



## Clinical trial results:

### Phase 2a, Randomized, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ISIS 702843 Administered Subcutaneously to Patients with Non-Transfusion Dependent -Thalassemia Intermedia

#### Summary

EudraCT number	2019-003505-96
Trial protocol	GR
Global end of trial date	28 March 2023

#### Results information

Result version number	v1 (current)
This version publication date	12 April 2024
First version publication date	12 April 2024

#### Trial information

##### Trial identification

Sponsor protocol code	ISIS 702843-CS2
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04059406
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, CA, United States, 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 (760) 931-9200, globalregulatoryaffairs@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 (760) 931-9200, globalregulatoryaffairs@ionisph.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	28 March 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 March 2023
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of sapablursen administered subcutaneously to participants with non-transfusion dependent  $\beta$ -Thalassemia Intermedia.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2020
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	Türkiye: 7
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Lebanon: 4
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Thailand: 11
Worldwide total number of subjects	29
EEA total number of subjects	4

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)	29

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

71 subjects were screened and 29 subjects were randomized in the study at 15 investigative sites in Australia, Greece, Lebanon, Thailand, and Turkey from 24 September 2020 to 28 March 2023.

### Pre-assignment

Screening details:

Subjects with a diagnosis of  $\beta$ -Thalassemia were enrolled in either cohorts A, B, or C to receive sapablursen.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort A: Sapablursen

Arm description:

Subjects initially received 30 mg/0.3 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Arm type	Experimental
Investigational medicinal product name	Sapablursen
Investigational medicinal product code	
Other name	ISIS 702843, IONIS TMPRSS6-LRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

30 mg/0.3 millilitre (mL) for at least 1 dose, then 120 mg/1.2 mL by SC route.

<b>Arm title</b>	Cohort B: Sapablursen
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Arm description:

Subjects initially received 50 mg/0.5 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Arm type	Experimental
Investigational medicinal product name	Sapablursen
Investigational medicinal product code	
Other name	ISIS 702843, IONIS TMPRSS6-LRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg/1.2 mL by SC route.

<b>Arm title</b>	Cohort C: Sapablursen
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Arm description:

Subjects initially received 80 mg/0.8 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Arm type	Experimental
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Investigational medicinal product name	Sapablursen
Investigational medicinal product code	
Other name	ISIS 702843, IONIS TMRSS6-LRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg/1.2 mL for 3 consecutive doses, then 160 mg/1.6 mL if dose escalation was allowed based on a demonstration of adequate safety by SC route.

<b>Number of subjects in period 1</b>	Cohort A: Sapablursen	Cohort B: Sapablursen	Cohort C: Sapablursen
Started	6	6	17
Completed	1	1	2
Not completed	5	5	15
Voluntary Withdrawal	-	2	4
Investigator Judgement	-	-	1
Adverse Event or Serious Adverse Event (SAE)	-	1	-
Study Terminated by Sponsor	5	2	10

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort A: Sapablursen
Reporting group description:	Subjects initially received 30 mg/0.3 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.
Reporting group title	Cohort B: Sapablursen
Reporting group description:	Subjects initially received 50 mg/0.5 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.
Reporting group title	Cohort C: Sapablursen
Reporting group description:	Subjects initially received 80 mg/0.8 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Reporting group values	Cohort A: Sapablursen	Cohort B: Sapablursen	Cohort C: Sapablursen
Number of subjects	6	6	17
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	35.0 ± 12.12	31.7 ± 10.44	32.0 ± 10.88
Gender categorical Units: Subjects			
Male	2	2	7
Female	4	4	10
Race Units: Subjects			
White	3	5	9
Asian	3	1	8
Ethnicity Units: Subjects			
Not Hispanic or Latino	6	6	17

Reporting group values	Total		
Number of subjects	29		
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Male	11		

Female	18		
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Race Units: Subjects			
White	17		
Asian	12		
Ethnicity Units: Subjects			
Not Hispanic or Latino	29		

## End points

### End points reporting groups

Reporting group title	Cohort A: Sapablursen
Reporting group description: Subjects initially received 30 mg/0.3 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.	
Reporting group title	Cohort B: Sapablursen
Reporting group description: Subjects initially received 50 mg/0.5 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.	
Reporting group title	Cohort C: Sapablursen
Reporting group description: Subjects initially received 80 mg/0.8 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.	

### Primary: Percentage of Subjects with a $\geq 1.0$ Grams per Deciliter (g/dL) Increase from Baseline in Hemoglobin (Hb) at Week 27

End point title	Percentage of Subjects with a $\geq 1.0$ Grams per Deciliter (g/dL) Increase from Baseline in Hemoglobin (Hb) at Week 27 <sup>[1]</sup>
End point description: Full analysis set (FAS) included all randomised subjects who received at least 1 dose of ISIS 702843 and who had at least 1 Hb assessment collected after Day 1. Subjects analysed is the number of subjects available for analysis.	
End point type	Primary
End point timeframe: Baseline and Week 27	

#### 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: Full analysis set (FAS) included all randomized subjects who received at least 1 dose of sapablursen and who had at least 1 Hb assessment collected after Day 1. Subjects analyzed is the number of subjects available for analysis.

End point values	Cohort A: Sapablursen	Cohort B: Sapablursen	Cohort C: Sapablursen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	15	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Percentage of Participants	0 (0.0 to 45.9)	0 (0.0 to 45.9)	6.7 (0.2 to 31.9)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with a $\geq 1.0$ Milligram of Iron per Gram of Dry Weight of Liver (mg Fe/g) Decrease from Baseline in Liver Iron Concentration (LIC) at Week 53

End point title	Percentage of Subjects with a $\geq$ 1.0 Milligram of Iron per Gram of Dry Weight of Liver (mg Fe/g) Decrease from Baseline in Liver Iron Concentration (LIC) at Week 53
End point description:	FAS included all randomised subjects who received at least 1 dose of ISIS 702843 and who had at least 1 Hb assessment collected after Day 1. Subjects analysed is the number of subjects available for analysis.
End point type	Secondary
End point timeframe:	Baseline and Week 53

End point values	Cohort A: Sapablursen	Cohort B: Sapablursen	Cohort C: Sapablursen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Percentage of Participants	33.3 (4.3 to 77.7)	50.0 (11.8 to 88.2)	28.6 (8.4 to 58.1)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with a $\geq$ 1.5 g/dL Increase from Baseline in Hemoglobin (Hb) at Week 53

End point title	Percentage of Subjects with a $\geq$ 1.5 g/dL Increase from Baseline in Hemoglobin (Hb) at Week 53
End point description:	FAS included all randomised subjects who received at least 1 dose of ISIS 702843 and who had at least 1 Hb assessment collected after Day 1. Subjects analysed is the number of subjects available for analysis.
End point type	Secondary
End point timeframe:	Baseline and Week 53

End point values	Cohort A: Sapablursen	Cohort B: Sapablursen	Cohort C: Sapablursen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	14	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Percentage of Participants	0 (0.0 to 45.9)	0 (0.0 to 45.9)	0 (0.0 to 23.2)	

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent to early termination (up to 733 days).

Adverse event reporting additional description:

Safety set included all randomized subjects who received at least 1 dose of sapablursen.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Cohort A: Sapablursen
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Reporting group description:

Subjects initially received 30 mg/0.3 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Reporting group title	Cohort C: Sapablursen
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Reporting group description:

Subjects initially received 80 mg/0.8 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

Reporting group title	Cohort B: Sapablursen
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Reporting group description:

Subjects initially received 50 mg/0.5 mL of sapablursen by SC injection once every four weeks (Q4W) up to Week 105. After the protocol Amendment 2 the dose was increased to a maximum of 160 mg.

<b>Serious adverse events</b>	Cohort A: Sapablursen	Cohort C: Sapablursen	Cohort B: Sapablursen
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Cohort A: Sapablursen	Cohort C: Sapablursen	Cohort B: Sapablursen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	14 / 17 (82.35%)	6 / 6 (100.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection Site Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection Site Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injection Site Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Peripheral Swelling			

subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
<b>Injection Site Rash</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
<b>Vaccination Site Pain</b>			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	1 / 6 (16.67%)
occurrences (all)	3	3	1
<b>Pyrexia</b>			
subjects affected / exposed	1 / 6 (16.67%)	5 / 17 (29.41%)	0 / 6 (0.00%)
occurrences (all)	3	9	0
<b>Fatigue</b>			
subjects affected / exposed	4 / 6 (66.67%)	1 / 17 (5.88%)	1 / 6 (16.67%)
occurrences (all)	5	2	1
<b>Reproductive system and breast disorders</b>			
<b>Amenorrhoea</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
<b>Adnexa Uteri Mass</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
<b>Ovulation Pain</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
<b>Heavy Menstrual Bleeding</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
<b>Dysmenorrhoea</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Cough</b>			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
<b>Oropharyngeal Pain</b>			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 4	1 / 17 (5.88%) 1	1 / 6 (16.67%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 2	0 / 6 (0.00%) 0
Nasal Congestion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 2	0 / 6 (0.00%) 0
Pulmonary Hypertension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Psychiatric disorders Panic Attack subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Investigations Blood Urine Present subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Injury, poisoning and procedural complications Vaccination Complication subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	2 / 17 (11.76%) 4	1 / 6 (16.67%) 1
Forearm Fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Congenital, familial and genetic disorders Odontogenic Cyst subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Nervous system disorders Headache			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 17 (11.76%) 2	2 / 6 (33.33%) 2
Sciatica subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Tension Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Tunnel Vision subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Blood and lymphatic system disorders Haemolysis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Ear and labyrinth disorders Ear Discomfort subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Eye disorders Lacrimal Disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	2 / 6 (33.33%) 3
Abdominal Distension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	2 / 6 (33.33%) 2
Abdominal Pain			

subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 17 (11.76%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Dental Caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Periodontal Disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Umbilical Hernia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			

Jaundice			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hepatomegaly			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatic Mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
<b>Skin and subcutaneous tissue disorders</b>			
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin Ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
<b>Renal and urinary disorders</b>			
Renal Disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Microalbuminuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypertonic Bladder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haematuria			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Endocrine disorders Thyroid Mass subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	3 / 17 (17.65%) 4	1 / 6 (16.67%) 1
Back Pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 17 (11.76%) 2	2 / 6 (33.33%) 3
Arthralgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Bone Pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 17 (0.00%) 0	0 / 6 (0.00%) 0
Flank Pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 2
Neck Pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 17 (0.00%) 0	1 / 6 (16.67%) 1
Osteopenia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 17 (5.88%) 1	0 / 6 (0.00%) 0
Pain in Jaw			

subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pain in Extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
<b>Infections and infestations</b>			
<b>Hordeolum</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
<b>Bacterial Vaginosis</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
<b>Tonsillitis</b>			
subjects affected / exposed	1 / 6 (16.67%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
<b>Impetigo</b>			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
<b>Influenza</b>			
subjects affected / exposed	2 / 6 (33.33%)	1 / 17 (5.88%)	2 / 6 (33.33%)
occurrences (all)	2	1	3
<b>Upper Respiratory Tract Infection</b>			
subjects affected / exposed	2 / 6 (33.33%)	4 / 17 (23.53%)	0 / 6 (0.00%)
occurrences (all)	3	8	0
<b>COVID-19</b>			
subjects affected / exposed	6 / 6 (100.00%)	11 / 17 (64.71%)	4 / 6 (66.67%)
occurrences (all)	3	5	0
<b>Urinary Tract Infection</b>			
subjects affected / exposed	1 / 6 (16.67%)	2 / 17 (11.76%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
<b>Pneumonia</b>			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 17 (5.88%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infected Skin Ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 17 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Staphylococcal Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 17 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2020	The following changes were made as part of Amendment 1: 1. Added sections related to the coronavirus disease 2019 (COVID-19) pandemic. 2. For Inclusion Criterion 4, changed the definition of non-transfusion dependent from no more than 6 to no more than 8 transfusions in the past 12-month period. 3. Changed Inclusion Criterion 7 from "Chelators was permitted provided the patient has been on a stable dose for at least 3 months prior to Day 1..." to "Chelators was permitted provided the dose has not been increased for at least 2 months prior to Day 1..." 4. Added Exclusion Criterion 9b for proteinuria manifesting as urine protein-to-creatinine ratio (UPCR) $\geq$ 0.50 milligrams per milligram (mg/mg). 5. Added the platelet count safety panel. 6. Changed the stopping rule related to proteinuria from permanently stopping sapablursen treatment based on a confirmed UPCR result $\geq$ 0.50 mg/mg to a dose pause based on a confirmed UPCR result that was either: (i) $\geq$ 0.50 mg/mg that also represented an increase from baseline of at least 2 x, or (ii) $\geq$ 0.70 mg/mg. 7. Added the allowed concomitant therapy of treatment with either luspatercept-aamt (Reblozyl®) or erythropoietin (EPO), not both, after Day 365 (Week 53).
17 May 2021	The following changes were made as part of Amendment 2: 1. Increased the sapablursen dose levels from 30 mg in Cohort A, 50 mg in Cohort B, and 80 mg in Cohort C to those identified in Section 9.1 and the maximum dose per 28-day interval from 120 to 160 mg based on the safety profiles and nonclinical toxicity results at that time. 2. Decreased the number of evaluable subjects planned from approximately 36 to approximately 24 subjects overall, reduced the thresholds for the number of subjects needed for the Interim Analysis (IA)s , and decreased maximum enrollment from 45 to 30 subjects. 3. For Inclusion Criterion 5, widened the upper limit of the mean Hb acceptable range from 10.0 to 10.5 g/dL and revised the temporary stopping rules for Hb results to correspond with this increase of 0.5 g/dL. 4. For Exclusion Criterion 6, decreased the lower limit for platelet count Screening results from lower limit of normal to 120,000/ cubic millimeters (mm <sup>3</sup> ).

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 March 2023	The study was terminated by the Sponsor's decision.	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated as per Sponsor's decision due to a lack of efficacy.

Notes: