Clinical trial results:
An Open-Label Extension Trial of IONIS GHR-LRX, an Antisense Inhibitor of the Growth Hormone Receptor Administered Monthly Subcutaneously to Patients with Acromegaly Being Treated with Long-Acting Somatostatin Receptor Ligands (SRL)

Summary

EudraCT number	2019-000591-42
Trial protocol	HU LT PL RO
Global end of trial date	07 July 2022

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	ISIS766720-CS3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03967249
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc
Sponsor organisation address	2855 Gazelle Court, Carlsbad, CA 92010, United States,
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	07 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of extended dosing with ISIS 766720 in subjects with acromegaly.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2019
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	Poland: 4
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Russian Federation: 16
Worldwide total number of subjects	39
EEA total number of subjects	14

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)	37
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 39 subjects were enrolled at 22 centres in the United States (US), Poland, Serbia, Hungary, Lithuania, and the Russian Federation from 27 August 2019 to 08 Apr 2021.

Pre-assignment

Screening details:

All 39 subjects rolled over from the index study ISIS 766720-CS2 (2017-004259-22) and were started at the same ISIS 766720 dose as the previous study of either 60, 80, 120, or 160 mg subcutaneous (SC) injection, every 28 days as an add-on to somatostatin receptor ligand (SRL) therapy for 53 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ISIS 766720 Maximum Low Dose

Arm description:

Subjects who received 60 mg or 80 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.

Arm type	Experimental
Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	IONIS GHR-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 766720 60 mg, administered subcutaneously.

Investigational medicinal product name	Somatostatin Receptor Ligand (SRL)
Investigational medicinal product code	
Other name	Lanreotide, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SRL therapy (lanreotide, octreotide) at the same dose and regimen as ISIS 766720-CS2 throughout this study.

Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	IONIS GHR-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 766720 80 mg, administered subcutaneously.

Arm title	ISIS 766720 Maximum High Dose

Arm description:

Subjects who received 120 mg or 160 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose

administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.

Arm type	Experimental
Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	IONIS GHR-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 766720 120 mg, administered subcutaneously.

Investigational medicinal product name	Somatostatin Receptor Ligand (SRL)
Investigational medicinal product code	
Other name	Lanreotide, Octreotide
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

SRL therapy (lanreotide, octreotide) at the same dose and regimen as ISIS 766720-CS2 throughout this study.

Investigational medicinal product name	ISIS 766720
Investigational medicinal product code	
Other name	IONIS GHR-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 766720 160 mg, administered subcutaneously.

Number of subjects in period 1	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose
Started	16	23
Completed	15	22
Not completed	1	1
Voluntary Withdrawal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	ISIS 766720 Maximum Low Dose
Reporting group description:	
Subjects who received 60 mg or 80 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.	
Reporting group title	ISIS 766720 Maximum High Dose
Reporting group description:	
Subjects who received 120 mg or 160 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.	

Reporting group values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose	Total
Number of subjects	16	23	39
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.4	47.0	
standard deviation	± 11.4	± 12.8	-
Gender categorical Units: Subjects			
Female	13	11	24
Male	3	12	15
Race Units: Subjects			
Black	0	1	1
White	16	22	38
Ethnicity Units: Subjects			
Not Hispanic or Latino	16	23	39

End points

End points reporting groups

Reporting group title	ISIS 766720 Maximum Low Dose

Reporting group description:

Subjects who received 60 mg or 80 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.

Reporting group title	ISIS 766720 Maximum High Dose

Reporting group description:

Subjects who received 120 mg or 160 mg of ISIS 766720 in the index study, ISIS 766720-CS2, started at the same dose of ISIS 766720. Dose-escalated subjects are summarized by the maximum dose administered subcutaneously once every 28 days for 53 weeks with the option to continue treatment for another 52 weeks as add-on to SRL therapy in this study.

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product. A TEAE is defined as an event that occurred after the initiation of the study drug dosing and before the end of the follow-up period. Safety Set included all subjects who were enrolled and received at least 1 dose of ISIS 766720 in the present study.

End point type	Primary

End point timeframe:

From the first dose of the study drug up to end of study (up to approximately 3 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As prespecified in the protocol only descriptive statistics were planned for this endpoint.

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	23		
Units: subjects	15	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Insulin-like Growth Factor I (IGF-1) Levels

End point title	Percent Change From Baseline in Insulin-like Growth Factor I (IGF-1) Levels

End point description:

IGF-1 is a hormone that manages the effects of growth hormone (GH) in the body. Percent (%) change from baseline in IGF-1 levels was measured at Days 169 and 365. Pooled baseline was used for analysis, defined as 1) ISIS 766720-CS2 baseline for subjects with gap between last dose of ISIS 766720-CS2 and the first dose of ISIS 766720-CS3 <=45 days or 2) ISIS 766720-CS3 baseline for subjects with gap between last dose of ISIS 766720-CS2 and first dose of ISIS 766720-CS3 >45 days or subjects randomised to placebo in ISIS 766720-CS2 study. Negative % change from baseline indicates improvement. Per Protocol Set (PPS) included all Full Analysis Set (FAS) subjects who completed at least 9 of the 14 doses of ISIS 766720 and had no significant protocol deviations that would have been expected to affect efficacy. Number of subjects analysed indicates the number of subjects with data available for analyses. This analysis uses the Per-Protocol Set with IGF-1 >1.3 x ULN at ISIS 766720-CS3 Day 1.

End point type	Secondary

End point timeframe:

Baseline, Days 169 and 365

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	17		
Units: percent change				
arithmetic mean (standard deviation)				
Day 169 (n=9, 17)	14.4 (± 12.0)	-5.8 (± 21.1)		
Day 365 (n=8, 15)	-6.2 (± 12.3)	-11.7 (± 19.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Normalised IGF-1 Levels to Within 1.2 Times of Gender and Age-Adjusted Upper Limits

End point title	Percentage of Subjects Achieving Normalised IGF-1 Levels to Within 1.2 Times of Gender and Age-Adjusted Upper Limits

End point description:

Normalisation of circulating IGF-1 is a validated marker for the treatment of acromegaly. Normal IGF-1 levels for a subject differs based on age and gender. Number of subjects with a normal IGF-1 level which were 1.2 times within gender and age limits at Days 169 and 365 are presented where IGF-1 level is defined as the ratio of the serum IGF-1 level and the subject's upper limit of normal (ULN). The ULN varied among subjects due to gender and age. Subjects whose calculated ratios were ≤1.2 or 1.0 were deemed as achieving normalised IGF. FAS included all enrolled subjects who received at least 1 dose of the study drug and had at least 1 post-baseline efficacy or pharmacodynamic (PD) assessment. Number of subjects analysed indicates the number of subjects with data available for analyses. 'n' indicates the number of subjects analysed at the specified time point.

End point type	Secondary

End point timeframe:

Days 169 and 365

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: percentage of subjects				
number (not applicable)				
Day 169 (n=14, 22)	21.4	9.1		
Day 365 (n=11, 18)	36.4	22.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Normalised IGF-1 Levels to Within 1.0 Times of Gender and Age-Adjusted Upper Limits

End point title	Percentage of Subjects Achieving Normalised IGF-1 Levels to Within 1.0 Times of Gender and Age-Adjusted Upper Limits

End point description:

Normalisation of circulating IGF-1 is a validated marker for the treatment of acromegaly. Normal IGF-1 levels for a subject differs based on age and gender. Number of subjects with a normal IGF-1 level which were 1.0 times within gender and age limits at Days 169 and 365 are presented where IGF-1 level is defined as the ratio of the serum IGF-1 level and the subject's ULN. The ULN varied among subjects due to gender and age. Subjects whose calculated ratios were ≤1.2 or 1.0 were deemed as achieving normalised IGF. FAS included all enrolled subjects who received at least 1 dose of the study drug and had at least 1 post-baseline efficacy or PD assessment. Number of subjects analysed indicates the number of subjects with data available for analyses. 'n' indicates the number of subjects analysed at the specified time point.

End point type	Secondary

End point timeframe:

Days 169 and 365

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: percentage of subjects				
number (not applicable)				
Day 169 (n=14, 22)	21.4	0.0		
Day 365 (n=11, 18)	27.3	5.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Began Other Acromegaly Medication

End point title	Percentage of Subjects who Began Other Acromegaly

	Medication

End point description:

FAS included all enrolled subjects who received at least 1 dose of the study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Secondary

End point timeframe:

From the first dose of the study drug up to approximately 3 years

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	23		
Units: percentage of subjects				
number (not applicable)	0.0	13.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From First Dose of ISIS 766720 in This Open-label Extension (CS3) Study to Date of Initiation of Other Acromegaly Medications

End point title	Time From First Dose of ISIS 766720 in This Open-label Extension (CS3) Study to Date of Initiation of Other Acromegaly Medications

End point description:

FAS included all enrolled subjects who received at least 1 dose of the study drug and had at least 1 post-baseline efficacy or PD assessment.

End point type	Secondary

End point timeframe:

From the first dose of the study drug up to approximately 3 years

End point values	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	3		
Units: days				
median (full range (min-max))	(to)	376.0 (158.0 to 419.0)		

Notes:

[2] - Number of subjects analysed for the endpoint included subjects who began other acromegaly medication

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of the study drug up to end of study (up to approximately 2 years)

Adverse event reporting additional description:

Safety Set included all subjects who were enrolled and received at least 1 dose of ISIS 766720 in the present study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	ISIS 766720 Maximum Low Dose

Reporting group description:

Subjects who received 60 mg or 80 mg of ISIS 766720 in the index study, ISIS 766720-CS2, continued to receive the same dose of ISIS 766720 as the maximum dose administered subcutaneously once every 28 days for 105 weeks as add-on to SRL therapy in this study.

Reporting group title	ISIS 766720 Maximum High Dose

Reporting group description:

Subjects who received 120 mg or 160 mg of ISIS 766720 in the index study, ISIS 766720-CS2, continued to receive the same dose of ISIS 766720 as the maximum dose administered subcutaneously once every 28 days for 105 weeks as add-on to SRL therapy in this study.

Serious adverse events	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	9 / 23 (39.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
IIIrd nerve disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterovaginal prolapse			
subjects affected / exposed[1]	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug dependence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Osteoarthritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 16 (0.00%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

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

Non-serious adverse events	ISIS 766720 Maximum Low Dose	ISIS 766720 Maximum High Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	20 / 23 (86.96%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Uterine leiomyoma			
subjects affected / exposed[2]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 16 (18.75%)	1 / 23 (4.35%)	
occurrences (all)	7	1	
Arteriosclerosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypotension			

subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Raynaud's phenomenon			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Varicose vein			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Administration site haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Administration site pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Administration site pruritus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Administration site swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Chills			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Injection site erythema			

subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed[3]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cervical polyp			
subjects affected / exposed[4]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed[5]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gynaecomastia			
subjects affected / exposed[6]	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pelvic prolapse			
subjects affected / exposed[7]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal inflammation			
subjects affected / exposed[8]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	2 / 16 (12.50%)	2 / 23 (8.70%)	
occurrences (all)	5	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 16 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Coronavirus test positive			

subjects affected / exposed	1 / 16 (6.25%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Blood glucose increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood pressure diastolic increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	3	
Red blood cell sedimentation rate increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Radius fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Road traffic accident			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	0 / 16 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 16 (0.00%)	4 / 23 (17.39%)	
occurrences (all)	0	4	
Sinus bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Arrhythmia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Bundle branch block left			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Ventricular failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 16 (18.75%)	1 / 23 (4.35%)	
occurrences (all)	6	1	
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Diabetic neuropathy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
IIIrd nerve disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Intercostal neuralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Radiculopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	3 / 16 (18.75%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Thrombocytosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Astigmatism			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	2 / 16 (12.50%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	6	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	4	
Abdominal pain lower			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Chronic gastritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Malpositioned teeth			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Cholecystitis acute			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nonalcoholic fatty liver disease			

subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 16 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Hyperoxaluria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Goitre			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			

subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pituitary cyst			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 23 (8.70%)	
occurrences (all)	1	3	
Osteoarthritis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Arthritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Spinal osteoarthritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	1 / 16 (6.25%)	6 / 23 (26.09%)	
occurrences (all)	1	7	
Urinary tract infection			

subjects affected / exposed	2 / 16 (12.50%)	4 / 23 (17.39%)	
occurrences (all)	2	6	
Viral infection			
subjects affected / exposed	3 / 16 (18.75%)	0 / 23 (0.00%)	
occurrences (all)	7	0	
Gingivitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Periodontitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis chronic			

subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Urethritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed[9]	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Dyslipidaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Hyperglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Glucose tolerance impaired			
subjects affected / exposed	0 / 16 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hyperalbuminaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event term is based on the female population in this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported