Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED, MULTICENTER, 2-PART PHASE II STUDY ON REPLACEMENT OF STEROIDS BY IFX-1 IN ACTIVE GRANULOMATOSIS WITH POLYANGIITIS (GPA) AND MICROSCOPIC POLYANGIITIS (MPA)

Summary

EudraCT number	2018-000768-27
Trial protocol	CZ DE SE NL IE GB ES DK BE IT
Global end of trial date	08 June 2021

Results information

Result version number	v1 (current)
This version publication date	24 July 2022
First version publication date	24 July 2022

Trial information

Trial identification

Sponsor protocol code	IFX-1-P2.5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03895801
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	InflaRx GmbH
Sponsor organisation address	Winzerlaer Str. 2, Jena, Germany,
Public contact	InflaRx GmbH, InflaRx GmbH, +49 3641508180, info@inflarx.de
Scientific contact	InflaRx GmbH, InflaRx GmbH, +49 3641508180, info@inflarx.de

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	22 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2021
Global end of trial reached?	Yes
Global end of trial date	08 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of IFX-1 treatment as a replacement for glucocorticoids [GC] therapy in subjects with GPA and MPA.

Protection of trial subjects:

The study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with International Council for Harmonization (ICH) guideline on Good Clinical Practice (GCP). All persons participating in the conduct of the study (e.g., sponsor, investigators) committed themselves to observe the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) as well as all pertinent national laws and the ICH guidelines for GCP (June 2017) and CPMP/ICH/135/95 (September 1997). Only subjects that met all inclusion criteria and no exclusion criteria were to enter the study. All patients were free to discontinue their participation in the study at any time.

Background therapy:

Immunosuppressive therapy administered during Remission-Induction Phase: Rituximab or Cyclophosphamide;
Immunosuppressive therapy administered during Remission-Maintenance Phase: Rituximab or Cyclophosphamide or Azathioprine or Methotrexate or Mycophenolate Mofetil or Mycophenolate Sodium;

Evidence for comparator: -

Actual start date of recruitment	03 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Russian Federation: 1
Worldwide total number of subjects	57
EEA total number of subjects	53

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)	39
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 91 subjects screened, 57 were enrolled in the study and randomized to treatment. Reasons for subjects failing screening included failure to meet randomization criteria, physician decision, withdrawal by subject, and other.

Period 1

Period 1 title	Treatment and follow-up period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	IFX-1 + Placebo-GC

Arm description:

IFX-1: intravenously administered; Placebo-Glucocorticoid (Placebo-GC): orally administered

Arm type	Experimental
Investigational medicinal product name	IFX-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects randomized to treatment group "IFX-1 + Placebo-GC" or "IFX-1 + Reduced Dose GC" received 800 mg IFX-1 on Days 1, 4, and 8, and then every other week from Week 2 (Day 15) to Week 16.
Subjects randomized to treatment group "Placebo-IFX-1 + Standard Dose GC" received Placebo infusions.

Arm title	Placebo-IFX-1 + Standard Dose GC

Arm description:

Placebo-IFX-1: intravenously administered; Glucocorticoid (GC): orally administered

Arm type	Active comparator
Investigational medicinal product name	Glucocorticoid (GC)
Investigational medicinal product code	
Other name	Prednisone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized into treatment group "Placebo-IFX-1 + Standard Dose GC" started with a standard-dose of 60 mg GC daily and were tapered down subsequently.
Subjects randomized into treatment group "IFX-1 + Reduced Dose GC", received only half of the starting dose received by subjects in "Placebo-IFX-1 + Standard Dose GC".
Subjects randomized into treatment group "IFX-1 + Placebo-GC", only received Placebo GC.

Arm title	IFX-1 + Reduced Dose GC

Arm description:

IFX-1: intravenously administered; Glucocorticoid (GC): orally administered

Arm type	Experimental

Investigational medicinal product name	IFX-1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects randomized to treatment group "IFX-1 + Placebo-GC" or "IFX-1 + Reduced Dose GC" received 800 mg IFX-1 on Days 1, 4, and 8, and then every other week from Week 2 (Day 15) to Week 16.
Subjects randomized to treatment group "Placebo-IFX-1 + Standard Dose GC" received Placebo infusions.

