Clinical trial results:
An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-LRX, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly

Summary

EudraCT number	2020-000675-20
Trial protocol	HU LT PL LV IT RO
Global end of trial date	04 May 2023

Results information

Result version number	v1 (current)
This version publication date	19 May 2024
First version publication date	19 May 2024

Trial information

Trial identification

Sponsor protocol code	ISIS 766720-CS5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04522180
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 Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760-603-2387, ClinicalTrials@ionisph.com
Scientific contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760-603-2387, ClinicalTrials@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	04 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 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 determine the safety, tolerability, and efficacy of IONIS-GHR-LRx subcutaneous (SC) injection as monotherapy in patients with acromegaly.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2021
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	Russian Federation: 13
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	34
EEA total number of subjects	16

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)	27
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 22 investigational sites in United States of America, Estonia, Hungary, Italy, Lithuania, Poland, Russia, and Serbia from 4 January 2021 to 18 Jan2022.

Pre-assignment

Screening details:

Participants with acromegaly were enrolled and assigned to receive an initial dose of GHR-LRX 120 mg or GHR-LRX 160 mg up to week 17 (when the first post-baseline IGF-1 results were available). After Week 17, patients may have received a higher dose up to 160 mg for efficacy, if necessary, up to 73 weeks.

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
Arm title	GHR-LRX 120 mg

Arm description:

Participants received GHR-LRX 120 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)

Arm type	Experimental
Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	GHR-LRX
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

120 mg of GHR-LRX was administered by SC injection.

Arm title	GHR-LRX 160 mg

Arm description:

Participants received GHR-LRX 160 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)

Arm type	Experimental
Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	GHR-LRX
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

160 mg of GHR-LRX was administered by SC injection.

Number of subjects in period 1	GHR-LRX 120 mg	GHR-LRX 160 mg
Started	18	16
Per Protocol Set (Initial Dose)	18	14
Completed	18	13
Not completed	0	3
Reason Not specified	-	2
Pregnancy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	GHR-LRX 120 mg
Reporting group description:	
Participants received GHR-LRX 120 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)	
Reporting group title	GHR-LRX 160 mg
Reporting group description:	
Participants received GHR-LRX 160 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)	

Reporting group values	GHR-LRX 120 mg	GHR-LRX 160 mg	Total
Number of subjects	18	16	34
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 57.0 ± 11.09	 48.3 ± 10.88	 -
Gender categorical Units: Subjects			
Male	10	7	17
Female	8	9	17
Race Units: Subjects			
White	18	15	33
Multiple Race	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	18	16	34

End points

End points reporting groups

Reporting group title	GHR-LRX 120 mg
Reporting group description:	
Participants received GHR-LRX 120 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)	
Reporting group title	GHR-LRX 160 mg
Reporting group description:	
Participants received GHR-LRX 160 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)	
Subject analysis set title	GHR-LRX 120 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received initial dose of GHR-LRX 120 mg SC injection once every month for up to 73 weeks with a booster dose administered on Day 15 (Week 3)	
Subject analysis set title	GHR-LRX 160 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received initial dose of GHR-LRX 160 mg SC injection once every month for up to 73 weeks with a booster dose administered on Day 15 (Week 3)	
Subject analysis set title	GHR-LRX Total
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Overall number of participants analyzed is the number of participants available for analyses. Total of all participants in the Per Protocol Set (received initial doses of 120 mg or 160 mg doses).	

Primary: Percent Change in Insulin-like Growth Factor I (IGF-1) from Baseline to Week 27

End point title	Percent Change in Insulin-like Growth Factor I (IGF-1) from Baseline to Week 27[1]
End point description:	
IGF-1 is a hormone that manages the effects of growth hormone (GH) in the body. Baseline of IGF-1 is defined as the average value of Screening and Day 1. A negative percent change from baseline indicated improvement.	
End point type	Primary
End point timeframe:	
Baseline to 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: Only descriptive analysis was planned for this endpoint.

End point values	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	10	26	
Units: percent change				
arithmetic mean (standard deviation)				
At Week 27	-10.47 (± 11.418)	-1.68 (± 27.848)	-7.09 (± 19.402)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum IGF-1 Over Time

End point title	Change From Baseline in Serum IGF-1 Over Time

End point description:

IGF-1 is a hormone that manages the effects of growth hormone (GH) in the body. A negative change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73

End point values	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3[2]	29[3]	32	
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
At Week 3 (n =3, 29, 32)	-30.00 (± 44.908)	5.03 (± 49.932)	1.74 (± 49.896)	
At Week 5 (n =3, 29, 32)	-50.67 (± 101.186)	-45.53 (± 87.817)	-46.01 (± 87.341)	
At Week 7 (n =3, 29, 32)	-84.33 (± 133.829)	-39.46 (± 80.258)	-43.66 (± 84.558)	
At Week 9 (n =3, 29, 32)	-109.00 (± 111.959)	-25.28 (± 93.924)	-33.13 (± 96.909)	
At Week 11(n =3, 29, 32)	-157.67 (± 144.923)	-14.28 (± 64.463)	-27.73 (± 83.134)	
At Week 13 (n =3, 29, 32)	-89.67 (± 130.989)	-38.01 (± 68.885)	-42.85 (± 75.013)	
At Week 15 (n =3, 27, 30)	-112.00 (± 112.618)	-28.97 (± 79.942)	-37.28 (± 85.124)	
At Week 17 (n =3, 29, 32)	-89.33 (± 136.433)	-36.91 (± 88.212)	-41.82 (± 92.034)	
At Week 21 (n =2, 24, 26)	-123.25 (± 136.118)	-51.91 (± 92.746)	-57.39 (± 95.030)	
At Week 25 (n =2, 24, 26)	-99.75 (± 126.926)	-36.99 (± 78.236)	-41.82 (± 81.034)	
At Week 27 (n =2, 24, 26)	-58.75 (± 87.328)	-49.45 (± 112.579)	-50.16 (± 109.415)	
At Week 29 (n =2, 23, 25)	-90.25 (± 126.219)	-40.25 (± 80.174)	-44.25 (± 82.145)	
At Week 33 (n =2, 23, 25)	-75.25 (± 110.662)	-53.12 (± 72.494)	-54.89 (± 73.247)	
At Week 37 (n =2, 23, 25)	-98.75 (± 179.252)	-32.55 (± 107.499)	-37.85 (± 110.760)	

At Week 41 (n =2, 23, 25)	-93.25 (± 146.018)	-43.12 (± 97.911)	-47.13 (± 99.341)	
At Week 45 (n =2, 21, 23)	-86.75 (± 175.009)	-52.80 (± 110.595)	-55.75 (± 112.282)	
At Week 49 (n =2, 19, 21)	-81.75 (± 109.955)	-64.59 (± 105.493)	-66.23 (± 103.184)	
At Week 53 (n =2, 18, 20)	-90.25 (± 158.745)	-68.71 (± 81.822)	-70.86 (± 85.793)	
At Week 57 (n =2, 17, 19)	-73.75 (± 91.570)	-59.43 (± 90.080)	-60.93 (± 87.744)	
At Week 61 (n =2, 15, 17)	-125.75 (± 199.051)	-83.08 (± 112.428)	-88.10 (± 117.206)	
At Week 65 (n =1, 11, 12)	74.00 (± 99999)	-103.30 (± 102.760)	-88.52 (± 110.540)	
At Week 69 (n =1, 8, 9)	-22.00 (± 99999)	-85.59 (± 53.018)	-78.53 (± 53.934)	
At Week 73 (n =1, 7, 8)	-1.00 (± 99999)	-91.18 (± 79.166)	-79.91 (± 79.928)	

Notes:

[2] - The standard deviation was not estimable for a single participant.

[3] - The standard deviation was not estimable for a single participant.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Normalized IGF-1 Levels to Within 1.0 Times Gender and Age Limits at Day 183 (Week 27)

End point title	Percentage of Participants Who Achieved Normalized IGF-1 Levels to Within 1.0 Times Gender and Age Limits at Day 183 (Week 27)

End point description:

Normalized IGF-1 level is defined as the ratio of the serum IGF-1 level and the participant’s ULN.

End point type	Secondary

End point timeframe:

At Week 27

End point values	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	10	26	
Units: Percentage of participants				
number (confidence interval 95%)				
At Week 27	0 (0.0 to 20.6)	0 (0.0 to 30.8)	0 (0.0 to 13.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Normalized IGF-1 Levels to Within 1.2 Times Gender and Age Limits at Day 183 (Week 27)

End point title	Percentage of Participants Who Achieved Normalized IGF-1 Levels to Within 1.2 Times Gender and Age Limits at Day 183 (Week 27)

End point description:

Normalized IGF-1 level is defined as the ratio of the serum IGF-1 level and the participant's upper limit of normal (ULN).

End point type	Secondary

End point timeframe:

At Week 27

End point values	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	10	26	
Units: percentage of participants				
number (confidence interval 95%)	0 (0.0 to 20.6)	0 (0.0 to 30.8)	0 (0.0 to 13.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Serum IGF-1 Over Time

End point title	Percent Change From Baseline in Serum IGF-1 Over Time

End point description:

IGF-1 is a hormone that manages the effects of growth hormone (GH) in the body. A negative percent change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 3, 5, 7, 9, 11, 13, 15, 17, 21, 25, 27, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73

End point values	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3[4]	29[5]	32	
Units: percent change				
arithmetic mean (standard deviation)				
At Week 3 (n =3, 29, 32)	-3.73 (± 5.072)	2.64 (± 11.936)	2.04 (± 11.571)	
At Week 5 (n =3, 29, 32)	-5.67 (± 12.296)	-8.28 (± 18.158)	-8.04 (± 17.554)	
At Week 7 (n =3, 29, 32)	-9.57 (± 16.297)	-7.16 (± 16.637)	-7.39 (± 16.360)	
At Week 9 (n=3,29,32)	-17.43 (± 11.285)	-2.95 (± 16.995)	-4.31 (± 16.955)	
At Week 11 (n =3, 29, 32)	-26.56 (± 15.966)	-1.15 (± 16.235)	-3.54 (± 17.638)	

At Week 13 (n =3, 29, 32)	-10.32 (± 17.934)	-6.35 (± 16.837)	-6.72 (± 16.679)	
At Week 15 (n =3, 27, 30)	-17.81 (± 13.377)	-5.40 (± 21.168)	-6.64 (± 20.698)	
At Week 17 (n =3, 29, 32)	-9.36 (± 20.529)	-4.59 (± 20.631)	-5.04 (± 20.338)	
At Week 21 (n =2, 24, 26)	-19.07 (± 8.695)	-9.98 (± 22.994)	-10.68 (± 22.261)	
At Week 25 (n =2, 24, 26)	-13.28 (± 12.010)	-6.58 (± 16.164)	-7.10 (± 15.794)	
At Week 27 (n =2, 24, 26)	-6.20 (± 10.803)	-7.16 (± 20.100)	-7.09 (± 19.402)	
At Week 29 (n =2, 23, 25)	-10.55 (± 14.242)	-7.92 (± 18.173)	-8.13 (± 17.656)	
At Week 33 (n =2, 23, 25)	-8.10 (± 13.484)	-10.10 (± 16.351)	-9.94 (± 15.905)	
At Week 37 (n =2, 23, 25)	-6.25 (± 27.791)	-4.29 (± 25.161)	-4.45 (± 24.755)	
At Week 41 (n =2, 23, 25)	-8.89 (± 19.345)	-9.01 (± 23.250)	-9.00 (± 22.608)	
At Week 45 (n =2, 21, 23)	-3.24 (± 29.617)	-8.26 (± 23.791)	-7.82 (± 23.590)	
At Week 49 (n =2, 19, 21)	-10.12 (± 11.603)	-12.83 (± 22.932)	-12.57 (± 21.924)	
At Week 53 (n =2, 18, 20)	-6.37 (± 23.892)	-14.81 (± 19.811)	-13.97 (± 19.697)	
At Week 57 (n =2, 17, 19)	-10.11 (± 8.205)	-10.50 (± 19.795)	-10.46 (± 18.763)	
At Week 61 (n =2, 15, 17)	-11.72 (± 26.723)	-18.94 (± 25.675)	-18.09 (± 25.044)	
At Week 65 (n =1, 11, 12)	35.41 (± 99999)	-21.36 (± 25.392)	-16.63 (± 29.235)	
At Week 69 (n =1, 8, 9)	-10.53 (± 99999)	-23.32 (± 14.391)	-21.89 (± 14.120)	
At Week 73 (n =1, 7, 8)	-0.48 (± 99999)	-22.62 (± 20.556)	-19.85 (± 20.578)	

Notes:

[4] - The standard deviation was not estimable for a single participant.

[5] - The standard deviation was not estimable for a single participant.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to the end of study follow-up (up to 121 week)

Adverse event reporting additional description:

All participants who were randomized and received at least 1 dose of GHR-LRX. Data for all-cause mortality, serious and non-serious adverse events is reported as per the maximum dose received by participants per arm considering dose escalation was allowed in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	GHR-LRX 120 mg

Reporting group description:

Participants received GHR-LRX 120 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)

Reporting group title	GHR-LRX 160 mg

Reporting group description:

Participants received GHR-LRX 160 mg SC injection once every month for 73 weeks with a booster dose administered on Day 15 (Week 3)

Reporting group title	GHR-LRX Total (Per Protocol Set)

Reporting group description:

Overall number of participants analyzed is the number of participants available for analyses. Total of all participants in the Per Protocol Set (received maximum doses of 120 mg or 160 mg doses).

Serious adverse events	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total (Per Protocol Set)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 31 (6.45%)	3 / 34 (8.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 3 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

COVID-19 pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 31 (3.23%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	GHR-LRX 120 mg	GHR-LRX 160 mg	GHR-LRX Total (Per Protocol Set)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	26 / 31 (83.87%)	29 / 34 (85.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	5 / 31 (16.13%)	5 / 34 (14.71%)
occurrences (all)	0	7	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 31 (12.90%)	5 / 34 (14.71%)
occurrences (all)	1	4	5
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Cough			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	5	5
Weight increased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Injury, poisoning and procedural complications			
Post procedural hypothyroidism			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	11	11
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	5	5
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	4	4
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	3	3
Headache			
subjects affected / exposed	0 / 3 (0.00%)	11 / 31 (35.48%)	11 / 34 (32.35%)
occurrences (all)	0	20	20
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	1	2	3

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	3	3
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	4 / 31 (12.90%)	5 / 34 (14.71%)
occurrences (all)	1	7	8
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 31 (12.90%)	4 / 34 (11.76%)
occurrences (all)	0	5	5
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Flatulence			
subjects affected / exposed	1 / 3 (33.33%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Diverticulum intestinal			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	11	11
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1

Hepatic cyst			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	4	4
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Dermal cyst			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Rosacea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	2 / 3 (66.67%)	0 / 31 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 31 (6.45%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 31 (9.68%)	4 / 34 (11.76%)
occurrences (all)	1	9	10

Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Pyelonephritis chronic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 31 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	3	3
COVID-19			
subjects affected / exposed	1 / 3 (33.33%)	6 / 31 (19.35%)	7 / 34 (20.59%)
occurrences (all)	1	6	7
Respiratory tract infection viral			
subjects affected / exposed	1 / 3 (33.33%)	3 / 31 (9.68%)	4 / 34 (11.76%)
occurrences (all)	1	3	4
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	4 / 31 (12.90%)	4 / 34 (11.76%)
occurrences (all)	0	4	4
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 31 (9.68%)	3 / 34 (8.82%)
occurrences (all)	0	4	4
Asymptomatic COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 31 (6.45%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Hypercholesterolaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 31 (3.23%)	2 / 34 (5.88%)
occurrences (all)	2	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2021	1. Revised inclusion and exclusion criteria. 2. Revised the platelet count criterion from lower limit of normal (LLN) to < 125,000 cubic millimeters (mm^3).
31 July 2021	1) Updated patient eligibility criteria. 2) Updated ability to conduct home health care visits and patient contact. 3) Updated the Clinical Experience and Rationale for Dose and Schedule sections of the protocol with information from ongoing Phase 2 studies.
12 December 2021	1. Updated the subject randomization. 2. Clarified enrollment of treatment dose groups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 May 2023	The study was terminated early due to the Sponsor's decision. The amount of safety data accumulated on ISIS 766720 after all participants had completed 1 year of treatment was adequate and ended the study.	-

Notes:

Limitations and caveats

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

The study is terminated early due to the Sponsor's decision. The amount of safety data accumulated on ISIS 766720 after all participants had completed 1 year of treatment was adequate and ended the study.

Notes: