



## Clinical trial results:

### A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-LRX, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)

#### Summary

EudraCT number	2017-004259-22
Trial protocol	HU AT LT CZ PL RO
Global end of trial date	02 April 2021

#### Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

#### Trial information

##### Trial identification

Sponsor protocol code	ISIS 766720-CS2
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548415
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, 92010
Public contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760603-3804, ClinicalTrials@ionisph.com
Scientific contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760603-3804, 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	02 April 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To evaluate the efficacy of ISIS 766720 subcutaneous (SC) injection on serum insulin-like growth factor 1 (IGF-1) vs. placebo as an add-on therapy to long acting somatostatin receptor ligands (SRL) octreotide or lanreotide.
- To evaluate the safety and tolerability of ISIS 766720 SC injection vs. placebo on add-on therapy of SRL.

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2018
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: 17
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Lithuania: 9
Worldwide total number of subjects	43
EEA total number of subjects	17

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Adult subjects diagnosed with acromegaly took part in the study at 24 investigative sites in Lithuania, Hungary, the United States of America, Serbia, Russia, Poland, and Romania from 13 September 2018 to 02 April 2021.

### Pre-assignment

Screening details:

Subjects were randomized into 4 cohorts [A and B in 2:1 ratio; C and D in 5:1 ratio] to receive IONIS GHR-LRx or placebo. Due to enrollment difficulties associated with (COVID-19) pandemic, treatment groups IONIS GHR-LRx, 120 mg and IONIS GHR-LRx, 160 mg did not complete enrollment resulting in cohort sizes smaller than planned.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Subjects received placebo by subcutaneous injection (SC) once every 4 weeks for 16 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IONIS GHR-LRx-matching placebo administered subcutaneously.

<b>Arm title</b>	Cohort A: IONIS GHR-LRx, 60 mg
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Arm description:

Subjects received IONIS GHR-LRx, 60 milligrams (mg), SC, once every 4 weeks for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	IONIS-GHR-LRx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IONIS GHR-LRx, 60 mg, administered subcutaneously.

<b>Arm title</b>	Cohort B: IONIS GHR-LRx, 80 mg
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Arm description:

Subjects received IONIS GHR-LRx, 80 mg, SC, once every 4 weeks for 16 weeks.

Arm type	Experimental
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Investigational medicinal product name	IONIS-GHR-LRx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IONIS GHR-LRx, 80 mg, administered subcutaneously.

<b>Arm title</b>	Cohort C: IONIS GHR-LRx, 120 mg
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Arm description:

Subjects received IONIS GHR-LRx, 120 mg, SC, once every 4 weeks for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	IONIS-GHR-LRx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IONIS GHR-LRx, 120 mg, administered subcutaneously.

<b>Arm title</b>	Cohort D: IONIS GHR-LRx, 160 mg
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Arm description:

Subjects received IONIS GHR-LRx, 160 mg, SC, once every 4 weeks for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	IONIS-GHR-LRx
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IONIS GHR-LRx, 160 mg, administered subcutaneously.

<b>Number of subjects in period 1</b>	Placebo	Cohort A: IONIS GHR-LRx, 60 mg	Cohort B: IONIS GHR-LRx, 80 mg
Started	12	12	11
Per-Protocol Set	12	11	11
Completed	12	11	11
Not completed	0	1	0
Adverse Event or Serious Adverse Event	-	1	-

<b>Number of subjects in period 1</b>	Cohort C: IONIS GHR-LRx, 120 mg	Cohort D: IONIS GHR-LRx, 160 mg
Started	2	6
Per-Protocol Set	2	5
Completed	2	5
Not completed	0	1
Adverse Event or Serious Adverse Event	-	1



## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo by subcutaneous injection (SC) once every 4 weeks for 16 weeks.	
Reporting group title	Cohort A: IONIS GHR-LRx, 60 mg
Reporting group description:	
Subjects received IONIS GHR-LRx, 60 milligrams (mg), SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort B: IONIS GHR-LRx, 80 mg
Reporting group description:	
Subjects received IONIS GHR-LRx, 80 mg, SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort C: IONIS GHR-LRx, 120 mg
Reporting group description:	
Subjects received IONIS GHR-LRx, 120 mg, SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort D: IONIS GHR-LRx, 160 mg
Reporting group description:	
Subjects received IONIS GHR-LRx, 160 mg, SC, once every 4 weeks for 16 weeks.	

Reporting group values	Placebo	Cohort A: IONIS GHR-LRx, 60 mg	Cohort B: IONIS GHR-LRx, 80 mg
Number of subjects	12	12	11
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: years			
arithmetic mean	45.3	48.9	52.1
standard deviation	± 11.7	± 13.6	± 14.9
Gender categorical			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
Female	8	9	6
Male	4	3	5
Ethnicity (NIH/OMB)			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	12	12	11
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0

White	12	12	11
More than one race	0	0	0

Reporting group values	Cohort C: IONIS GHR-LRx, 120 mg	Cohort D: IONIS GHR-LRx, 160 mg	Total
Number of subjects	2	6	43
Age categorical			
Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
Age continuous			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: years			
arithmetic mean	53.5	46.0	
standard deviation	± 2.1	± 13.3	-
Gender categorical			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
Female	0	4	27
Male	2	2	16
Ethnicity (NIH/OMB)			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2	6	43
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	2	5	42
More than one race	0	0	0



## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received placebo by subcutaneous injection (SC) once every 4 weeks for 16 weeks.	
Reporting group title	Cohort A: IONIS GHR-LRx, 60 mg
Reporting group description: Subjects received IONIS GHR-LRx, 60 milligrams (mg), SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort B: IONIS GHR-LRx, 80 mg
Reporting group description: Subjects received IONIS GHR-LRx, 80 mg, SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort C: IONIS GHR-LRx, 120 mg
Reporting group description: Subjects received IONIS GHR-LRx, 120 mg, SC, once every 4 weeks for 16 weeks.	
Reporting group title	Cohort D: IONIS GHR-LRx, 160 mg
Reporting group description: Subjects received IONIS GHR-LRx, 160 mg, SC, once every 4 weeks for 16 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description: Per-protocol Set included all randomized subjects who received at least one dose of Study Drug and had at least one post-baseline efficacy or pharmacodynamic assessment, received at least 5 of the 6 doses of Study Drug with the first 3 doses administered on schedule, and had no significant protocol deviations that would have been expected to affect efficacy.	
Subject analysis set title	ISIS 766720 Low Dose
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received IONIS GHR-LRx, 60 or 80 mg, SC, once every 4 weeks for 16 weeks.	
Subject analysis set title	ISIS 766720 High Dose
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received IONIS GHR-LRx, 120 or 160 mg, SC, once every 4 weeks for 16 weeks.	

### Primary: Percent Change in Serum Insulin-like Growth Factor-1 (IGF-1) From Baseline to 28 Days After Last Dose

End point title	Percent Change in Serum Insulin-like Growth Factor-1 (IGF-1) From Baseline to 28 Days After Last Dose
End point description: IGF-1 is a hormone that manages effects of growth hormone (GH) in the body. Percent(%)change from Baseline in IGF-1 levels was measured at Day 141. Baseline was defined as last non-missing value prior to first administration of Study Drug (ISIS 766720 or placebo). Negative % change from Baseline indicated improvement. To perform a meaningful assessment of pharmacodynamic (PD) activity of ISIS 766720, lower dose groups (60 mg and 80 mg) and higher dose groups (120mg &160mg) were combined to achieve group size of 7 or more for PD assessments and these were designated as low-dose and high-dose groups respectively. Per-protocol Set included all randomised subjects who received at least one dose of Study Drug and had at least one post-baseline efficacy or PD assessment, received at least 5 of the 6 doses of Study Drug with first 3 doses administered on schedule, and had no significant protocol deviations that would have been expected to affect efficacy. Low dose=60/80 mg, high=120/160 mg.	
End point type	Primary
End point timeframe: Baseline and 28 days after last dose (Day 141)	

End point values	Placebo	ISIS 766720 Low Dose	ISIS 766720 High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	22	7	
Units: percent change				
arithmetic mean (standard deviation)	8.9 (± 31.5)	-2.8 (± 33.1)	-7.5 (± 16.3)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ISIS 766720 Low Dose
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306
Method	Van Elteren test

## Primary: Number of Subjects With TEAEs Related to Clinically Significant Vital Sign Findings

End point title	Number of Subjects With TEAEs Related to Clinically Significant Vital Sign Findings <sup>[1]</sup>
End point description:	
Vitals signs included blood pressure, heart rate, respiratory rate, and temperature recorded throughout the study. Clinical significance was determined by the investigator. The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.	
End point type	Primary
End point timeframe:	
Up to 211 days	

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: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of subjects).

End point values	Placebo	Cohort A: IONIS GHR-LRx, 60 mg	Cohort B: IONIS GHR-LRx, 80 mg	Cohort C: IONIS GHR-LRx, 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	11	2
Units: subjects				
Hypotension	0	1	0	0
Hypertension	0	0	1	0

<b>End point values</b>	Cohort D: IONIS GHR- LRx, 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
Hypotension	0			
Hypertension	0			

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With TEAEs Related to Clinically Significant Physical Examination Findings

End point title	Number of Subjects With TEAEs Related to Clinically Significant Physical Examination Findings <sup>[2]</sup>
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End point description:

Physical examination included weight and body mass index (BMI) recorded throughout the study. Clinical significance was determined by the investigator. The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.

End point type	Primary
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End point timeframe:

Up to 211 days

Notes:

[2] - 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: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of subjects).

<b>End point values</b>	Placebo	Cohort A: IONIS GHR- LRx, 60 mg	Cohort B: IONIS GHR- LRx, 80 mg	Cohort C: IONIS GHR- LRx, 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	11	2
Units: subjects	0	0	0	0

<b>End point values</b>	Cohort D: IONIS GHR- LRx, 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

## Statistical analyses

No statistical analyses for this end point

**Primary: Number of Subjects With TEAEs Related to Clinically Significant Laboratory Evaluation Findings**

End point title	Number of Subjects With TEAEs Related to Clinically Significant Laboratory Evaluation Findings <sup>[3]</sup>
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End point description:

Clinical laboratory assessments included clinical chemistry, hematology, and urinalysis. Clinically-significant abnormal laboratory values were reported as TEAEs if the results may, in the opinion of the Investigator, constitute or be associated with an AE. The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.

End point type	Primary
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End point timeframe:

Up to 211 days

Notes:

[3] - 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: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of subjects).

End point values	Placebo	Cohort A: IONIS GHR- LRx, 60 mg	Cohort B: IONIS GHR- LRx, 80 mg	Cohort C: IONIS GHR- LRx, 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	11	2
Units: subjects				
Blood urine present	0	0	0	1
Mean cell volume increased	0	1	0	0
Urine protein/creatinine ratio increased	0	0	1	0
Hyperglycaemia	1	0	0	1

End point values	Cohort D: IONIS GHR- LRx, 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects				
Blood urine present	0			
Mean cell volume increased	0			
Urine protein/creatinine ratio increased	0			
Hyperglycaemia	0			

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of Subjects With TEAEs Related to Clinically Significant Electrocardiogram (ECG) Findings**

End point title	Number of Subjects With TEAEs Related to Clinically Significant Electrocardiogram (ECG) Findings <sup>[4]</sup>
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End point description:

ECG assessments included QT, QRS duration, PR interval, ventricular rate, QTcB, QTcF. The Safety Set

included all subjects who were randomized and received at least one dose of Study Drug.

End point type	Primary
End point timeframe:	
Up to 211 days	

Notes:

[4] - 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: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of subjects).

End point values	Placebo	Cohort A: IONIS GHR- LRx, 60 mg	Cohort B: IONIS GHR- LRx, 80 mg	Cohort C: IONIS GHR- LRx, 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	11	2
Units: subjects	2	2	1	1

End point values	Cohort D: IONIS GHR- LRx, 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	0			

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects Who Required Concomitant Medications

End point title	Number of Subjects Who Required Concomitant Medications <sup>[5]</sup>
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End point description:

Number of subjects who used medication other than the study drug were reported. The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.

End point type	Primary
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End point timeframe:

Up to 211 days

Notes:

[5] - 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: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of subjects).

End point values	Placebo	Cohort A: IONIS GHR- LRx, 60 mg	Cohort B: IONIS GHR- LRx, 80 mg	Cohort C: IONIS GHR- LRx, 120 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	11	2
Units: subjects	12	12	11	2

<b>End point values</b>	Cohort D: IONIS GHR- LRx, 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: subjects	6			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Achieving Normalized IGF-1 Levels to Within 1.2 Times of Gender and Age Limits at 28 Days After Last Dose

End point title	Number of Subjects Achieving Normalized IGF-1 Levels to Within 1.2 Times of Gender and Age Limits at 28 Days After Last Dose
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End point description:

Normalization of circulating IGF-1 is a validated marker for the treatment of acromegaly. IGF-1 assessments were based on a single serum sample taken in fasting conditions, prior to the study drug administration. Normal IGF-1 levels for a participant differ based on age and gender. Number of participants with a normal IGF-1 level which were 1.2 times within gender and age limits after 28 days of the last dose (Day 141) are presented. To perform a meaningful assessment of the pharmacodynamic activity of ISIS 766720, the lower dose groups (60 mg and 80 mg) and higher dose groups (120 mg and 160 mg) were combined to achieve group size of 7 or more for PD assessments and these were designated as low-dose and high-dose groups respectively. Per-protocol Set. Low dose refers to 60 mg or 80 mg, High dose refers to 120 mg or 160 mg.

End point type	Secondary
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End point timeframe:

Baseline to 28 days after last dose (Day 141)

<b>End point values</b>	Placebo	ISIS 766720 Low Dose	ISIS 766720 High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	22	7	
Units: subjects	0	5	1	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Achieving Normalized IGF-1 Levels to Within 1.0 Times of Gender and Age Limits at 28 Days After Last Dose

End point title	Number of Subjects Achieving Normalized IGF-1 Levels to Within 1.0 Times of Gender and Age Limits at 28 Days After Last Dose
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**End point description:**

Normalization of circulating IGF-1 is a validated marker for the treatment of acromegaly. IGF-1 assessments were based on a single serum sample taken in fasting conditions, prior to the study drug administration. Normal IGF-1 levels for a participant differ based on age and gender. Number of participants with a normal IGF-1 level which were 1.0 times within gender and age limits after 28 days of the last dose (Day 141) are presented. To perform a meaningful assessment of the pharmacodynamic activity of ISIS 766720, the lower dose groups (60 mg and 80 mg) and higher dose groups (120 mg and 160 mg) were combined to achieve group size of 7 or more for PD assessments and these were designated as low-dose and high-dose groups respectively. Per-protocol Set. Low dose refers to 60 mg or 80 mg, High dose refers to 120 mg or 160 mg.

End point type	Secondary
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**End point timeframe:**

Baseline to 28 days after last dose (Day 141)

End point values	Placebo	ISIS 766720 Low Dose	ISIS 766720 High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	22	7	
Units: subjects	0	2	0	

**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
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**End point description:**

IGF-1 is a hormone that manages effects of GH in body. Change from Baseline in IGF-1 levels was measured at multiple timepoints up to Day 211. Baseline was defined as the last non-missing value prior to the first administration of Study Drug (ISIS 766720 or placebo). A negative change from Baseline indicated improvement. To perform a meaningful assessment of the PD activity of ISIS 766720, the lower dose groups (60 mg and 80 mg) and higher dose groups (120 mg and 160 mg) were combined to achieve group size of 7 or more for PD assessments and these were designated as low-dose and high-dose groups respectively. Per-protocol Set. Number analyzed is the number of subjects with data available at specific timepoints. Low dose refers to 60 mg or 80 mg, High dose refers to 120 mg or 160 mg.

End point type	Secondary
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**End point timeframe:**

Baseline, Days 15, 29, 43, 57, 71, 85, 99, 112, 127, 141, 155, 183, and 211

End point values	Placebo	ISIS 766720 Low Dose	ISIS 766720 High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	22	7	
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=12, 22, 7)	386 (± 154)	422 (± 214)	419 (± 143)	
CFB at Day 15 (n=12, 22, 7)	33 (± 112)	-46 (± 108)	-10 (± 47)	

CFB at Day 29 (n=12, 22, 7)	23 (± 71)	-30 (± 140)	-68 (± 55)	
CFB at Day 43 (n=12, 21, 7)	17 (± 114)	-41 (± 142)	-88 (± 95)	
CFB at Day 57 (n=12, 22, 7)	52 (± 120)	-39 (± 147)	-74 (± 63)	
CFB at Day 71 (n=12, 22, 7)	9 (± 115)	-71 (± 163)	-78 (± 76)	
CFB at Day 85 (n=12, 22, 7)	9 (± 91)	-55 (± 136)	-90 (± 14)	
CFB at Day 99 (n=12, 22, 7)	13 (± 124)	-49 (± 104)	-104 (± 78)	
CFB at Day 112 (n=12, 22, 7)	31 (± 93)	-36 (± 100)	-61 (± 70)	
CFB at Day 127 (n=12, 21, 7)	19 (± 83)	-48 (± 133)	-74 (± 69)	
CFB at Day 141 (n=12, 22, 7)	20 (± 100)	-39 (± 140)	-48 (± 92)	
CFB at Day 155 (n=8, 20, 3)	1 (± 91)	-47 (± 144)	-98 (± 112)	
CFB at Day 183 (n=8, 18, 3)	-13 (± 87)	-45 (± 155)	-15 (± 146)	
CFB at Day 211 (n=8, 17, 2)	13 (± 116)	-55 (± 161)	-92 (± 97)	

## 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 GH in the body. Percent change from Baseline in IGF-1 levels was measured at multiple timepoints up to Day 211. Baseline was defined as the last non-missing value prior to the first administration of Study Drug (ISIS 766720 or placebo). A negative percent change from Baseline indicated improvement. To perform a meaningful assessment of the pharmacodynamic activity of ISIS 766720, the lower dose groups (60 mg and 80 mg) and higher dose groups (120 mg and 160 mg) were combined to achieve group size of 7 or more for PD assessments and these were designated as low-dose and high-dose groups respectively. Per-protocol Set. Low dose refers to 60 mg or 80 mg, High dose refers to 120mg or 160mg.	
End point type	Secondary
End point timeframe:	
Baseline, Days 15, 29, 43, 57, 71, 85, 99, 112, 127, 155, 183, and 211	

End point values	Placebo	ISIS 766720 Low Dose	ISIS 766720 High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	22	7	
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n=12, 22, 7)	386 (± 154)	422 (± 214)	419 (± 143)	
Percent CFB at Day 15 (n=12, 22, 7)	11.2 (± 31.3)	-6.0 (± 24.5)	-0.2 (± 11.9)	
Percent CFB at Day 29 (n=12, 22, 7)	9.3 (± 26.2)	-3.5 (± 30.0)	-14.8 (± 6.8)	
Percent CFB at Day 43 (n=12, 21, 7)	9.6 (± 35.7)	-41 (± 28.4)	-18.3 (± 18.5)	
Percent CFB at Day 57 (n=12, 22, 7)	14.3 (± 34.5)	-3.4 (± 31.9)	-16.6 (± 11.6)	
Percent CFB at Day 71 (n=12, 22, 7)	8.8 (± 33.4)	-9.0 (± 42.0)	-16.5 (± 12.3)	
Percent CFB at Day 85 (n=12, 22, 7)	4.2 (± 27.2)	-5.6 (± 32.5)	-16.7 (± 19.4)	
Percent CFB at Day 99 (n=12, 22, 7)	6.6 (± 38.8)	-7.1 (± 30.1)	-25.1 (± 18.0)	
Percent CFB at Day 112 (n=12, 22, 7)	12.1 (± 29.8)	-4.0 (± 33.6)	-12.3 (± 9.3)	
Percent CFB at Day 127 (n=12, 21, 7)	6.3 (± 19.6)	-4.7 (± 30.2)	-16.0 (± 9.0)	
Percent CFB at Day 141 (n=12, 22, 7)	8.9 (± 31.5)	-2.8 (± 33.1)	-7.5 (± 16.3)	



Percent CFB at Day 155 (n=8, 20, 3)	4.1 (± 26.0)	-3.5 (± 32.0)	-18.1 (± 14.1)	
Percent CFB at Day 183 (n=8, 18, 3)	0.1 (± 26.2)	-2.5 (± 38.7)	1.6 (± 25.9)	
Percent CFB at Day 211 (n=8, 17, 2)	2.2 (± 30.6)	-8.2 (± 32.7)	-15.6 (± 10.5)	

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 211 days

Adverse event reporting additional description:

The Safety Set included all subjects who were randomized and received at least one dose of Study Drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo by subcutaneous injection (SC) once every 4 weeks for 16 weeks.

Reporting group title	Cohort A: IONIS GHR-LRx, 60 mg
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Reporting group description:

Subjects received IONIS GHR-LRx, 60 milligrams (mg), SC, once every 4 weeks for 16 weeks.

Reporting group title	Cohort B: IONIS GHR-LRx, 80 mg
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Reporting group description:

Subjects received IONIS GHR-LRx, 80 mg, SC, once every 4 weeks for 16 weeks.

Reporting group title	Cohort C: IONIS GHR-LRx, 120 mg
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Reporting group description:

Subjects received IONIS GHR-LRx, 120 mg, SC, once every 4 weeks for 16 weeks.

Reporting group title	Cohort D: IONIS GHR-LRx, 160 mg
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Reporting group description:

Subjects received IONIS GHR-LRx, 160 mg, SC, once every 4 weeks for 16 weeks.

Serious adverse events	Placebo	Cohort A: IONIS GHR-LRx, 60 mg	Cohort B: IONIS GHR-LRx, 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 11 (9.09%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Gastrointestinal disorders			
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (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
Pancreatitis acute			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (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			
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (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
Septic shock			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (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

Serious adverse events	Cohort C: IONIS GHR-LRx, 120 mg	Cohort D: IONIS GHR-LRx, 160 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Cohort A: IONIS GHR-LRx, 60 mg	Cohort B: IONIS GHR-LRx, 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	11 / 12 (91.67%)	7 / 11 (63.64%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Renal cancer stage I			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Poor peripheral circulation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Injection site erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	5
Injection site inflammation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Snoring			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Bacterial test positive			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	2 / 11 (18.18%)
occurrences (all)	1	1	2
Blood urine present			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Heart rate irregular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Mean cell volume increased			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Meniscus injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Muscle strain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Wound subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Congenital, familial and genetic disorders			
Type V hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0



Bundle branch block			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Coronary artery disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	2 / 11 (18.18%)
occurrences (all)	1	1	9
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Somnolence			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 11 (9.09%)
occurrences (all)	0	3	1
Frequent bowel movements			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Glossitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Intra-abdominal haemorrhage			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	1 / 11 (9.09%)
occurrences (all)	2	2	1
Pancreatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pancreatitis acute			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cholelithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Bladder pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Haematuria			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Renal cyst subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0
Endocrine disorders Acromegaly subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Muscle spasms subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Infections and infestations Cervicitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 11 (0.00%) 0
Enterovirus infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Gastrointestinal bacterial infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 11 (9.09%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 12 (0.00%) 0	0 / 11 (0.00%) 0
Periodontitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis chronic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Septic shock			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

<b>Non-serious adverse events</b>	Cohort C: IONIS GHR-LRx, 120 mg	Cohort D: IONIS GHR-LRx, 160 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	5 / 6 (83.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Renal cancer stage I			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Poor peripheral circulation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Chills			

subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site inflammation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Snoring			

subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Bacterial test positive			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood urine present			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Heart rate irregular			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Mean cell volume increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urine protein/creatinine ratio			



increased subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Limb injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Meniscus injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Wound			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Bradycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Bundle branch block			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Coronary artery disease subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Myocardial infarction subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Palpitations subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Headache subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Somnolence subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Eye disorders Asthenopia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	1 / 6 (16.67%) 1	
Frequent bowel movements subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Gastritis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Glossitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Intra-abdominal haemorrhage subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Nausea			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 2	
Pancreatitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Pancreatitis acute subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Cholelithiasis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Renal and urinary disorders Albuminuria subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Bladder pain subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Dysuria subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Haematuria subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Nephrolithiasis			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Renal cyst subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Endocrine disorders Acromegaly subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 6 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Infections and infestations Cervicitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Enterovirus infection subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Gastrointestinal bacterial infection subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	1 / 6 (16.67%) 1	
Periodontitis subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 6 (0.00%) 0	
Pharyngitis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Septic shock			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2018	Amendment 1 clarified inconsistencies within the protocol and included flexibility with protocol procedures to improve operational logistics at the study centers and included recommendations from the Food and Drug Administration (FDA).
10 August 2018	Amendment 2 updated the inclusion criteria pertaining to the use of contraceptive methods for Women of Child Bearing Potential (WOCBP) and men who were engaged in sexual relations with WOCBP so that the requirements corresponded to the latest International Council for Harmonisation (ICH) Clinical Trial Facilitation Group (CTFG) recommendations dated 15 September 2014. Reference to pituitary tumor in the section on Study Drug discontinuation was revised to be consistent with exclusion criterion #4.
14 May 2019	<p>Amendment 3 added Cohort C (120 mg) to explore the safety and efficacy of a higher dose to facilitate Phase 3 dose selection. Since the protocol was powered for 30 subjects , it was planned that recruitment for Cohorts A and B would be stopped at or about 30 subjects and Cohort C initiated. The amendment included the potential to enroll Cohort D (160 mg) but data from the lower dose cohorts would be reviewed prior to initiation of that cohort. The amendment also incorporated clarifications that had been provided in "Memos to Investigators."</p> <p>Addendum 1 to Amendment 3 (17 July 2020) formalized guidance given in the 1 May 2020 memo "ISIS 766720-CS2: Coronavirus COVID-19 Guidance" to Investigators. The addendum allowed for additional visits and procedures to be conducted via home health visits when in-clinic visits were affected due to local precautions and restrictions related to the COVID-19 pandemic that may have limited the subject's ability to go to the clinic.</p>
18 May 2020	Amendment 4 updated several requirements for patient eligibility for the study based on available safety data, formalized the procedures added to the protocol based on the guidance given in the 1 May 2020 Memo to Investigators, and updated the protocol to reflect the decision to conduct Cohort D.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Not specified

Notes: