Clinical trial results:
A Multicenter, Open-label Extension Study to Evaluate the Long-term Safety and Clinical Activity of Subcutaneously Administered ALN-AS1 in Patients with Acute Intermittent Porphyria who have Completed a Previous Clinical Study with ALN-AS1

Summary

EudraCT number	2016-002638-54
Trial protocol	SE GB
Global end of trial date	05 November 2021

Results information

Result version number	v1 (current)
This version publication date	21 November 2022
First version publication date	21 November 2022

Trial information

Trial identification

Sponsor protocol code	ALN-AS1-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02949830
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, United States, 02142
Public contact	Clinical Trial Information Line, Alnylam Pharmaceuticals Inc, + 8772569526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals Inc, +1 8772569526, clinicaltrials@alnylam.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine the long-term safety, tolerability and pharmacokinetics of givosiran (ALN-AS1) in AIP patients who completed study ALN-AS1-001.

Protection of trial subjects:

The Investigator ensured that each patient was provided full an adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. The patient was also notified that they were free to discontinue the study at any time. The patient was given the opportunity to ask questions and was allowed time to consider the information provided. The patient's signed and dated IRB/IEC-approved informed consent was obtained before any study procedures were conducted. The Investigator maintained the original signed ICF, and a copy was given to the patient. All active patients signed an updated ICF if revisions were made to the ICF during the course of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	16
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with acute intermittent porphyria (AIP) were enrolled at five sites in Sweden, United Kingdom and the United States.

Pre-assignment

Screening details:

Patients who completed parent study ALN-AS1-001 (NCT02452372) and met all eligibility criteria for this study (ALN-AS1-002) were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Givosiran

Arm description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

Arm type	Experimental
Investigational medicinal product name	Givosiran
Investigational medicinal product code	
Other name	GIVLAARI, ALN-AS1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

Number of subjects in period 1	Givosiran
Started	16
Completed	14
Not completed	2
Adverse event, non-fatal	1
Withdrawal by Subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Givosiran
Reporting group description:	
At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.	

Reporting group values	Givosiran	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	37.4		
standard deviation	± 12.0	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	2	2	
Race Units: Subjects			
Asian	1	1	
Black or African American	2	2	
White	13	13	
Ethnicity Units: Subjects			
Not Hispanic or Latino	15	15	
Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Givosiran

Reporting group description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

Primary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)[1]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigational patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Statistical Analysis Set (SAS): All patients who received any amount of study drug.

End point type	Primary

End point timeframe:

Through Month 49

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As unit is percentage of participants, no statistical analysis is needed.

End point values	Givosiran			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of participants				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) as Measured by Percent Decrease From Baseline

End point title	The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) as Measured by Percent Decrease From Baseline

End point description:

The PD effect of givosiran was evaluated by spot urine ALA levels normalized to spot urine creatinine levels.

Patients from the PD Analysis Set (all patients who received any amount of study drug and who had at least 1 post-dose blood sample for PD), who were treated with givosiran 2.5 mg/kg SC injection QM. Values that occurred during a porphyria attack were excluded as a means of controlling for potential confounding by hemin. Overall number of participants analyzed is the number of participants available at the given time point.

End point type	Secondary

End point timeframe:

Baseline; Month 48

End point values	Givosiran			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent decrease				
arithmetic mean (standard error)	92.531 (± 1.879)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) as Measured by Percent Decrease From Baseline

End point title	The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) as Measured by Percent Decrease From Baseline

End point description:

The PD effect of givosiran was evaluated by spot urine PBG levels normalized to spot urine creatinine levels.

Patients from the PD Analysis Set (all patients who received any amount of study drug and who had at least 1 post-dose blood sample for PD), who were treated with givosiran 2.5 mg/kg SC injection QM. Values that occurred during a porphyria attack were excluded as a means of controlling for potential confounding by hemin. Overall number of participants analyzed is the number of participants available at the given time point.

End point type	Secondary

End point timeframe:

Baseline; Month 48

End point values	Givosiran			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percent decrease				
arithmetic mean (standard error)	94.194 (± 2.617)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Composite Porphyria Attacks

End point title	Annualized Rate of Composite Porphyria Attacks

End point description:

Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs, no other medically determined cause, and required treatment with intravenous (IV) dextrose or hemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. Composite porphyria attacks included porphyria attacks that required hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home. The annualized attack rate (AAR) was calculated as the number of composite porphyria attacks/total person-years.

SAS: All patients who received any amount of study drug.

End point type	Secondary

End point timeframe:

Through Month 48

End point values	Givosiran			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: annualized attack rate				
arithmetic mean (standard error)	0.4 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Annualized Days of Hemin Use

End point title	Percent Change in Annualized Days of Hemin Use

End point description:

The percent change in hemin use was calculated as the mean annualized days of hemin use during the study compared with the mean annualized days of hemin use during the Run-in Period. A negative change from Baseline indicates a reduction in annualized days of hemin use.

End point type	Secondary

End point timeframe:

Through Month 49

End point values	Givosiran			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent change				
number (not applicable)	-97.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs with onset after first administration of study drug through end of exposure, or any AE that was present at Baseline but worsened in severity or subsequently considered drug-related by the Investigator (up to approximately 52 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Givosiran

Reporting group description:

At the beginning of this study, participants received either givosiran 2.5 mg/kg subcutaneous (SC) injection once monthly (QM), givosiran 5.0 mg/kg SC injection QM, or givosiran 5.0 mg/kg SC injection once every 3 months (Q3M). Within a year, all participants were transitioned to givosiran 2.5 mg/kg SC injection QM.

Serious adverse events	Givosiran		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Synovitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis bacterial			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Givosiran		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Superficial vein prominence			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Chills			

subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Discomfort				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Facial pain				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Fatigue				
subjects affected / exposed	7 / 16 (43.75%)			
occurrences (all)	12			
Feeling abnormal				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injection site bruising				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injection site discolouration				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	9			
Injection site dryness				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injection site erythema				
subjects affected / exposed	6 / 16 (37.50%)			
occurrences (all)	29			
Injection site indentation				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injection site pain				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Injection site pruritus				
subjects affected / exposed	4 / 16 (25.00%)			
occurrences (all)	11			
Injection site rash				

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
Injection site swelling			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	6		
Injection site urticaria			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Drug hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Oral allergy syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Seasonal allergy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Menorrhagia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	16		
Metrorrhagia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oligomenorrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Allergic bronchitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Asthma			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	7		
Pharyngeal erythema			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Attention deficit hyperactivity disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Panic attack			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
Albumin urine present			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Anticoagulation drug level below therapeutic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
Bilirubin conjugated increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood bilirubin increased			

subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Blood homocysteine increased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Blood sodium decreased				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
C-reactive protein increased				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Carbon dioxide increased				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Coronavirus test positive				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Creatinine urine increased				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Gamma-glutamyltransferase increased				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	3			
Glomerular filtration rate decreased				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	7			
International normalised ratio increased				
subjects affected / exposed	4 / 16 (25.00%)			
occurrences (all)	5			
Lipase increased				

subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Liver function test increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Protein urine present			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Prothrombin level increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Urine ketone body present			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Urine output decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Humerus fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Procedural pain			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Venomous sting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Dysaesthesia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	19		
Hypoaesthesia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	10		
Neuropathy peripheral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Tremor			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutrophilia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Eye pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Swelling of eyelid			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	19		
Abdominal pain lower			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Irritable bowel syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 16 (50.00%)		
occurrences (all)	26		
Stomatitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Teething			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Angioedema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Palmar erythema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Skin ulcer			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Renal impairment			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	9		
Costochondritis			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	6		
Neck pain			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Pain in jaw			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		

Folliculitis				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	4 / 16 (25.00%)			
occurrences (all)	4			
Gastroenteritis viral				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
Nasopharyngitis				
subjects affected / exposed	8 / 16 (50.00%)			
occurrences (all)	17			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Skin infection				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	3			

Varicella subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Gluten sensitivity subjects affected / exposed occurrences (all) Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 14 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2016	Amendment 1 - The primary purpose for this protocol amendment is to clarify that based on review of data from the ongoing ALN-AS1-001 study, the Safety Review Committee (SRC) has determined the study starting dose and dosing regimen for administration in study ALN-AS1-002 is to be 5.0 mg/kg administered every 3 months. Additionally, minor changes were made to schedules of assessment to increase consistency and clarity.
01 December 2016	Amendment 2 - The primary purpose of this amendment is to implement additional safety monitoring; specifically to require lipase monitoring and review of recent clinical laboratory results prior to dosing. These changes are being made in accordance with the study's Safety Review Committee recommendation pursuant to an unlikely related SAE of hemorrhagic pancreatitis with fatal outcome. Additionally, out of date text describing the nonclinical and clinical experience with ALN-AS1 has been removed and replaced with a reference to the current Investigator's Brochure, which has been updated to include a description of the aforementioned unlikely related fatal SAE.
03 February 2017	Amendment 3 - The purpose of this amendment is to update the risk-benefit assessment of the study protocol to align with the current Investigator's Brochure, to add regular monitoring of prothrombin time (PT), International Normalized Ratio (INR), and c-reactive protein (CRP), and to clarify the timing of the review of clinical laboratory assessments prior to scheduled dosing.
02 August 2017	Amendment 4 - This protocol is being amended to update the electrocardiogram (ECG) assessments to obtain triplicate 12-lead ECGs using central equipment and paired with plasma PK at times corresponding to nominal maximum concentration (Cmax). Also, Schedule of Assessments footnotes and related text were updated to define the visit range in which previously noted predose interpretation of hematology, coagulation, and chemistry test results are required.

03 May 2018	Amendment 5 - 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. The event of anaphylactic reaction was previously reported to applicable regulatory authorities and Institutional Review Boards/Ethics Committees. Benefit-Risk Assessment modified to align with potential risks in the Investigator's Brochure. Information on reproductive health moved to Contraceptive Requirements and cytochrome P450 (CYP) inhibition moved to Concomitant Medications. Update guidance and procedures on patient withdrawal from study. Schedule of Assessments footnotes were updated to: Update end of study visit, early termination visit, and safety follow-up visit timing and assessments. Clarify clinical laboratory testing required prior to dosing. Clarify timing of ECG assessments for patients administered ≤ 2.5 mg/kg and >2.5 mg/kg ALN-AS1 provide the following clarifications: o patient withdrawal details regarding subsequent visits and data collection o definition of sexual abstinence o contraception with an intrauterine hormone-releasing system also requires use of a barrier method
28 May 2019	Amendment 6 - 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 acute intermittent porphyria (AIP) patients who are asymptomatic high excreters in the concomitant medications section. The results of the study indicated that ALN-AS1 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. This amendment also extends the treatment period to 48 months to continue the study until ALN-AS1 is anticipated to be commercially available in the countries where the study sites are located. Additional updates are being implemented as noted below: clarification that patients may continue to receive ALN-AS1 until it is commercially available in the patient's territory, addition of guidance for serious breaches of protocol, and deletion of Section 11.3, List of Sensitive CYP3A substrates and those with a Narrow Therapeutic Range.
29 April 2020	Amendment 7 - 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.
29 March 2021	Amendment 8 - 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 ALN-AS1 treatment, increases in blood homocysteine levels have been observed compared to levels before ALN-AS1 treatment. Thus, monitoring for changes in blood homocysteine levels during treatment with ALN-AS1 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 ALN-AS1 treatment is unknown.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported