M, Lutz JD, Masson E, et al. Use of a cocktail probe to assess potential drug interactions with cytochrome P450 after administration of belatacept, a costimulatory immunomodulator. Br J Clin Pharmacol. 2017;83(2):370-80.

22. Marsden JT, Guppy S, Stein P, Cox TM, Badminton M, Gardiner T, et al. Audit of the Use of Regular Haem Arginate Infusions in Patients with Acute Porphyria to Prevent Recurrent Symptoms. JIMD Rep. 2015;22:57-65.

23. Ventura P, Corradini E, Di Pierro E, Marchini S, Marcacci M, Cuoghi C, et al. Hyperhomocysteinemia in patients with acute porphyrias: A potentially dangerous metabolic crossroad? Eur J Intern Med. 2020;79:101-7.

24. To-Figueras J, Lopez RM, Deulofeu R, Herrero C. Preliminary report: hyperhomocysteinemia in patients with acute intermittent porphyria. Metabolism. 2010;59(12):1809-10.

25. Maron BA, Loscalzo J. The treatment of hyperhomocysteinemia. Annu Rev Med. 2009;60:39-54.

26. QualityMetric. User's Manual for the SF-12v2 Health Survey. Third ed. Lincoln, RI2012.

27. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

28. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373-80.

11. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENT TIME POINTS

Table 8 contains a detailed schedule for the collection of ECG and blood samples for PK and ADA analysis. Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

Table 8: Pharmacokinetic, ECG, and ADA Time Points for All Patients (Except Patients at East Asian Sites)

Study Period	Study Month/ Study Day	Protocol Time (hh:mm)	PK	Triplicate ECG	Single 12-Lead ECG[1]	ADA
6-Month Treatment Period	Month 0 (Day 1)	Predose	X	X		X
		02:00 (±15 min)	X	X		
		24:00 (±2 hours)	X[2]	X[2]		
	Month 1 (Day 29±7 days)	Predose	X			X
	Month 3 (Day 85±7 days)	Predose	X			X
	Month 5 (Day 141±7 days)	Predose	X	X		
		02:00 (±15 min)	X	X		
	Month 6 (Day 169±7 days)	Predose	X	X		X
		02:00 (±15 min)	X	X		
		04:00 (±15 min)[3]	X			
		24:00 (±2 hours)	X[2]	X[2]		
Open-Label Extension Period	Month 7 (Day 197±7 days)	Predose	X			X
		Predose	X	X		X

Study Period	Study Month/ Study Day	Protocol Time (hh:mm)	PK	Triplicate ECG	Single 12-Lead ECG[1]	ADA
	Month 12 (Day 337±7 days)	02:00 (±15 min)	X	X		
		04:00 (±15 min)3	X			
	Month 18 (Day 505±7 days)	Predose	X			X
	Month 24 (Day 673±14 days)[4]	Predose	X			X
	Month 36 (Day 1009±14 days)/EOS[4]	Any time				X

Abbreviations: ADA=anti-drug antibodies; ECG=electrocardiogram; EOS=end of study; hh=hours; mm=minutes

[1] Single 12-lead ECGs should also be performed at Screening. For further details, see Section 7.5.4. With the implementation of Amendment 6, single 12-lead ECGs are no longer required at the Month 24 and 36 visits.

[2] In a prespecified subset of approximately 24 patients at prespecified study centers (including all patients at East Asian study centers), an additional 24-hour (±2 hours) PK and triplicate ECG sample (see Section 7.5.4) will be collected on Day 1 and Month 6.

[3] For patients receiving 1.25 mg/kg givosiran monthly (patients who received their first dose in the open-label extension period under protocol amendment version 3), additional blood samples for PK will be collected 4 hours post-dose at the Month 6 and Month 12 visits.

[4] Pharmacokinetic and ADA assessments that cannot be collected in the intended visit window may be completed within 6 months at the next study center visit.

Table 9 provides a schedule for the collection of ECG and blood samples for PK and ADA analysis in all patients at East Asian study centers (in Japan, Taiwan, and South Korea). Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

Table 9: Pharmacokinetic, ECG, and Anti-Drug Antibody Assessment Time Points for Patients at East Asian Study Centers (Blood Samples)

Study Period	Study Month (Study Day)	Sampling Time (hh:mm)	PK	Triplicate ECG	Single 12-Lead ECG[1]	ADA
6-Month Treatment Period	Month 0 (Day 1)	Predose	X	X		X
		00:15 (±5 min)	X			
		00:30 (±5 min)	X			
		01:00 (±10 min)	X			
		02:00 (±15 min)	X	X		
		04:00 (±15 min)	X			
		06:00 (±15 min)	X			
		08:00 (±15 min)	X			
		24:00 (±2 hours)	X	X		
	Month 1 (Day 29±7 days)	Predose	X			X
	Month 3 (Day 85±7 days)	Predose	X			X
	Month 5 (Day 141±7 days)	Predose	X	X		
		02:00 (±15 min)	X	X		
	Month 6 (Day 169±7 days)	Predose	X	X		X
		00:15 (±5 min)	X			
		00:30 (±5 min)	X			

Study Period	Study Month (Study Day)	Sampling Time (hh:mm)	PK	Triplicate ECG	Single 12-Lead ECG[1]	ADA
		01:00 (±10 min)	X			
		02:00 (±15 min)	X	X		
		04:00 (±15 min)	X			
		06:00 (±15 min)	X			
		08:00 (±15 min)	X			
		24:00 (±2 hours)	X	X		
Open-Label Extension Period	Month 7 (Day 197±7 days)	Predose	X			X
	Month 12 (Day 337±7 days)	Predose	X	X		X
		02:00 (±15 min)	X	X		
	Month 18 (Day 505±7 days)	Predose	X			X
	Month 24 (Day 673±14 days)[2]	Predose	X			X
	Month 36 (Day 1009±14 days)/ EOS[2]	Any time				X

Abbreviations: ADA=anti-drug antibodies; ECG=electrocardiogram; EOS=end of study; hh=hours; mm=minutes
[1] Single 12-lead ECGs should also be performed at Screening. For further details, see Section 7.5.4. With the implementation of Amendment 6, single 12-lead ECGs are no longer required at the Month 24 and 36 visits.
[2] Pharmacokinetic and ADA assessments that cannot be collected in the intended visit window may be completed within 6 months at the next study center visit.

Table 10 provides a schedule for the collection of spot (predose) and pooled urine samples for analysis of PK, PD, and ADA in patients at East Asian study centers. Volume must be recorded.

Table 10: Urine Pharmacokinetic/Pharmacodynamic Time points for Patients at East Asian Study Centers

Study Period	Study Month (Study Day)	Sampling Time (hh:mm)	PK	ALA and PBG
6-Month Treatment Period	Month 0 (Day 1)	Predose	X	X[b]
		0-6 hours (±30 min)[a]	X	X[b]
		6-12 hours (±30 min)[a]	X	X[b]
		12-24 hours (±2 hours)[a]	X	
	Month 0 (Day 15±2 days)	Any time		X[c]
	Month 1 (Day 29±7 days)	Predose		X[c]
	Month 2 (Day 57±7 days)	Predose		X[c]
	Month 3 (Day 85±7 days)	Predose		X[c]
	Month 4 (Day 113±7 days)	Predose		X[c]
	Month 5 (Day 141±7 days)	Predose		X[c]
	Month 6 (Day 169±7 days)	Predose	X	X[b]
		0-6 hours (±30 min)[a]	X	X[b]
		6-12 hours (±30 min)[a]	X	X[b]
		12-24 hours (±2 hours)[a]	X	

Study Period	Study Month (Study Day)	Sampling Time (hh:mm)	PK	ALA and PBG

Abbreviations: ALA=aminolevulinic acid; hh=hours; mm=minutes; PBG=porphobilinogen; PK=pharmacokinetics

[a] On Day 1 and Month 6, all postdose urine samples collected within a collection interval will be pooled

[b] At time points where PK sampling is performed, urine samples for ALA and PBG measurement will be aliquoted from individual timepoint (non-pooled) urine samples obtained for PK assessments

[c] Spot urine samples for ALA, PBG, and ALAS1 mRNA measurement during the study should be collected predose; however, if hemin is used for an attack, scheduled urinary ALA, PBG and ALAS1 mRNA will be collected 4 days (+4 days) after the patient's last hemin dose. Where applicable country and local regulations and infrastructure allow, urine samples for ALA, PBG, and ALAS1 mRNA assessments may be collected by a home healthcare professional, sent to the study center by mail, or brought to the study center at the next visit.

11.1. Biochemical Diagnosis of AHP in the Absence of Identified Mutation in a Porphyria-related Gene

Table 11: Biochemical Criteria in Addition to ALA and PBG for Diagnosis of AHP in the Absence of an Identified Mutation in a Porphyria-related Gene

	AIP without identified gene mutation	HCP without identified gene mutation	VP without identified gene mutation	ADP without identified gene mutation
Plasma Porphyrins	• <4.5 µg/dL, or <5-fold increase (relative to ULN of 0.9 µg/dL) • Fluorescence scanning at neutral pH shows no peak or a small peak at ~620 nm. *Note*: AIP patients with severe renal disease are an exception and may have substantial increases in plasma porphyrins.	• <5 µg/dL, or <5-fold increase (relative to ULN of 0.9 µg/dL) • Fluorescence scanning at neutral pH shows no peak or a small peak at ~620 nm. *Note:* this criterion applies to HCP patients without skin lesions. Skin lesions are rare in this disease, but if present are often accompanied by substantial increases in plasma porphyrins. An exception will be made for this criterion in such cases.	• >2.7 µg/dL, or >3-fold increase (relative to ULN of 0.9 µg/dL) • Fluorescence scanning at neutral pH showing a peak at ~626 nm.	• Plasma: same as AIP • Erythrocytes: marked increase in zinc protoporphyrin IX (>400 µg/dL)
Total Fecal Porphyrins	• WNL (< 400 µg/g dry weight or <2-fold increase (relative to ULN of 200 µg/g dry weight)	• >400 µg/g dry weight or >2-fold increase (relative to ULN of 200 µg/g dry weight) • Predominance of coproporphyrin III and a coproporphyrin III/I ratio >1.5	• >400 µg/g dry weight or >2-fold increase (relative to ULN of 200 µg/g dry weight) • Predominance of coproporphyrin III and protoporphyrin IX	• WNL or modest increase (<500 µg/g dry weight or <2.5-fold increase (relative to ULN of 200 µg/g dry weight)

Abbreviations: ADP=ALAD deficient porphyria; AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALAD=ALA dehydratase; HCP=hereditary coproporphyria; ULN=upper limit of normal; VP=variegate porphyria; WNL=within normal limits

11.2. Anaphylactic Reactions

Table 12: Sampson Criteria for Anaphylactic Reactions

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Adapted from Sampson et al. 2006 (28)

ALN-AS1-003 PROTOCOL AMENDMENT 7
SUMMARY OF CHANGES DATED 29 MARCH 2021

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

1. RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this protocol amendment is to recommend testing of blood homocysteine levels. In addition, it is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6.

These recommendations are being made because during givosiran treatment, increases in blood homocysteine levels have been observed compared to levels before givosiran treatment. Thus, monitoring for changes in blood homocysteine levels during treatment with givosiran has been incorporated into the protocol. Blood homocysteine levels may also be increased in patients with acute hepatic porphyria (AHP), vitamin deficiencies, or chronic kidney disease. The clinical relevance of the elevations in blood homocysteine during givosiran treatment is unknown.

Detailed reasons for each change are provided in Section 2. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting, as well as administrative changes are not detailed.

2. PROTOCOL AMENDMENT 7 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 7 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~ and added text is indicated by **bold** font, relevant to each purpose described.

Purpose: Add measuring blood homocysteine levels as part of the exploratory biomarker assessment.

The primary change occurs in Section 7.6.1 Exploratory Biomarkers

Revised text: (only first paragraph with revision is shown)

Where allowed per local regulations and IRB/EC approval and patient consent (and assent, where applicable), serum, plasma, and urine samples will be collected and may be archived and used for analyses of exploratory biomarkers related to metabolic profiling or the effects of givosiran or other proteins related to AHPs and their complications. **Samples may also be used for testing homocysteine levels.**

Sections also reflecting this change:

- Table 1, Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6) (footnote o)
- Table 2, Schedule of Assessments – Open-Label Extension Period: After Month 6 through Month 18 (footnote l)
- Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study (footnote j)

Purpose: To add increases in blood homocysteine levels to the benefit-risk assessment, noting the unknown clinical relevance, and to inform the Investigator about the possibility to supplement with vitamin B6 should increases in homocysteine levels occur.

The primary change occurs in Section 1.5 Benefit-Risk Assessment

Added text: (3rd to last paragraph)

Blood homocysteine levels may be increased in patients with AHP, vitamin deficiencies, or chronic kidney disease.(23-25) During treatment with givosiran, increases in blood homocysteine levels have been observed compared to levels before treatment. The clinical relevance of the elevations in blood homocysteine during givosiran treatment is unknown. The protocol includes monitoring for changes in blood homocysteine levels during treatment with givosiran. It is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6 (see Section 6.3.4).

Purpose: To add that vitamin B6 supplementation is an accepted potential concomitant medication if increases in blood homocysteine levels occur.

The changes include the addition of Section 6.3.4 Vitamin B6 Supplementation

Added text: (Section 6.3.4)

Section 6.3.4 Vitamin B6 Supplementation

During treatment with givosiran, blood homocysteine levels may show an increase compared to levels before treatment. Blood homocysteine levels will be assessed as indicated in the Schedule of Assessments (Table 1, Table 2, and Table 3). It is recommended that patients with increased blood homocysteine levels receive a supplement containing vitamin B6. All vitamin supplements should be recorded on the concomitant medications eCRF.

Section also reflecting this change:

- Section 6, Concomitant Medications (final sentence added a cross-link to the vitamin B6 supplementation section)

ALN-AS1-003 PROTOCOL AMENDMENT 6
SUMMARY OF CHANGES DATED 23 APRIL 2020

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

1. RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. These changes are in line with guidance from both the European Medicines Agency and the United States Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic.[EMA 2020; FDA 2020]

The USM modifications and new procedures are outlined below, and a detailed summary of the protocol changes is provided in Section 2. These changes should be adopted immediately per the Dear Investigator Letter dated 07 April 2020.

- **Givosiran Dosing Outside the Study Center by Patient or Caregiver**

  Following appropriate training on givosiran administration and the use of epinephrine (epi pen or equivalent), dosing will be permitted at a location other than the study center (eg, at home) by the patient or caregiver at all time points under the oversight of the Investigator and following consultation with the medical monitor. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

- **Study Visit Window**

  Except for assessments with other specified timing requirements (as noted below), study assessments and dosing are to be performed within a visit window of ±14 days (previously ±7 days). Study drug doses must be administered at least 14 days apart, and this is expected to be tolerated based on safety data from the Phase 1 study (ALN-AS1-001), which evaluated dosing at 5.0 mg/kg monthly (twice the therapeutic dose of 2.5◦mg/kg monthly).

- **Assessments of Adverse Events, Concomitant Medications (including hemin use), Hospitalizations/Procedures, and Porphyria Attacks**

  In situations where a study visit cannot be completed at the study center or offsite by a healthcare professional visit, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events, concomitant medications (including hemin use), hospitalizations/procedures, and porphyria attacks.

- **Liver Function Tests**

  Alanine aminotransferase (ALT) and total bilirubin results must be obtained from a central or local laboratory and reviewed within 6 weeks (previously 14 days) prior to each givosiran dose.

  In clinical studies to date, transaminase elevations have primarily occurred between 3 and 5 months following initiation of givosiran treatment. Since all patients in Study ALN-AS1-003 have received at least 18 months of dosing with givosiran, the requirement to review the results of liver function tests obtained within 6 weeks of dosing is considered justified. This is also aligned with the US and EU prescribing information that state that the liver function tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter.

- **Time Period to Obtain Weight for Dose Determination**

  Dose will be based on weight obtained within 6 months (previously at the current or prior study visit) prior to dosing. Dosing weight may be collected during clinical study center visits or offsite.

  Given the expanded use of offsite administration, use of a prior weight permits accurate determination of dose and volume without manual calculations or verbal orders. All patients are adult; therefore, substantial fluctuations in body weight over a 6-month period are not expected. Prior analyses of the study data have shown mean body weight to be stable over time.

- **Quality of Life (QOL) and Porphyria Patient Experience Questionnaire (PPEQ) Assessments**

  In situations where a planned study visit cannot be completed at the study center, the patient will complete the QOL and PPEQ questionnaires at home.

- **Assessment of ECG**

  Further assessment of ECG is no longer warranted, because no clinically significant ECG findings, including QT interval prolongation, have been observed following comprehensive analyses across the ALN-AS1-003 Study and the Phase 1/2 open-label extension study (ALN-AS1-002) to date. To minimize exposure to COVID-19, decrease the burden on patients and trial sites, and align with the US and EU prescribing information, which do not require ECG assessment for dosing, ECGs are no longer required in this study. For further information, refer to the givosiran (ALN-AS1) Investigator's Brochure.

- **Assessments Required to be Performed at Study Center Visits**

  Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study assessments including targeted physical exam/body system assessment, assessments for vital signs, and collection of blood and urine samples for safety laboratory assessments, and pharmacodynamic (PD) assessments, at all timepoints as specified in the Schedule of Assessments.

In the event that givosiran is administered offsite by the patient or caregiver, safety laboratory assessments (other than liver function tests) must be obtained from a central or local laboratory within 3 months prior to dosing (previously at the clinical study center visit). This same frequency for laboratory assessments was implemented in the Phase 1/2, open-label, extension Study ALN-AS1-002 after 18 months (to date all patients treated for ≥30 months) and this has been acceptable for safety monitoring.

- **Pharmacokinetic and Anti-drug Antibody Assessments Required to be Performed at Study Center Visits**

  Given the expanded use of offsite dosing, pharmacokinetic (PK) and anti-drug antibody (ADA) assessments may be completed within 6 months at the next study center visit (previously at the clinical study center visit).

  All patients have completed 18 months of treatment in Study ALN-AS1-003. The PK of givosiran have been well characterized based on the available study data. Results show that exposure to givosiran and its metabolites is consistent across study visits. Data from study visits after Month 18 are not expected to significantly alter the current understanding of givosiran PK.

  The incidence of ADAs due to givosiran has been very low in the current study, as well as in other clinical studies of givosiran. In the current study, there has been only 1 case of treatment-emergent ADAs due to givosiran. The antibody titer was low and transient, with the patient subsequently testing negative. Based on the collective evidence to date, givosiran is considered to have a very low risk of eliciting an immune response.

- **Collection of Information Related to COVID-19**

  Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient. Additional information regarding collection of this information, including completion of a new case report form specific to COVID-19, will be provided separately.

  This change is implemented to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to Study Administration**

  Text was updated to provide clarification on Investigator responsibilities regarding communication of new study information to patients and Institutional Review Boards (IRB)/Independent Ethics Committees (IECs).

References:

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 1.0 (20/03/2020). https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic

2. PROTOCOL AMENDMENT 6 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 6 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~ and added text is indicated by **bold** font, relevant to each purpose described.

Purpose: To expand the use of offsite administration to include givosiran dosing by the patient or caregiver.

The primary changes occur in Section 6.2.2, Dose and Administration,

Revised text:

1st paragraph:

~~Givosiran will be administered by a qualified and authorized health care professional trained in the recognition and management of anaphylactic reactions.~~ The study drug should be injected into the abdomen or upper arms or thighs. Detailed instructions for study drug administration are presented in the Pharmacy Manual. As is consistent with good medical practice for subcutaneous drug administration, patients will be observed for a minimum of 20 minutes after each injection. Treatment for anaphylactic reactions should be readily available where patients are being dosed and follow country and/or local hospital treatment guidelines (25).

2nd paragraph:

Givosiran will be administered by a qualified and authorized health care professional trained in the recognition and management of anaphylactic reactions, whenever possible. Study drug administration may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor, during particular study visits, as specified in the Schedules of Assessments (Table 2 and Table 3). **If the patient is unable to come to the study site, and a visit by a home healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, givosiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the medical monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on givosiran administration and the use of epinephrine (epi pen or equivalent) prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.** However, study drug administration at the study center should be considered for patients who have ongoing study drug-related AEs or known risk factors for developing anaphylactic reactions, including but not limited to: prior history of an anaphylactic reaction to food, medications or due to unknown etiology, worsening injection site reactions with repeat dosing, or anyone in the opinion of the investigator that would benefit from clinical observation following dosing.

Last paragraph:

Detailed instructions for study drug administration are presented in the Pharmacy Manual. **In addition, instructions and procedures related to administration of givosiran by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.**

Section(s) also reflecting this change:

- Synopsis
- Section 4.1
- Section 6.2.4

Purpose: To expand the study visit window.

The primary change occurs in Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study.

Revised text: In Table 3, the visit window was changed to ±**14 days** (previously ±7 days) for all visits.

Section(s) also reflecting this change:

- Section 5.3.1

Purpose: To allow the study Investigator (or delegate) to verbally contact the patient within the study visit window to assess for any adverse events, concomitant medications (including hemin use), hospitalizations/procedures, and porphyria attacks.

The changes occur in the second bullet point following Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study.

Revised text:

- Study procedures, including givosiran administration, may occur at the patient's home at the discretion of the Investigator, based on safety and tolerability. **In situations where a study visit cannot be completed at the study center or offsite by a home healthcare professional visit, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events, concomitant medications (including hemin use), hospitalizations/procedures, and porphyria attacks.**

Purpose: To expand the window for ALT and total bilirubin tests for decisions on givosiran dosing.

The primary change occurs in Section 6.2.2., Dose and Administration, 3rd paragraph

Revised text: ALT and total bilirubin (TBL) results collected within **6 weeks** ~~**14 days**~~ of study drug administration must be reviewed prior to dosing. In the event that givosiran is administered offsite by the patient or caregiver, safety laboratory assessments other than ALT and TBL must be obtained from a central or local laboratory within 3 months prior to dosing. For patients with new signs or symptoms, appropriate evaluation, including laboratory assessments, should be performed based on investigator judgment prior to study drug administration.

Section(s) also reflecting this change:

- Table 3, footnote f
- Section 6.2.3.1
- Section 7.5.5

Purpose: To increase the window for obtaining body weight for dose determination.

The primary change occurs in Section 7.5.2, Weight and Height, 3rd paragraph

Revised text: Body weight **obtained within 6 months during a clinical study center visit or offsite** ~~**either at the previous study center visit or current study center visit**~~ may be used for dosing calculations.

Section(s) also reflecting this change:

- Table 3, footnote c

Purpose: To allow for remote contact and completion of QOL and PPEQ questionnaires.

The changes occur in Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study

Revised text:

Footnote m

[m] QOL questionnaires to be completed include SF-12, EQ-5D-5L, and missed days of work/school. **In situations where a planned study visit cannot be completed at the study center, the patient will complete the QoL questionnaires at home.**

Footnote n

[n] The PPEQ is a set of questions to assess treatment experience and impacts to the patient's life not collected by the other QOL assessments. **In situations where a planned study visit cannot be completed at the study center, the patient will complete the PPEQ questionnaire at home.**

Purpose: To remove requirements for ECGs.

The primary change occurs in Section 7.5.4, Electrocardiogram, 1st paragraph

Revised text: A single standard 12-lead ECG will be recorded at Screening~~, Month 24, and at the End of Treatment (EOS) Visit~~; all other ECGs will be performed in triplicate, using centralized ECG service equipment, with readings approximately 1 minute apart. Triplicate ECGs will be performed predose and at 2 hours postdose in all patients on Study Day 1 and at the Month 5, Month 6, and Month 12 visits (Table 8 and Table 9); these assessments will be paired with PK measurements.

Section(s) also reflecting this change:

- Table 3, 7th row and footnote e
- Table 8
- Table 9

Purpose: To allow certain study visit assessments to be performed offsite and provide a window for safety laboratory results prior to dosing by the patient or caregiver.

The change occurs in Section 7, Study Assessments.

Revised text: The schedule of study assessments is provided in Table 1 (Screening and 6-Month Treatment Period), Table 2 (Open-label Extension Study: After Month 6 through Month 18), and Table 3 (Open-label Extension Study: Month 19 through EOS).

Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study assessments including targeted physical exam/body system assessment, assessments for vital signs, and collection of blood and urine samples for safety laboratory assessments, and PD assessments, at all timepoints as specified in the Schedule of Assessments.

Additionally, Section 6.2.2, Dose and Administration, 3rd paragraph, is affected by these changes.

Revised text:

ALT and total bilirubin (TBL) results collected within 6 weeks of study drug administration must be reviewed prior to dosing. **In the event that givosiran is administered offsite by the patient or caregiver, safety laboratory assessments other than ALT and TBL must be obtained from a central or local laboratory within 3 months prior to dosing.** For patients with new signs or symptoms, appropriate evaluation, including laboratory assessments, should be performed based on investigator judgment prior to study drug administration.

Other section(s) also reflecting these changes:

- Table 3, footnotes b, c, d, and f
- Section 7.5.2
- Section 7.5.5

Purpose: To broaden the window for PK and ADA assessments required to be performed at study center visits.

The primary changes occur in Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study.

Revised text:

Footnote k

[k] Blood samples for PK analysis will be collected prior to dosing at the time points listed in Table 8 or Table 9. **PK assessments may be completed within 6 months, at the next study center visit.**

Footnote l

[l] Samples will be collected predose. **ADA assessments may be completed within 6 months, at the next study center visit**.

Section(s) also reflecting these changes:

- Table 8
- Table 9

Purpose: Collect information related to the impact of the COVID-19 pandemic on patient participation in the study, to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

The primary change occurs in a newly added Section 7.7, COVID-19 Data Collection.

Added text:

Section 7.7 COVID-19 Data Collection

Information will be collected on the coronavirus disease 2019 (COVID-19) infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study.

Section(s) also reflecting this change:

- Section 8.2.9

Purpose: To provide clarification on Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

These changes occur in Section 9.1.1, Informed Consent, and Section 9.1.2, Ethical Review.

Added text:

Section 9.1.1, 3rd paragraph

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

Section 9.1.2, 2nd paragraph

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study **(except those that support the need to remove an apparent immediate hazard to the patient)**. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

ALN-AS1-003 PROTOCOL AMENDMENT 5
SUMMARY OF CHANGES DATED 12 FEBRUARY 2020

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to increase the dose of givosiran for patients receiving 1.25 mg/kg givosiran subcutaneously (SC) once monthly to the recommended dose of 2.5 mg/kg givosiran SC once monthly, which was approved by the United States Food and Drug Administration (FDA) in November 2019 and received a Committee for Medicinal Products for Human Use (CHMP) positive opinion in January 2020. Data from the 6-month randomized, placebo-controlled, double-blind (DB) period and open-label extension (OLE) period through the Month 12 data-cut have demonstrated that treatment at 2.5 mg/kg givosiran SC once monthly resulted in sustained lowering of the disease causal factors aminolevulinic acid (ALA) and porphobilinogen (PBG) and is associated with substantial benefits including reducing debilitating neurovisceral attacks and improving chronic disease aspects such as hemin use, daily pain, analgesic use, physical functioning, and quality of life. These beneficial effects were accompanied by an acceptable and manageable safety profile through the Month 12 data-cut, which supports a favorable benefit-risk profile for givosiran at the 2.5-mg/kg SC once monthly dose. A trend toward increased benefit as indicated by greater reduction in composite attacks, hemin use, and ALA and PBG levels was observed during the first 6 months of treatment in the OLE with the 2.5-mg/kg SC once monthly dose compared to the 1.25-mg/kg SC once monthly dose in patients who received placebo during the DB period. Furthermore, Investigators requested to increase the dose to 2.5 mg/kg givosiran SC once monthly for 14 of the 37 patients (38%) receiving 1.25 mg/kg givosiran SC once monthly in the OLE because of inadequate clinical response as permitted in Section 6.2.3.4 of the protocol. Given the trend toward increased benefit with the 2.5-mg/kg SC once monthly dose of givosiran compared to the 1.25-mg/kg SC once monthly dose and considering that acute hepatic porphyria (AHP) is a disease in which each attack is serious, highly morbid, and carries potential for irreversible neurologic damage, all patients, in the absence of ongoing clinically relevant transaminase elevations, will be treated with the recommended dose of 2.5 mg/kg givosiran SC once monthly.

The following additional changes are also being implemented:

- Allow patients who develop a transaminase elevation that meets a protocol-defined dose holding rule while receiving 2.5 mg/kg givosiran SC once monthly to resume dosing at either the 1.25- or 2.5-mg/kg givosiran SC once monthly dose after resolution of alanine aminotransferase (ALT) to ≤2×upper limit of normal (ULN; or ≤2×baseline for patients who had elevated baseline ALT) per the Investigator's judgement and after discussion with the medical monitor. This change will enable the collection of robust safety data at the commerical dose after a dose interruption for ALT elevation in a clinical trial setting.

- Discontinuation of monitoring by the Data Monitoring Committee (DMC): In October 2019, the DMC for Study ALN-AS1-003 met and reviewed all available data, which included at least 12 months of data for all patients on the study (6 months during the DB period and 6 months during the OLE period). The DMC determined that the safety profile for givosiran continued to be acceptable and agreed with the Sponsor's recommendation to terminate the DMC for the remainder of the OLE period of the study. Based on the favorable safety profile for givosiran, approval of givosiran by the FDA in November 2019, and CHMP positive opinion in January 2020, the DMC charter is being amended in parallel with this amendment to permit discontinuation of the DMC. Patient safety will continue to be monitored on a regular basis by the Sponsor according to standard operating procedures.
- Removal of the requirement to test and review the results for international normalized ratio (INR) within 14 days prior to dosing: Based on data from the givosiran development program, testing of INR prior to dosing has not enhanced the detection of acute hepatic injury beyond the predose assessment of ALT and total bilirubin (TBL). Additionally, no clinically significant changes in coagulation parameters have been seen in patients with ALT elevations >3×ULN. Moreover, testing of INR on each patient prior to dosing requires collection of additional and unnecessary blood samples. In all patients with ALT elevation >3×ULN, INR testing will still be required to provide further information on the severity of hepatic injury (see Section 6.2.3.1). Evaluation of ALT and TBL within 14 days prior to dosing and testing of INR with regular clinical laboratories as specified in the Schedule of Assessments will continue.
- Update potential safety concerns to be consistent with emerging data and to align with the Investigators Brochure.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between protocol amendments 4 and 5) are not detailed.

Table 1: Protocol Amendment 5 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 5 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: To increase the dose of givosiran for patients receiving 1.25 mg/kg givosiran SC once monthly to the recommended dose of 2.5 mg/kg givosiran SC once monthly.

The primary change occurs in Section 6.2.3.4, Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period

Now reads:

6.2.3.4 Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period

After implementation of amendment 3 and until implementation of amendment 5, patients assigned to the once monthly 1.25-mg/kg treatment group may be allowed to have their monthly dose increased to 2.5 mg/kg ~~S~~starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed **at 1.25 mg/kg**), **based on discussion and agreement by the Investigator and medical monitor. Dose escalation may be considered**~~patients receiving open-label givosiran at SC doses of 1.25 mg/kg monthly may be permitted to increase their monthly dose to 2.5 mg/kg based on Investigator judgement. Investigators may consider dose escalation~~ if the following criteria are met:

- Tolerability to givosiran at 1.25 mg/kg once monthly has been demonstrated based on no dose interruptions due to LFT elevations at the 1.25 mg/kg once monthly dose level (see Section 6.2.3.1) and no significant safety concerns due to other AEs that would preclude a patient from receiving a higher dose of givosiran as judged by the Investigator and Sponsor.
- Urine ALA levels (mmol/mol Cr) are not stably maintained ≤ULN or are inducible
- Patient has inadequate clinical response (eg, breakthrough attacks or ongoing chronic symptoms), according to Investigator judgement.

Upon implementation of amendment 5, all patients receiving 1.25 mg/kg givosiran once monthly who do not have ongoing clinically relevant transaminase elevations will have their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. Dose increases should take effect as of the date that sufficient study drug material can be made available for the patient.

~~Urine ALA analyses may be conducted at a local laboratory or ALA results from previous visits may be evaluated in patients on the 1.25 mg/kg monthly dose in whom dose escalation to 2.5 mg/kg once monthly is being considered~~

~~The decision to increase the givosiran dose from 1.25 mg/kg monthly to 2.5 mg/kg monthly will be discussed and agreed upon by the Investigator and medical monitor prior to initiation of the next dose.~~

~~Upon increase of the givosiran dose to 2.5 mg/kg monthly:~~

- ~~LFTs, INR, and TBL will be monitored every 2 weeks (±7 days) for the first month following the dose increase to 2.5 mg/kg, then monthly (±7 days or during the scheduled study visits) as per the Schedule of Assessments~~
- ~~Laboratory monitoring and dosing rules in response to LFT elevation will follow Table 4 guidelines~~
- ~~For patients in whom givosiran dosing is withheld due to elevated ALT, resumption of dosing may be considered based on the guidance in Section 6.2.3.1.1.~~

Section(s) also containing this change:

- Synopsis, Study Design
- Table 3, footnotes h and j
- Section 1.3, Study Design Rationale
- Section 1.4, Dose Rationale
- Section 4.1, Summary of Study Design
- Figure 2, Study Design
- Section 6.2.2.2, During the Open-Label Extension Period (After Month 6 through End of Treatment)
- Section 6.2.3, Dose Modifications

Purpose: Allow patients who develop a transaminase elevation that meets a protocol defined dose holding rule while receiving 2.5 mg/kg givosiran SC once monthly to resume dosing at either the 1.25- or 2.5-mg/kg givosiran SC once monthly dose after resolution of ALT to ≤2×ULN (or ≤2×baseline for patients who had elevated baseline ALT) per the Investigator's judgement and after discussion with the medical monitor.

The primary change occurs in Section 6.2.3.1.1, Criteria for Rechallenge of Givosiran After Being Withheld for ALT Elevation

Now reads:

6.2.3.1.1 Criteria for Rechallenge of Givosiran After Being Withheld for ALT Elevation

For patients in whom givosiran dosing is withheld due to elevated ALT, resumption of dosing may be considered using the following guidelines:

- Patients who did not meet criteria for study drug discontinuation per Table 4 may be considered for rechallenge following consultation with the medical monitor and resolution of ALT to ≤ 2× ULN or ≤ 2× baseline (for patients who had elevated baseline ALT)
- The decision to rechallenge the patient should be discussed and agreed upon by the patient, Investigator, and medical monitor
- The dose regimen for patients who meet rechallenge criteria, regardless of their dose at the time of the ALT elevation, is a dose of **either** 1.25 **or 2.5** mg/kg monthly **per Investigtor judgement and after discussion with the medical monitor**:
  - LFTs, INR and TBL will be monitored every 2 weeks (±7 days) for the first month, then monthly (±7 days or during the scheduled study visits) as per the Schedule of Assessments
  - Laboratory monitoring and dosing rules in response to LFT elevation will follow Table 4 guidelines
- If dose withholding rules per Table 4 are met on ~~this~~**rechallenge with the 1.25-mg/kg** dose, permanently discontinue dosing
- ~~For patients treated with 2.5 mg/kg monthly givosiran at the time of the ALT elevation, dose re-escalation to 2.5 mg/kg monthly may be considered if the following criteria are met:~~
  - ~~Approval by the medical monitor after at least 3 doses of 1.25 mg/kg monthly for patients who meet both criteria below:~~

~~○ Patient has not met dose withholding or discontinuation rules per Table 4 during treatment with 1.25 mg/kg monthly~~

~~○ Patient has inadequate control of porphyria symptoms on the 1.25 mg/kg monthly regimen, per investigator's assessment~~

~~– LFTs, INR, and TBL will be monitored every 2 weeks (±7 days) for the first month after dose re-escalation, and then monthly as per the Schedule of Assessments~~

- If a patient experiences a second dose hold due to LFT elevation while on 2.5 mg/kg monthly:
  - Follow Table 4 guidelines for monitoring and evaluations
  - If ALT resolves to ≤2×ULN, redosing with 1.25 mg/kg monthly may be considered ~~if this dose was previously tolerated and there is approval by~~**after discussion with** the Alnylam medical monitor. If dosing is resumed, follow the guidance above for rechallenge regimen regarding laboratory monitoring and dosing rules. No subsequent re-escalation to 2.5 mg/kg monthly will be allowed

    ~~○ LFTs, INR, and TBL will be monitored every 2 weeks (±7 days) for the first month after dose resuming 1.25 mg/kg, and then monthly as per the Schedule of Assessments~~

Purpose: Discontinuation of monitoring by the Data Monitoring Committee (DMC)

The primary change occurs in Section 4.7, Independent Data Monitoring Committee

Now reads:

4.7 Independent Data Monitoring Committee

An external independent DMC will monitor safety over the course of the **double-blind treatment period and until all patients have been in the OLE period for at least 6 months**~~study~~. Analyses for the DMC are provided by an independent biostatistics group. Details are provided in the DMC Charter.

Section(s) also containing this change:

- Synopsis, Study Design
- Section 1.5, Benefit-Risk Assessment
- Section 4.1, Summary of Study Design

- Figure 2, Study Design
- Section 6.2.2.2, During the Open-Label Extension Period (After Month 6 through End of Treatment)
- Section 6.2.3, Dose Modifications

Purpose: Removal of the requirement to test and review the results for international normalized ratio (INR) within 14 days prior to dosing

The primary change occurs in Section 6.2.2, Dose and Administration

Now reads: ALT **and**~~,~~ total bilirubin (TBL)~~ and INR~~ results collected within 14 days of study drug administration must be reviewed prior to dosing.

Section(s) also containing this change:

- Table 3, footnote f
- Section 6.2.3.1, Monitoring and Dosing Rules Based on Liver Function Test Results
- Section 7.5.5, Clinical Laboratory Assessments

Purpose: Update potential safety concerns to be consistent with emerging data and to align with the Investigators Brochure.

The primary change occurs in Section 1.5, Benefit-Risk Assessment

Now reads: Given the biological target of givosiran, the available nonclinical and clinical data, and the mode of administration, other ~~important~~ potential ~~risks~~**safety concerns** include injection site reactions (ISRs), **elevation of** liver transaminases ~~abnormalities~~, **increased serum creatinine/decreased estimated glomerular filtration rate (eGFR),** pancreatitis, and anaphylactic reaction~~s~~.

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting[, including administrative changes, if appropriate]

These changes are not listed individually.

ALN-AS1-003 PROTOCOL AMENDMENT 4
SUMMARY OF CHANGES DATED 28 MAY 2019

ENVISION: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to provide updated information from a recently completed drug-drug interaction study (ALN-AS1-004) performed in AIP patients who are asymptomatic high excreters (also referred to as chronic high excreters [CHE]) in the concomitant medications section (Section 6.3). The results of the study indicated that givosiran treatment resulted in moderate reduction in CYP1A2 and CYP2D6 activity, weak reduction in CYP3A4 and CYP2C19 activity, and no change in the activity of CYP2C9.

Additional updates are being implemented as noted below: clarification that patients may continue to receive givosiran until it is commercially available in the patient's territory, update to clarify that staff do not need to wait until the end of the study before obtaining local ALA or PBG measurements, updates to be consistent with changes made in amendment 3, addition of guidance for serious breaches of protocol, updated PK, ECG and ADA time points, and deletion of Section 11.2, List of Sensitive CYP3A substrates and those with a Narrow Therapeutic Range.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between protocol amendments 3 and 4) are not detailed.

Table 1: Protocol Amendment 4 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 4 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated Section 1.2.2, Summary of Clinical Data with Givosiran, with results of the open-label drug-drug interaction study (ALN-AS1-004) to support changes in Section 6.3, Concomitant Medications.

The primary change is the addition of Section 1.2.2.3, Drug-drug Interaction Study ALN-AS1-004

Added text:

1.2.2.3 Drug-drug Interaction Study ALN-AS1-004

An open-label drug-drug interaction (DDI) study (ALN-AS1-004) was conducted in AIP patients who are CHE to evaluate the effect of a single dose of 2.5 mg/kg givosiran administered SC on the pharmacokinetics of probe substrates for 5 major cytochrome P450 (CYP) enzymes that account for the metabolism of approximately 80% of prescribed drugs (24, 25). Results from this study demonstrated that givosiran treatment resulted in weak to moderate reduction in the metabolic activity of some of the 5 CYP enzymes studied, thereby leading to higher concentrations of some substrates and their metabolites. Treatment with givosiran resulted in an approximately 3-fold increase in exposure (as measured by AUC) to caffeine (a sensitive substrate for CYP1A2) and an approximately 2-fold increase in exposure to dextromethorphan (a sensitive substrate for CYP2D6). Exposure of midazolam (a sensitive substrate for CYP3A4) and omeprazole (a sensitive substrate for CYP2C19) increased less than 2-fold after treatment with givosiran. There was no effect of givosiran treatment on losartan (a sensitive substrate for CYP2C9).

Purpose: Clarify that subjects may continue until givosiran is commercially available or the givosiran development program is discontinued.

The primary change is the addition of 2 sentences to Section 4.1, Summary of Study Design.

Added text:

During the OLE Period, patients may receive givosiran as long as they do not fulfill any of the study discontinuation criteria (see Section 5.3) or until givosiran is commercially available in the patient's territory or the givosiran development program is discontinued (whichever comes first).

All patients are asked to participate in the Safety Follow-up visit after they have received their last dose of givosiran.

Section(s) also containing this change:

- *Synopsis, Study Design*

Purpose: Updated concomitant medications to indicate that givosiran treatment could affect drugs that are metabolized primarily by CYP2D6 and CYP1A2.

The primary change occurs in Section 6.3, Concomitant Medications

Formerly read:

Patients with porphyria could have altered heme synthesis and treatment with givosiran could also modulate this pathway and can secondarily impact cytochrome p450 (CYP) enzyme activity. Studies in monkeys could not exclude the potential for givosiran to alter the clearance of drugs metabolized by the CYP3A enzymes. Investigators will review all medications at the study start and monitor the response to these medications during the study. Medications with a narrow therapeutic index that require regular monitoring may need to be monitored more frequently in the initial stages of the study to determine whether a dose adjustment of the concomitant medication is required. A list of common medications that are sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic range can be found in Section 11.2. For more detailed and up-to-date information on CYP3A substrates, see: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Now reads:

Patients with porphyria could have altered **hepatic** heme synthesis, and treatment with givosiran could also modulate this pathway and ~~can~~ secondarily impact ~~cytochrome p450 (~~CYP~~)~~ enzyme activity . ~~Studies~~**Results from a DDI study** in ~~monkeys could not exclude the potential for~~ **AIP patients who are CHE are presented in Section 1.2.2.3. The DDI study demonstrated that** givosiran to alter~~the clearance~~**treatment resulted in weak to moderate reduction in activity of some of the CYP enzymes resulting in corresponding low to moderate increase in the plasma levels** of drugs **that are** metabolized **by these CYP enzymes. Based on the moderate decrease in** ~~by the CYP3A enzymes. CYP2D6 or CYP1A2 activity,~~ ~~I~~**i**nvestigators will review all **concomitant** medications **that are primarily metabolized by these enzymes**~~at the study start~~ and monitor the **patient's** clinical response to these medications during the study. Medications **metabolized primarily by CYP2D6 and CYP1A2** with a narrow therapeutic index **(ie,** that require regular **laboratory** monitoring) may need to be monitored more frequently ~~in the initial stages of the study~~ to determine ~~whether~~ **if** a dose adjustment of the concomitant medication is required. ~~A list of commonmedications that are sensitive CYP3A substrates or CYP3A substrates~~**For patients**

who require new medications while on study, selection of medications that are not primarily metabolized by CYP2D6 or CYP1A2 should be considered. Refer to the individual product's prescription information to determine if there is a need to monitor concomitant medications for differences in safety or efficacy of the medication based on reported DDIs with ~~a narrow therapeutic range can be found in Section 11.2.~~**CYP2D6 or CYP1A2.** For more detailed and up-to-date information on CYP~~3A~~ substrates, see: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Purpose: Correct an error in Section 7.3 so that staff do not need to wait until the end of the study before obtaining a local ALA or PBG measurement.

The primary change occurs in Section 7.3, Pharmacodynamic Assessments

Formerly read: Urine samples will be collected for assessment of givosiran PD parameters prior to dosing. The PD effect of givosiran will be evaluated by spot urine ALA and PBG levels normalized to spot urine creatinine levels. Urine samples will be collected for assessment of circulating ALAS1 mRNA levels. Analysis of urine ALAS1 mRNA levels will be performed at Alnylam; all other urine PD analyses will take place at a central laboratory. Since Investigators are blinded to treatment assignments, they will also be blinded to ALA and PBG results analyzed at the central laboratory. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining local ALA or PBG measurements until at least 12 weeks after the month 6 visit or until the subject ends the study, whichever is later (to avoid potential unblinding). If ALA or PBG is measured during this period, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Now reads: Urine samples will be collected for assessment of givosiran PD parameters prior to dosing. The PD effect of givosiran will be evaluated by spot urine ALA and PBG levels normalized to spot urine creatinine levels. Urine samples will be collected for assessment of circulating ALAS1 mRNA levels. Analysis of urine ALAS1 mRNA levels will be performed at Alnylam; all other urine PD analyses will take place at a central laboratory. Since Investigators are blinded to treatment assignments, they will also be blinded to ALA and PBG results analyzed at the central laboratory. In addition, investigators and staff involved with this trial and all medical staff involved in the subject's medical care should refrain from obtaining local ALA or PBG measurements until at least 12 weeks after the month 6 visit ~~or until the subject ends the study, whichever is later~~ (to avoid potential unblinding). If ALA or PBG is measured during this period, all reasonable steps must be undertaken to avoid informing the subject and study personnel of the results.

Purpose: Updated window for vital signs, triplicate 12-lead ECGs, and PK samples at the 2 hour time points at the Day 1 and Month 5, 6, and 12 visits from 10 to 15 minutes to be consistent with changes implemented in Amendment 3.

The primary change occurs in Synopsis, Table 1, Footnotes h and j

Formerly read:

[h] Vital signs include blood pressure, heart rate, body temperature, and respiratory rate and will be measured when patients are in a seated or supine position (should be consistent across study visits with each patient) after the patient has rested for 10 min. On the Day 1 and Month 6 visit, vital signs will be collected predose and 2 hours postdose (± 10 minutes). On all other dosing days, vital signs will be collected predose.

[i] Single 12-lead ECG will be performed in the supine position after the patient has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.

[j] Triplicate 12-lead ECGs will be performed at predose and 2-hours (± 10 minutes) post-dose on the Day 1, Month 5, and Month 6 visits, using validated ECG services equipment from a central facility; triplicate measurements should be separated by approximately 1 minute with the patient in the supine position after he or she has rested comfortably for 5 minutes. When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECG assessments should be performed before blood samples are drawn. In a prespecified subset of approximately 24 patients at prespecified study centers (including all patients at East Asian study centers [in Japan, South Korea, and Taiwan]), an additional ECG (with paired PK assessment) at 24 hours (±2 hours) post-dose will be collected at Day 1 and Month 6.

Now reads:

[h] Vital signs include blood pressure, heart rate, body temperature, and respiratory rate and will be measured when patients are in a seated or supine position (should be consistent across study visits with each patient) after the patient has rested for 10 min. On the Day 1 and Month 6 visit, vital signs will be collected predose and 2 hours postdose (± ~~10~~ **15** minutes). On all other dosing days, vital signs will be collected predose.

[i] Single 12-lead ECG will be performed in the supine position after the patient has rested comfortably for 5 minutes. ECGs will be collected prior to any blood draws.

[j] Triplicate 12-lead ECGs will be performed at predose and 2-hours (± ~~10~~ **15** minutes) post-dose on the Day 1, Month 5, and Month 6 visits, using validated ECG services equipment from a central facility; triplicate measurements should be separated by approximately 1 minute with the patient in the supine position after he or she has rested comfortably for 5 minutes. When ECG and blood sample collection (eg, for PK assessment) occur at the same time, ECG assessments should be performed before blood samples are drawn. In a prespecified subset of approximately 24 patients at prespecified study centers (including all patients at East Asian study centers [in Japan, South Korea, and Taiwan]), an additional ECG (with paired PK assessment) at 24 hours (±2 hours) post-dose will be collected at Day 1 and Month 6.

Section(s) also containing this change:

- *Synopsis, Table 2, Footnote f*
- *Section 7.4, Pharmacokinetic Assessments*

Purpose: Section 9.1.3, Serious Breach of Protocol, was added to align with the process for the reporting potential serious breaches of protocol.

The primary change is the addition of Section 9.1.3, *Serious Breach of Protocol*

Added text: **9.1.3. Serious Breach of Protocol**

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

Purpose: Updated Table 8, Pharmacokinetic, ECG, and ADA Time Points for All Patients (Except Patients at East Asian Sites), to indicate that ECG assessmentas are not required at 4 hours postdose at the Month 6 or Month 12 visits.

The primary change occurs in Section 11, *Pharmacokinetic/Pharmacodynamic Assessment Time Points*

Revised text: Removed Xs in Triplicate ECG column at the 4-hour postdose time points at the Month 6 and Month 12 visits.

Purpose: Because data from the human drug-drug interaction study showed that givosiran treatment resulted in a moderate (>2-fold) reduction of CYP2D6 and CYP1A2 metabolic activity, the guidance for investigators in Section 6.3 was updated to recommend that medications metabolized primarily by CYP2D6 and CYP1A2 with a narrow therapeutic index may need to be monitored more frequently to determine if a dose adjustment of the concomitant medication is required. In the absence of comprehensive lists of products metabolized by CYP2D6 and CYP1A2, Section 6.3 now directs the Investigator to the product information of any concomitant medication required and to the Table of Substrates for CYP enzymes on the FDA Website to determine if concomitant medications metabolized primarily by CYP2D6 and CYP1A2 need to be monitored more frequently. Section 11.2, List of Sensitive CYP3A Substrates and Those with a Narrow Therapeutic Range, was deleted because , based on the results from the human drug-drug interaction study, givosiran treatment results in only a weak (<2-fold) reduction of CYP3A4 metabolic activity, and the recommendation to monitor the drug response in patients on medications primarily metabolized by CYP3A4 was not considered necessary.

The primary change occurs in Section 11.2, List of Sensitive CYP3A Substrates and Those with a Narrow Therapeutic Range.

Section 11.2 was deleted.

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting

These changes are not listed individually.

ALN-AS1-003 PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES DATED 21 September 2018

ENVISION: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Rationale for Protocol Amendment

In light of liver transaminase elevations observed in the study, a lower givosiran dose of 1.25 mg/kg once monthly was introduced in Amendment 2 as a rechallenge dose for patients who resume dosing after resolution of liver transaminase elevations. In order to generate additional data at this dose level, evaluation of the 1.25 mg/kg once monthly dose is proposed for patients crossing over to the open-label extension [OLE] period under this amendment, after their completion of the 6 month double-blind placebo-controlled period. While the 2.5 mg/kg once monthly dose has been demonstrated to provide near-normalization of ALA levels in the majority of AIP patients with recurrent attacks in the completed Phase 1 ALN-AS1-001 study (Part C) and the ongoing Phase 1/2 ALN-AS1-002 open-label extension study, preliminary analyses of PK and PD data suggest that a givosiran dose of 1.25 mg/kg once monthly would reduce ALA levels in a substantial number of patients. This study design will enable the evaluation of the PD, efficacy, and safety of the 1.25 mg/kg once monthly dose of givosiran in the OLE period, while continuing to provide data on the 2.5 mg/kg once monthly dose.

The primary purpose for this protocol amendment is to:

- Implement the inclusion of an additional, lower dose of givosiran (1.25 mg/kg once monthly) during the open-label extension period
- Provide specific guidance for increasing dose from 1.25 mg/kg once monthly to 2.5 mg/kg once monthly in patients who tolerate 1.25 mg/kg once monthly dose but who are experiencing inadequate disease control.
- Add statistical analyses to evaluate the durability of the treatment effect.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between protocol amendments 2 and 3) are not detailed.

Table 1: Protocol Amendment 3 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 3 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Update the dose rationale to include the addition of the 1.25 mg/kg once monthly dose

The primary change occurs in Section 1.4 Dose Rationale.

Added text:

In light of LFT elevations observed in the study, a lower givosiran dose of 1.25 mg/kg once monthly has been introduced as a down-titration dose, as detailed in Section 6.2.3.1. In order to generate additional data at this dose level, evaluation of the 1.25 mg/kg once monthly dose is proposed for patients crossing over to the OLE period under amendment 3. While the 2.5 mg/kg once monthly dose has been demonstrated to provide near-normalization of ALA levels in the majority of AIP patients with recurrent attacks in the completed Phase 1 ALN-AS1-001 study (Part C) and the ongoing Phase 1/2 ALN-AS1-002 open-label extension study, preliminary analyses of PK and PD data suggest that a givosiran dose of 1.25 mg/kg once monthly would reduce ALA levels in a substantial number of patients. The proposed study design will enable the evaluation of the PD, efficacy, and safety of the 1.25 mg/kg monthly dose of givosiran, while continuing to provide data on the 2.5 mg/kg monthly dose.

The concentration of givosiran in the liver is the primary driver for its pharmacodynamic effects, which is primarily affected by body weight. Population pharmacokinetic-pharmacodynamic modeling and simulation across different body weights show similar liver exposures of givosiran **in adolescents and adults** following ~~2.5 mg/kg~~ monthly dosing and consequently similar extent and duration of urinary ALA suppression ~~in adolescents and adults. As a result, the 2.5 mg/kg monthly dose regimen was selected for the proposed Phase 3 pivotal study in~~. **Therefore, the same doses are proposed to be administered to both** adults and adolescents~~.~~ **in this study**.

Sections containing related changes:

- Section 1.3 Study Design Rationale
- Section 8.2.9 Other Analyses

Purpose: Revise the exploratory objective and endpoint to indicate that multiple doses will be assessed during the OLE period

The primary change occurs in Section 2.3 Exploratory Objectives

Revised text:

- Assess the ~~within patient~~ treatment effect of givosiran **at evaluated doses** over the OLE period in patients with AIP and in patients with any AHP who had previously been randomized to placebo treatment

Sections also containing this change:

- Synopsis
- Section 3.3 Exploratory Endpoints

Purpose: Update study design text and associated study design figure to include the crossover strategy for evaluation of a second dose (1.25 mg/kg once monthly) during the OLE period.

The primary change occurs in Section 4.1 Summary of Study Design

Added text:

Patients ~~entering the OLE period~~who crossed over to the OLE period prior to implementation of amendment 3 (ie, under amendment version 1 or 2) and are receiving a 2.5 mg/kg once monthly givosiran dose will remain on that dose. Upon entry to the OLE period under amendment version 3, patients will cross over to receive a 1.25 mg/kg once monthly dose of givosiran. Starting at the Month 13 Visit (when 6 months of open-label givosiran dosing have been completed), patients in the 1.25 mg/kg monthly treatment group who experience inadequate disease control may have their monthly dose increased to 2.5 mg/kg givosiran upon discussion and agreement by the Investigator and medical monitor and demonstration of tolerability to givosiran and if ALA criteria are met. For further details, see Section 6.2.3.4.

Patients will undergo efficacy and safety assessments every 2 weeks for the first month of the OLE period and then monthly through Month 18, and every 3 months thereafter.

Sections containing related changes:

- Synopsis
- Table 1: Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6); *new footnote added*
- Table 2: Schedule of Assessments – Open-Label Extension Period: After Month 6 through Month 18; *new footnote added*
- Table 3: Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study; *new footnote added*
- Figure 2: Study Design; *revised figure to show 1.25 mg/kg dose*
- Section 1.3 Study Design Rationale

- Section 1.4 Dose Rationale
- Section 6.2.2.2 During the Open-Label Extension Period (After Month 6 through End of Treatment)
- Section 6.2.3 Dose Modifications
- Section 6.2.3.4 Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period
- Section 8.2.9 Other Analyses
-

Purpose: Add new section on dose escalation guidance for patients receiving the 1.25 mg/kg once monthly dose.

The primary change occurs in Section 6.2.3.4 Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period

Added text:

Starting at the Month 13 Study Visit (when 6 months of open-label givosiran dosing have been completed), patients receiving open-label givosiran at SC doses of 1.25 mg/kg monthly may be permitted to increase their monthly dose to 2.5 mg/kg based on Investigator judgement. Investigators may consider dose escalation if the following criteria are met:

- **Tolerability to givosiran at 1.25 mg/kg once monthly has been demonstrated based on no dose interruptions due to LFT elevations at the 1.25 mg/kg once monthly dose level (see Section 6.2.3.1) and no significant safety concerns due to other AEs that would preclude a patient from receiving a higher dose of givosiran as judged by the Investigator and Sponsor.**
- **Urine ALA levels (mmol/mol Cr) are not stably maintained ≤ULN or are inducible.**
- **Patient has inadequate clinical response (eg, breakthrough attacks or ongoing chronic symptoms), according to Investigator judgement.**

Urine ALA analyses may be conducted at a local laboratory or ALA results from previous visits may be evaluated in patients on the 1.25 mg/kg monthly dose in whom dose escalation to 2.5 mg/kg once monthly is being considered.

The decision to increase the givosiran dose from 1.25 mg/kg monthly to 2.5 mg/kg monthly will be discussed and agreed upon by the Investigator and medical monitor prior to initiation of the next dose.

Upon increase of the givosiran dose to 2.5 mg/kg monthly:

- **LFTs, INR, and TBL will be monitored every 2 weeks (±7 days) for the first month following the dose increase to 2.5 mg/kg, then monthly (±7 days or during the scheduled study visits) as per the Schedule of Assessments.**
- **Laboratory monitoring and dosing rules in response to LFT elevation will follow Table 4 guidelines.**
- **For patients in whom givosiran dosing is withheld due to elevated ALT, resumption of dosing may be considered based on the guidance in Section 6.2.3.1.1.**

Sections containing related changes:

- Synopsis
- Table 2: Schedule of Assessments – Open-Label Extension Period: After Month 6 through Month 18; *new footnote added*
- Table 3: Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study; *new footnote added*
- Section 4.1 Summary of Study Design
- Section 6.2.2.2 During the Open-Label Extension Period (After Month 6 through End of Treatment)
- Section 6.2.3 Dose Modifications
-

Purpose: Add guidance on evaluation of urine ALA in the context of dose escalation from the 1.25 mg/kg once monthly dose to the 2.5 mg/kg once monthly dose.

The primary change occurs in Section 7.3 Pharmacodynamic Assessments

Added text: **Urine ALA analyses may be conducted at a local laboratory or ALA results from previous visits may be evaluated in patients on the 1.25 mg/kg monthly dose in whom dose escalation to 2.5 mg/kg once monthly is being considered due to inadequate clinical response and who have demonstrated tolerability to givosiran. Dose escalation in patients on the 1.25 mg/kg once monthly dose can occur starting at Month 13. See Section 6.2.3.4 for further information on dose escalation.**

Sections containing related changes:

- Section 6.2.3.4 Dose Escalation Guidance for Givosiran from 1.25 mg/kg Once Monthly to 2.5 mg/kg Once Monthly in the Open-Label Period
- Table 8: Pharmacokinetic, ECG, and ADA Time Points for All Patients (Except Patients at East Asian Sites)

Purpose: Remove sensitivity analysis details and emphasize the statistical analysis plan for these details.

The primary change occurs in Section 8.2.5.1 Primary Endpoint

Deleted text: ~~A sensitivity analysis of the annualized event rates, without adjustment for the length of time in the treatment period, will also be conducted. Additional sensitivity~~**Sensitivity** analyses will be detailed in the SAP.

Section also containing this change:

- Synopsis

Purpose: Update analysis method from analysis of covariance (ANCOVA) to mixed effect model repeated measurement (MMRM) for full double-blind analysis of ALA and change from baseline in physical component summary (PCS) of SF-12

The primary change occurs in Section 8.2.5.2 Secondary Endpoints

Revised text:

For the analysis of urinary ALA-related endpoints, the ALA levels will be compared between treatment arms using ~~an analysis of covariance (ANCOVA) model with~~**a mixed-effects model repeated measures (MMRM) with baseline ALA as a continuous covariate and** fixed effect ~~of~~**terms including** treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), ~~and with the baseline ALA as a covariate~~**visit and treatment by visit interaction**. PBG-related endpoints will also be analyzed using this methodology.

Daily pain, nausea, and fatigue scores will be analyzed separately using the area under the curve (AUC) approach: the AUC over 6 months in the respective score will be calculated for each patient, and the mean AUC will be compared between treatment arms in an ANCOVA model. The change from baseline in PCS of SF-12 at 6 months will ~~also~~ be analyzed use an ~~ANCOVA~~**MMRM** model. Details ~~on the ANCOVA model for each continuous secondary endpoint and the covariates to be included~~ will be described in the SAP.

Sections containing related changes:

- Synopsis
- Section 8.2.10 Interim Analysis

Purpose: Change analysis method on durability of effect for interim analysis from ANCOVA to MMRM.

The primary change occurs in Section 8.2.10 Interim Analysis

Revised text:

To assess durability of the study drug in lowering and maintaining ALA level over time, the ~~ALA levels at 1 and 2 months of those patients who are included in the interim analysis will also be analyzed using the ANCOVA model described above.~~**overall treatment effect from Month 1 through Month 3 will be evaluated through a mixed effect model repeated measurement (MMRM).**

Sections also containing related changes:

- Synopsis
- Section 8.2.5.2 Secondary Endpoints

Purpose: In Table 8, increase the sample collection time windows, and for the new 1.25 mg/kg once monthly dose, add 4-hours postdose assessments of PK and Triplicate ECG for Months 6 and 12.

The primary change occurs in Table 8: Pharmacokinetic, ECG, and ADA Time Points for All Patients (Except Patients at East Asian Sites)

Revised :

In table, for months 0, 5, 6, and 12, corrected the timepoint 02:00 (±10 min) to become: 02:00 (±15 min)

02:00 (±~~10~~**15** min)

For months 6 and 12, also added the timepoint 04:00 (±15 min) in PK and Triplicate ECG column cells and new footnote specific to this timepoint.

04:00 (±15 min)[3]

Footnote:

[3]For patients receiving 1.25 mg/kg givosiran monthly (patients who received their first dose in the open-label extension period under protocol amendment version 3), additional blood samples for PK will be collected 4 hours post-dose at the Month 6 and Month 12 visits.

Sections containing related changes:

- Table 9: Pharmacokinetic, ECG, and Anti-Drug Antibody Assessment Time Points for Patients at East Asian Study Centers (Blood Samples)

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting, and apply administrative changes.

These changes are not listed individually.

ALN-AS1-003 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 26 JULY 2018

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Rationale for Protocol Amendment

Due to recent case reports of an increase in liver transaminases, the primary purpose for this protocol amendment is to:

- Require investigators to review predose liver function tests prior to study drug administration
- Implement a standard hepatic assessment panel if patients develop significant ALT elevation
- Provide specific guidance for rechallenge using a lower dose in patients whose ALT resolves after study drug dosing has been withheld due to ALT elevation
- Expand the medical history collection to include a specific inquiry into iron overload and other liver disease

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between the amendment 1 and amendment 2) are not detailed.

Table 1: Protocol Amendment 2 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Add clinical laboratory assessments so that assessments occus at each study visit in the open-label extension period
The primary change occurs in Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study
Revised text: Added "Xs" in row "Clinical Laboratory Assessments" at Month 19/20, Month 22/23, Month 25/26, Month28/29, Month31/32, and Month 34/35.
Purpose: Add that dose modification is allowed in response to elevated LFTs.
The primary change occurs in Section 6.2.3, Dose Modifications
Added text: No study drug dose modifications will be allowed, **except in response to LFT elevations as described in Section 6.2.3.1.**
Purpose: Specify additional hepatic assessments for patients who develop significant ALT elevation; simplify text (first sentence).
The primary change occurs in Section 6.2.3.1, Monitoring and Dosing Rules Based on Liver Function Test Results
Revised text: ~~LFT~~ **ALT, TBL, and INR** results ~~from the previous visit~~ should be reviewed **within 14** days prior to dosing. For any ALT elevation >3× ULN (or >3× baseline in patients with elevated baseline) or >300 U/L (whichever is lower), results should be confirmed by the central laboratory (within 2 to 3 days, but no greater than 7 days). **If such ALT elevations are confirmed, the additional hepatic assessments shown in Table should be obtained.** Subjects with abnormally elevated hepatic laboratory values (eg. ALT, AST, ~~total bilirubin~~ [TBL]~~,~~ ~~or international normalized ratio~~ INR) or signs/symptoms of hepatitis may meet criteria for withholding study drug. Criteria for withholding, monitoring and stopping study drug dosing are detailed in Table 4.
Section(s) also containing this change: • Section 1.5, Benefit-Risk Assessment

Purpose: Update monitoring and dosing rules for patients who develop significant ALT elevation; remove redundancy (footnote e)

The primary change occurs in Table 4: Monitoring and Dosing Rules in Patients with Alanine Transaminase (ALT) Elevations

Revised text:

ALT Transaminase Level	Patients with Normal Baseline ALT	Patients with Elevated Baseline ALT[a]
>3× to 5× ULN or Baseline	• Discontinue dosing when ALT is >3×ULN and patient is symptomatic[b] ~~with~~ **or has** TBL ≥2×ULN or INR >1.5 (for patients not on warfarin) **, and there is no alternative cause** • Otherwise, dosing may continue with monitoring every 2 weeks (±7 days) [c] that includes ~~hematology, biochemistry, LFT, and coagulation assessments~~**LFTs** per Table ~~6~~ **7 and INR** • If the ALT elevation persists for ≥2 **months,** discussion with the medical monitor is required before continuing dosing.	• Discontinue dosing when ALT is >3× baseline or >300 U/L (whichever is lower) and patient is symptomatic[b], ~~with~~ **or has** TBL >2×ULN or INR >1.5 (for patients not on warfarin)**, and there is no alternative cause** • Otherwise, dosing may continue with monitoring every 2 weeks (±7 days) [d] that includes ~~hematology, biochemistry, LFT, and coagulation assessments~~**LFTs** per Table ~~6~~ **7 and INR** • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing
>5× to 8× ULN or Baseline	• Discontinue dosing when ALT >5× to 8× ULN and patient is symptomatic[b] ~~with~~ **or has** TBL ≥2×ULN or INR >1.5 (for **patients not on warfarin) and there is no alternative cause** • **For patients ~~not on warfarin)~~who are asymptomatic and do not have INR >1.5 or TBL ≥2x ULN:** ~~Holde~~**Hold** dosing if ALT >5×ULN, until ALT recovers to ≤2×ULN	• Discontinue dosing when ALT >5× to 8× baseline or >300 U/L (whichever is lower) and patient is symptomatic[b] ~~with~~ **or has** TBL ≥2×ULN or INR >1.5 (for patients not on warfarin) **and there is no alternative cause** • **For patients who are asymptomatic and do not have INR >1.5 or TBL ≥2x ULN:** ~~Holde~~**Hold** dosing if ALT >5×baseline or >300 U/L (whichever is lower), until ALT recovers to ≤2×baseline

	Dosing can be resumed when ALT recovers to ≤2 x ULN according to Section 6.2.3.1.1, and following discussion with the medical monitor • Perform weekly (±3 days) monitoring~~, including hematology, biochemistry, and coagulation~~ of LFTs per Table ~~6~~ 7 and INR until ALT declines to ≤3×ULN; then monitor every 2 weeks (±7 days) until ALT level reaches 2×ULN[c] • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.	**Dosing can be resumed when ALT recovers to ≤2 x baseline according to Section 6.2.3.1.1, and following discussion with the medical monitor** • Perform weekly (±3 days) monitoring~~, including hematology, biochemistry, and coagulation~~ of LFTs per Table ~~6~~ 7 and INR until ALT declines to ≤3×baseline; then monitor every 2 weeks (±7 days) until ALT level reaches 2× baseline[d] • If the ALT elevation persists for ≥2 months, discussion with the medical monitor is required before continuing dosing.

~~c After dosing is held, once ALT has decreased to ≤2×ULN or ≤2×baseline (whichever is higher), re-dosing may be considered. In patients with normal baseline ALT, permanently discontinue dosing if ALT increases to >5×ULN following repeat dosing. In patients with elevated baseline ALT, permanently discontinue dosing if ALT increases to >5×baseline or >300 U/L (whichever comes first) following repeat dosing.~~

Purpose: Clarify that samples are collected for analyses at the central laboratory.

The primary change occurs in Section 6.2.3.1, Monitoring and Dosing Rules Based on Liver Function Test Results

Revised text: For ALT, ~~AST, PT/INR~~TBL, and ~~TBL~~INR testing, local laboratory results may be used to inform dosing decisions; however, parallel samples should be ~~confirmed~~**collected for analysis** at the central laboratory.

Purpose: Add a standard hepatic assessment panel for patients who develop significant ALT elevation

The primary change occurs in (new) Table 5: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Added text:

Table 5: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Hematology	
CBC with differential	
Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	**Herpes Zoster Virus IgM, IgG**
HIV 1 and 2[a]	**HHV-6**
Cytomegalovirus antibodies, IgM, IgG	**HBs Ag, HBc antibody IgM and IgG**
Anti-nuclear antibodies	**Epstein-Barr Virus antibodies, IgM and IgG**
Anti-smooth muscle antibodies	**Anti-mitochondrial antibodies**
HCV antibody	**HAV antibody IgM**
HCV RNA PCR – qualitative and quantitative	**HEV antibody IgM**
CPK	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	**Alcohol consumption**
Other potentially hepatotoxic agents including any work-related exposures	**Recent travels to areas where hepatitis A or E is endemic**

Abbreviations: AAT=alpha-1 antitrypsin; anti-LKM=anti-liver-kidney microsomal antibodies; CBC=complete blood count; CPK=creatine phosphokinase; CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA=soluble liver antigen; TSH=thyroid-stimulating hormone

Note:

- **All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.**
- **Additional samples may be collected for assessment of potential alternative causes of liver injury, which may include AAT, ceruloplasmin, acetaminophen/paracetamol levels, anti-LKM antibodies, toxicology screen, ferritin, parvovirus B19, anti-SLA antibodies, gamma-globulins (including IgE and IgG levels), and transferrin saturation, as clinically indicated.**

[a] HIV testing will not be performed where prohibited by local regulations.

Purpose: Add specific guidance for rechallenge in patients who meet criteria after dose interruption

The primary change occurs in Section 6.2.3.1.1, Criteria for Rechallenge of Givosiran After Being Withheld for ALT Elevation

Added text:

For patients in whom givosiran dosing is withheld due to elevated ALT, resumption of dosing may be considered using the following guidelines:

- **Patients who did not meet criteria for study drug discontinuation per Table 4 may be considered for rechallenge following consultation with the medical monitor and resolution of ALT to ≤ 2x ULN or ≤ 2x baseline (for patients who had elevated baseline ALT)**
- **The decision to rechallenge the patient should be discussed and agreed upon by the patient, Investigator, and medical monitor**
- **The rechallenge regimen is a reduced dose of 1.25 mg/kg monthly:**

  LFTs and INR will be monitored every 2 weeks (±7 days) for the first month, then monthly (±7 days or during the scheduled study visits) as per the Schedule of Assessments

  Laboratory monitoring and dosing rules in response to LFT elevation will follow Table 4 guidelines

  If dose withholding rules per Table 4 are met on this dose, permanently discontinue dosing
- **Dose re-escalation to 2.5 mg/kg monthly may be considered if the following criteria are met:**

  Approval by the medical monitor after at least 3 doses of 1.25 mg/kg monthly for patients who meet both criteria below:

  - **Patient has not met dose withholding or discontinuation rules per Table 4 during treatment with 1.25 mg/kg monthly**
  - **Patient has inadequate control of porphyria symptoms on the 1.25 mg/kg monthly regimen, per investigator's assessment**

Added text (continued):

LFTs and INR will be monitored every 2 weeks (±7 days) for the first month after dose re-escalation, and then monthly as per the Schedule of Assessments

If a patient experiences a second dose hold due to LFT elevation while on 2.5 mg/kg monthly:

- **Follow Table 4 guidelines for monitoring and evaluations**
- **If ALT resolves to ≤2x ULN, redosing with 1.25 mg/kg monthly may be considered if this dose was previously tolerated and there is approval by the Alnylam medical monitor. If dosing is resumed, follow the guidance above for rechallenge regimen regarding laboratory monitoring and dosing rules. No subsequent escalation to 2.5 mg/kg monthly will be allowed**
- **LFTs and INR will be monitored every 2 weeks (±7 days) for the first month after dose resuming 1.25 mg/kg, and then monthly as per the Schedule of Assessment**

Purpose: Add that local laboratory results may be used to inform dosing decisions and clarify that samples are also to be collected for analyses at the central laboratory.

The primary change occurs in Section 6.2.3.2, Monitoring and Dosing Rules Based on Lipase and Amylase Results

Revised text

Lipase and amylase results~~from the previous visit~~ should be reviewed prior to dosing.

...For lipase and amylase testing, local laboratory results may be used to inform dosing decisions; however, parallel samples should be ~~confirmed~~ **collected for analysis** at the central laboratory.

Section(s) also containing this change:

- Section 1.5, Benefit-Risk Assessment

Purpose: Provide details that information on iron overload and other liver diseases are included in the collection of medical history.

The primary change occurs in Section 7.1, Screening Assessments

Added text:

Medical history collected will incorporate the patient's porphyria history, including their typical attack characteristics, triggers, and treatment, as well as central venous access history**, iron overload history, and prior liver disease history.**

Section(s) also containing this change:

- Table 1, Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6); footnote c

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Purpose: Add that investigators must review predose liver function tests within 14 days prior to study drug administration, which can be from a local laboratory. Clarify that additional samples are also collected for central laboratory analysis

The primary change occurs in Section 7.5.5, Clinical Laboratory Assessments

Added text: **ALT, TBL, and INR collected within 14 days prior to dosing must be reviewed by the Investigator before study drug administration. Locally analyzed results may be reviewed to inform dosing decisions, but additional samples for central analysis must also be collected on the day of dosing prior to the dose administration.**

Section(s) also containing this change:

- Table 1, Schedule of Assessments – Screening and 6-Month Treatment Period (Screening through Month 6); footnote j
- Table 2, Schedule of Assessments – Open-Label Extension Period: After Month 6 through Month 18; footnote f
- Table 3, Schedule of Assessments for Open-Label Extension Period: Month 19 through End of Study (EOS), footnote f
- Section 6.2.2, Dose and Administration

Purpose: Corrected punctuation, grammar, and formatting.

These changes are not listed individually.

ALN-AS1-003 Protocol Amendment 1

Summary of Changes (dated 04 May 2018) compared to Original Protocol (06 September 2017)

ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Rationale for Protocol Amendment

The purpose of the amendment is to:

- Include clinical data on a single case of anaphylactic reaction, information regarding the potential risk for anaphylactic reactions, and provide updated guidance for dosing and monitoring for anaphylactic reactions. The event of anaphylactic reaction was previously reported to applicable regulatory authorities and Institutional Review Boards/Ethics Committees.
- Add two quality of life measures:
  - Patient Global Impression of Change (PGIC) at Months 6 and 12
  - Porphyria Patient Experience Questionnaire (PPEQ) at Months 6, 12, 18, and 24.
- Update guidance and procedures on patient withdrawal from study.
- Clarify that ALA/PBG levels measured during screening are acceptable for use as entry criteria
- provide the following additional clarifications:
  - predose samples (not restricted to 60 minutes before dosing),
  - interim analysis for sample size reassessment is blinded
  - definition of sexual abstinence
  - contraception with an intrauterine hormone-releasing system also requires use of a barrier method

A detailed summary of the changes is provided in Table 1. Corrections to typographical errors formatting, and aligning text between sections, and other minor updates are not outlined in the table.

Table 1: Protocol Amendment 1 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in the protocol amendment are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Provide details of an anaphylactic reaction reported in Study ALN-AS1-002

The primary change occurs in Section 1.2.2.2 - Phase 1/2 Open-label Extension Study ALN-AS1-002

Added text: In addition, one patient in the 2.5 mg/kg monthly dose group with a history of asthma and multiple allergies experienced an SAE of anaphylactic reaction that was determined by the Investigator to be definitely related to study drug given the temporal relationship of givosiran treatment to the onset of the reaction (within minutes). The patient was treated and recovered and was discontinued from the study.

Section(s) also containing this change

- Section 1.5 Benefit-Risk Assessment

Purpose: Correct that patients will receive open-label givosiran for up to 29 months rather than up to 30 months. The final month is a post-dose observation period. This is not a change to the Schedule of Assessments.

The primary change occurs in Section 1.3 - Study Design Rationale

Now reads: The endpoints will be evaluated against a placebo comparator for the first 6 months of the study (the double-blind treatment period); after this, all patients will receive open-label givosiran for up to an additional ~~30~~ **29** months in the extension portion of the study.

Section(s) also containing this change

- Synopsis: Study Design
- Section 4.1: Summary of Study Design

Purpose: Add anaphylactic reaction to givosiran potential risks

The primary change occurs in Section 1.5 - Benefit-Risk Assessment

Now reads:

Further details on the nonclinical results and safety results for Study ALN-AS1-001 can be found in the givosiran IB. Given the biological target of givosiran, the available nonclinical and clinical data, and the mode of administration, other potential **important** ~~**theoretical**~~ risks include ~~**the risk of severe or serious**~~ injection site reactions (ISRs), liver transaminase abnormalities, pancreatitis**, and anaphylactic reaction**. A summary of preliminary clinical data from ongoing Phase 1 and Phase 1/2 studies of givosiran can be found in Section 1.2.2 and in the givosiran IB.

This clinical protocol includes exclusion criteria intended to minimize the risk of transaminitis, ISR and pancreatitis, and also incorporates ongoing monitoring for elevated transaminases, serum lipase, **and anaphylactic reaction (Section 6.2.3)**.

Purpose: Clarify that other medications may be considered in the definition of porphyria attack

The primary change occurs in Section 3.5 Definition of Porphyria Attacks

Added text:

requires treatment with IV dextrose or hemin, carbohydrates, or analgesics (opioid [synthetic and non-synthetic substances] or non-opioid)**, or other medications such as antiemetics,** at dose or frequency beyond the patient's usual daily porphyria management

Purpose: Clarify that this study may be replaced with a post-marketing study in regions that receive marketing authorization for givosiran

The primary change occurs in Section 4.1 Summary of Study Design

Added text:

Where required by local regulations, this trial may be replaced with a post-marketing clinical trial once marketing authorization for givosiran is received.

Purpose: Clarify that documented PBG or ALA elevations measured during screening are acceptable for use as entry criteria

The primary change occurs in Section 5.1 Inclusion Criteria #2

Added Text: at least one documented urinary or plasma PBG or ALA value ≥4× upper limit of normal (ULN) within the past year prior to or during Screening.

Purpose: Update inclusion regarding informed consent to clarify handling of consent for patients under legal age to consent

The primary change occurs in Section 5.1 Inclusion Criteria #7

Now reads: Be willing and able to comply with the study requirements and to provide written informed consent per local and ~~assent~~ **national requirements**. In the case of patients under the age of legal consent, ~~per local and national requirements~~ **legal guardian(s) must provide written informed consent and the patient should provide assent per local regulations and institutional standards.**

Purpose: Changed timing for planned surgery exclusion so it was not too restrictive for the target patient population

The primary change occurs in Section 5.2 Exclusion Criteria #11

Now reads: Has ~~planned elective~~ **a** major surgery ~~scheduled to occur~~ **planned** during the ~~study~~ **first 6 months of the study**.

Purpose: Updated section title and wording to reflect current Company language

The primary change occurs in Section 5.3 Discontinuation of Study Drug and/or Study (new title)

Now reads:

Patients or their legal guardians (in the case that the patient is a minor) are free to discontinue ~~study drug~~ treatment **and/or study** or withdraw ~~from the study~~ **their consent** at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or ~~withdrawal from~~ **of** the study must be fully documented in the electronic case report form (eCRF), and should be followed up by the Investigator. The Investigator may withdraw a patient **from the study** at any time if this is considered to be in the patient's best interest.

~~Procedures for the discontinuation~~**Discontinuation** of study drug and withdrawal from the study are described in Section 5.3.1 and Section 5.3.2 ~~respectively.~~ **, respectively. If a patient stops participation from the study or withdraws consent from the study, he/she will not be able to re-enroll in the study**

Purpose: Updated to clarify options for patients who prematurely discontinue study drug and to align protocol text with sample Informed Consent Form.

The primary change occurs in Section 5.3.2 Discontinuation from the Study

Now reads:

~~A patient may withdraw from the study at any time.~~ **A patient or their legal guardian may decide to stop the patient's participation in the study at any time. Patients considering to stop the study should be informed that they can discontinue treatment and complete study assessments including follow-up, as per the SOA, or alternatively may complete any minimal assessments for which the patient consents. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.**

However, study integrity and interpretation is best maintained if all randomized patients continue study assessments and follow-up. ~~Patients considering withdrawing from the study should be informed that they can discontinue treatment and complete their study assessments through the 6-month visit, including follow-up. If a patient still chooses to withdraw from the study prior to the completion of the 6-month treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the 6-month visit (see).~~

Stopping study participation could mean:

- **If a patient stops participation during the 6-month treatment period, they should be informed that they can discontinue treatment, but continue to complete their study assessments through the 6-month visit, including follow-up.**
- **If a patient stops participation during the open-label extension period, they should be asked to return for an Early Termination Visit as well as a Safety Follow-Up Visit 3 months after their last dose of study drug.**
- **A patient can stop taking the study drug and stop study-related visits, but allow the investigator and study team to review the patient's medical records, public records or be contacted in order to receive information about the patient's health**

When a patient ~~withdraws from~~**stops** the study, the ~~primary~~**discontinuation and** reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient ~~withdraws~~**stops the study** due to an adverse event (AE), including an SAE, the AE should be followed as described in Section 7.5.6.

If the patient wants to stop participation in the study, he/she should notify the study doctor in writing or in any other form that may be locally required. The personal data already collected during the study,

including patient's biological samples, will still be used together with the data collected on other patients in the study according to the informed consent and applicable laws.

In addition to stopping participation in the study, the patient could decide to withdraw his/her consent as explained in Section 5.3.3.

Purpose: New section added to discuss withdrawal of consent

The primary change occurs in Section 5.3.3 (new section) Withdrawal of Consent to Collect and Process the Patient's Personal Data

New text:

The patient may decide to withdraw his/her consent informing the study doctor at any time in writing, or in any other form that may be locally required. This means that the patient wants to stop participation in the study and any further collection of his/her personal data.

- The sponsor will continue to keep and use a patient's study information (including any data resulting from the analysis of the patient's biological samples until time of withdrawal) according to applicable law. This is done to guarantee the validity of the study, determine the effects of the study treatment, and ensure completeness of study documentation.
- The patient can also request that collected samples be destroyed or returned (to the extent it is permitted by applicable law) at any time.
- Patients who withdraw their consent to collect and use personal data should understand that public records may be reviewed to determine the patient's survival status as allowed per local and national regulations.

In US and Japan, otherwise, samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of the protocol and of the informed consent form.

In EU and rest of world, in any event, samples not yet analyzed at the time of withdrawal will not be used any longer, unless permitted by applicable law. They will be stored or destroyed according to applicable legal requirements.

Purpose: Provide guidance on monitoring and management of potential anaphylactic reactions due to study drug
(Note: no changes to the schedule of assessments regarding visits conducted at the study center vs. other locations were made in the amendment)

The primary change occurs in Section 6.2.2 Dose and Administration

Revised text:

Givosiran will be administered by a qualified and authorized ~~staff at the study center. In the event that a patient is unable to come to the study center for a scheduled clinical study visit~~, **health care professional trained in the recognition and management of anaphylactic reactions. The study drug should be injected into the abdomen or upper arms or thighs. Detailed instructions for study drug administration are presented in the Pharmacy Manual. As is consistent with good medical practice for subcutaneous drug administration, patients will be observed for a minimum of 20 minutes after each injection. Treatment for anaphylactic reactions should be readily available where patients are being dosed, and follow country and/or local hospital treatment** guidelines.[25]

Study drug administration may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor~~. For,~~ **during** particular **study** visits, as specified in the Schedules of Assessments (Table 2 and), ~~dosing may also be performed~~Table 3). **However, study drug administration** at ~~a location other than~~the study center should be ~~by a qualified home healthcare professional where applicable country and local regulations and infrastructure allow. The study drug~~ should be ~~injected into~~**considered for patients who have ongoing study drug-related AEs or known risk factors for developing anaphylactic reactions, including but not limited to: a prior history of an anaphylactic reaction to food, medications or unknown etiology, worsening injection site reactions with repeat dosing, or anyone in** the ~~abdomen or upper arms or thighs. Patients must demonstrate that they can tolerate dose~~opinion of the **investigator that would benefit from clinical observation following** dosing. ~~at a location other than the study center is permitted~~.

Section(s) also containing similar or related changes

- Section 6.2.3.3 (new section) Monitoring and Dosing Rules in Patients with Potential Anaphylactic Reactions

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Purpose: clarify that Month 6 ALA and PBG assessments (at the end of the double-blind period) must be completed prior to administration of the first open-label dose of givosiran

The primary change occurs in Section 6.2.2.1 During the 6-Month Treatment Period (Day 1 to Month 6)

Added text: At the Month 6 study visit, following the completion of all Month 6 assessments, **including the urine sample for ALA and PBG levels** (to end the double-blind period), patients will be administered their first open-label (unmasked) dose of givosiran to begin their participation in the open-label extension portion of the study.

Purpose: Add guidance and procedures for management of potential cases of anaphylactic reaction

Added text: An anaphylactic reaction is a severe, potentially fatal, systemic allergic reaction with acute onset (minutes to hours). For reference see Section 11.3.

Stop administering the study medication immediately if an anaphylactic reaction to the study medication is suspected. Study medication must be permanently discontinued in patients for whom an anaphylactic reaction is assessed as related to the study medication.

Laboratory testing: Obtain blood sample for tryptase, total IgE, and ADA antidrug antibodies (ADA), ideally within 15 minutes to 3 hours after the onset of a suspected anaphylactic reaction; however, up to 6 hours is acceptable. An additional blood sample to assess tryptase, total IgE, and ADA should be obtained between 1 to 2 weeks from onset of event. Local laboratory may be used to analyze samples; however, parallel samples should be sent to the central laboratory for analysis. Sample collection and shipping instructions are included in the Laboratory Manual.

Reporting: The PI or designee must notify the sponsor or designee within 24 hours of the occurrence of a suspected case of anaphylactic reaction or being informed of the case as required for AEs of Clinical Interest (AECI) and SAEs, per AE reporting requirements (Sections 7.5.6.1 through Section 7.5.6.3).

Section(s) also containing similar or related changes

- Section 7.5.5.1 Immunogenicity
- Section 7.5.6.1 Definitions, Adverse Events of Clinical Interest
- Section 10 List of References
- Section 11.3 Anaphylactic Reactions

Purpose: Revised definition of sexual abstinence to align with current standards and clarified that intrauterine hormone releasing system is a method requiring a barrier method

The primary change occurs in Section 6.4 Contraceptive Requirements

Now reads	Sexual abstinence, when **this is** in line with the preferred and usual lifestyle of the patient, **is considered an acceptable method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug (defined above).** Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not ~~acceptable methods of contraception.~~ **considered sexual abstinence and do not meet criteria for an acceptable method of birth control. As determined by the investigator, the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient**. Abstinent patients must agree to use 1 of the abovementioned contraceptive methods if they start ~~sexual relationships~~ **a heterosexual relationship** during the study and **continue to do so** for ~~3 months after their last dose administration.~~ **the entire period of risk associated with the study drug (defined above).**
Now reads	Established use of oral, implantable, injectable, ~~or~~ transdermal hormonal, **or intrauterine hormone-releasing system as** methods of contraception: Women of child-bearing potential using hormonal methods of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]). See Section 6.3 and Section 11.2.

Purpose: Clarify requirements PBG or ALA elevations during Screening

The primary change occurs in Section 7.1 Screening Assessments

Added text:	If required, ALA/PBG levels collected during the screening period for eligibility purposes should be analyzed locally.

Purpose: Clarify eDiary completion requirements during Screening

The primary change occurs in Section 7.2.2 Pain and Pain-Related Assessments

Added text:	During the screening period, there should be a minimum of 4 entries completed on days when the patient is not having an attack.

Purpose: Included an additional Quality of Life assessments

The primary change occurs in Section 7.2.4 Quality of Life (QOL)

Added text:

- PGIC: The Patient Global Impression of Change (PGIC) is one question answered according to a 7-point scale (ranging from very much improved to very much worse) for the assessment of a patient's perceived overall health status change since the beginning of the study. This questionnaire takes approximately 2 to 3 minutes to complete.
- PPEQ: The Porphyria Patient Experience Questionnaire (PPEQ) is a set of questions to assess treatment experience and impacts to the patient's life not collected by the other QOL assessments.

Section(s) also containing similar or related changes

- Table 1 and Footnotes to Table 1: Schedule of Assessments
- Table 2 and Footnotes to Table 2: Schedule of Assessments
- Table 3 and Footnotes to Table 3: Schedule of Assessments
- Section 2.3: Exploratory Objectives
- Section 3.3: Exploratory Endpoints

Purpose: to update the guidance on weight collection for dosing calculations

The primary change occurs in Section 7.5.2- Weight and Height

Added text:

Body weight **either** at the previous study center visit ~~where weight is collected will~~ **or current study center visit may** be used for dosing calculations.

Section(s) also containing similar or related changes

- Footnotes to Table 1: Schedule of Assessments
- Footnotes to Table 2: Schedule of Assessments
- Footnotes to Table 3: Schedule of Assessments

Purpose: Added anaphylactic reactions to list of Adverse Events of Clinical Interest

The primary change occurs in Section 7.5.6.1 Definitions

Added text: Anaphylactic Reactions. An anaphylactic reaction is a severe, potentially fatal, systemic allergic reaction with acute onset (minutes to hours). Symptoms of an anaphylactic reaction may include skin or mucosal tissue (e.g. generalized hives, pruritus, angioedema), respiratory compromise (e.g. wheezing, bronchospasm, hypoxia), reduced blood pressure or associated symptoms (e.g. syncope, hypotonia). See Section 11.3 for guidance on diagnosing anaphylactic reactions. [26]

Purpose: Updated details of statistical analyses for biomarkers

The primary change occurs in Section 8.2.5.2 Secondary Endpoint

Now reads: For the analysis of urinary ALA-related endpoints, the ALA levels will be compared between treatment arms using an analysis of covariance (ANCOVA) model **with fixed effect of treatment arms, stratification factors for AIP patients (prior hemin prophylaxis status and historical attack rates), and** with the baseline ALA as a covariate. PBG-related endpoints will also be analyzed using this methodology.

Section(s) also containing similar or related changes

- Section 8.2.10: Interim Analysis

Purpose: removed the prespecified window for predose sampling time for all urine PK, PD and ADA assessments

The primary change occurs in Section 11 Pharmacokinetic/Pharmacodynamic Assessment Time Points Table 7 (Pharmacokinetic, ECG, and ADA Time Points for All Patients [Except Patients at East Asian Sites]),

Now reads: Predose ~~(within 60 minutes before dosing)~~

Section(s) also containing similar or related changes

- Table 8 (Pharmacokinetic, ECG, and Anti-Drug Antibody (ADA) Assessment Time Points for Patients at East Asian Study Centers [Blood Samples])
- Table 9 (Urine Pharmacokinetic/Pharmacodynamic Time points for Patients at East Asian Study Centers)

Purpose: Add guidance for diagnosing anaphylactic reactions

The primary change occurs in Section 11.3 (new section) Anaphylactic Reactions

Added text:

Table 2 Sampson Criteria for Anaphylactic Reactions

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours)
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to and less than 90 mm Hg from 11 to 17 years.

Adapted from Sampson et al. 2006 [26]