Investigational medicinal product name	Glucocorticoid (GC)
Investigational medicinal product code	
Other name	Prednisone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized into treatment group "Placebo-IFX-1 + Standard Dose GC" started with a standard-dose of 60 mg GC daily and were tapered down subsequently.
Subjects randomized into treatment group "IFX-1 + Reduced Dose GC", received only half of the starting dose received by subjects in "Placebo-IFX-1 + Standard Dose GC".
Subjects randomized into treatment group "IFX-1 + Placebo-GC", only received Placebo GC.

Number of subjects in period 1	IFX-1 + Placebo-GC	Placebo-IFX-1 + Standard Dose GC	IFX-1 + Reduced Dose GC
Started	18	24	15
Completed	16	22	13
Not completed	2	2	2
Adverse event, serious fatal	1	-	-
Physician decision	-	-	1
Adverse event, non-fatal	-	1	-
Other reason	-	-	1
Progressive disease	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IFX-1 + Placebo-GC
Reporting group description:	
IFX-1: intravenously administered; Placebo-Glucocorticoid (Placebo-GC): orally administered	
Reporting group title	Placebo-IFX-1 + Standard Dose GC
Reporting group description:	
Placebo-IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	
Reporting group title	IFX-1 + Reduced Dose GC
Reporting group description:	
IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	

Reporting group values	IFX-1 + Placebo-GC	Placebo-IFX-1 + Standard Dose GC	IFX-1 + Reduced Dose GC
Number of subjects	18	24	15
Age categorical Units: Subjects			
Adults (18-64 years)	11	19	9
From 65-84 years	7	5	6
Age continuous Units: years			
arithmetic mean	60.8	55.0	58.5
standard deviation	± 11.4	± 12.3	± 14.0
Gender categorical Units: Subjects			
Female	6	6	5
Male	12	18	10
AAV disease type Units: Subjects			
GPA	10	16	11
MPA	8	8	4

Reporting group values	Total		
Number of subjects	57		
Age categorical Units: Subjects			
Adults (18-64 years)	39		
From 65-84 years	18		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	17		
Male	40		

AAV disease type Units: Subjects			
GPA	37		
MPA	20		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) consists of all subjects who received at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs). Subjects will be analyzed in the treatment group they were randomized to regardless of the treatment they actually received (intention-to-treat principle).

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set (SAF) consists of all subjects who received at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs). Subjects will be analyzed according to the treatment they actually received.

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	57	57	
Age categorical Units: Subjects			
Adults (18-64 years)	39	39	
From 65-84 years	18	18	
Age continuous Units: years			
arithmetic mean	57.8	57.8	
standard deviation	± 12.6	± 12.6	
Gender categorical Units: Subjects			
Female	17	17	
Male	40	40	
AAV disease type Units: Subjects			
GPA	37	37	
MPA	20	20	

End points

End points reporting groups

Reporting group title	IFX-1 + Placebo-GC
Reporting group description:	
IFX-1: intravenously administered; Placebo-Glucocorticoid (Placebo-GC): orally administered	
Reporting group title	Placebo-IFX-1 + Standard Dose GC
Reporting group description:	
Placebo-IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	
Reporting group title	IFX-1 + Reduced Dose GC
Reporting group description:	
IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consists of all subjects who received at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs). Subjects will be analyzed in the treatment group they were randomized to regardless of the treatment they actually received (intention-to-treat principle).	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set (SAF) consists of all subjects who received at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs). Subjects will be analyzed according to the treatment they actually received.	

Primary: Percentage of Subjects Achieving Clinical Response

End point title	Percentage of Subjects Achieving Clinical Response
End point description:	
Percentage of subjects achieving clinical response (reduction in Birmingham Vasculitis Activity Score [BVAS] of ≥50% compared to baseline and no worsening in any body system). Subjects who received rescue therapy after Day 1 or discontinued due to related adverse event, lack of efficacy or progressive disease are considered as non-responders at all subsequent visits.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	IFX-1 + Placebo-GC	Placebo-IFX-1 + Standard Dose GC	IFX-1 + Reduced Dose GC	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	18	23[1]	13[2]	54[3]
Units: Percentage				
Responder	89	96	77	89
Non-responder	11	4	23	11

Notes:

[1] - 1 subject with missing assessment

[2] - 2 subjects with missing assessment

[3] - 3 subjects with missing assessment

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

The experimental arm IFX-1 + Placebo-GC and the control arm Placebo-IFX-1 + Standard Dose GC were compared regarding the risk difference for the percentage of subjects with clinical response at Week 16 (FAS) and its 90% confidence interval (CI) based on the Farrington-Manning score.

Comparison groups	IFX-1 + Placebo-GC v Placebo-IFX-1 + Standard Dose GC
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-6.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.2
upper limit	6.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First administration of IFX-1 or Placebo IFX-1 until end of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	IFX-1 + Placebo-GC
Reporting group description: IFX-1: intravenously administered; Placebo-Glucocorticoid (Placebo-GC): orally administered	
Reporting group title	Placebo-IFX-1 + Standard Dose GC
Reporting group description: Placebo-IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	
Reporting group title	IFX-1 + Reduced Dose GC
Reporting group description: IFX-1: intravenously administered; Glucocorticoid (GC): orally administered	

Serious adverse events	IFX-1 + Placebo-GC	Placebo-IFX-1 + Standard Dose GC	IFX-1 + Reduced Dose GC
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	4 / 24 (16.67%)	3 / 15 (20.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Vascular disorders			
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (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

General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (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
Malaise			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (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
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (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
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary sepsis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	IFX-1 + Placebo-GC	Placebo-IFX-1 + Standard Dose GC	IFX-1 + Reduced Dose GC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	23 / 24 (95.83%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Haemangioma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 18 (11.11%)	6 / 24 (25.00%)	2 / 15 (13.33%)
occurrences (all)	2	7	2
Haematoma			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Deep vein thrombosis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Cyanosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Granulomatosis with polyangiitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vasculitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
White coat hypertension			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	4 / 24 (16.67%)	2 / 15 (13.33%)
occurrences (all)	0	4	2
Fat tissue increased			
subjects affected / exposed	1 / 18 (5.56%)	4 / 24 (16.67%)	0 / 15 (0.00%)
occurrences (all)	1	5	0
Adverse drug reaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Oedema peripheral			

subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Chest pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Condition aggravated			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Feeling cold			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Chills			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Feeling hot			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infusion site extravasation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Drug hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Secondary immunodeficiency			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Bronchostenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nasal crusting			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pulmonary pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Stridor			

subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 18 (5.56%)	4 / 24 (16.67%)	1 / 15 (6.67%)
occurrences (all)	1	4	1
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Mood swings			
subjects affected / exposed	0 / 18 (0.00%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Abnormal behaviour			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Decreased interest			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Persistent depressive disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight increased			
subjects affected / exposed	1 / 18 (5.56%)	5 / 24 (20.83%)	0 / 15 (0.00%)
occurrences (all)	1	5	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood sodium increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Intraocular pressure increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Liver function test increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Arthropod bite			

subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Epicondylitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Heavy exposure to ultraviolet light			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Spinal compression fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Traumatic haematoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Dermoid cyst			

subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Atrial thrombosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diastolic dysfunction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 18 (16.67%)	5 / 24 (20.83%)	2 / 15 (13.33%)
occurrences (all)	3	5	2
Disturbance in attention			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Carotid arteriosclerosis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Transient ischaemic attack			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 24 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Lymphopenia			
subjects affected / exposed	0 / 18 (0.00%)	4 / 24 (16.67%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Leukopenia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Eosinophilia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

Neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Corneal erosion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dacryoadenitis acquired			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Vision blurred			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Diarrhoea			

subjects affected / exposed	3 / 18 (16.67%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	3 / 15 (20.00%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gingivitis ulcerative			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	1 / 15 (6.67%)
occurrences (all)	1	2	1

Erythema			
subjects affected / exposed	0 / 18 (0.00%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Acne			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eczema asteatotic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hand dermatitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Seborrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nocturia			

subjects affected / exposed	2 / 18 (11.11%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Acute kidney injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Renal impairment			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)	6 / 24 (25.00%)	1 / 15 (6.67%)
occurrences (all)	1	7	1
Arthralgia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 24 (4.17%)	3 / 15 (20.00%)
occurrences (all)	4	1	4
Myalgia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 24 (4.17%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Limb discomfort			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Exostosis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Facet joint syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Muscle atrophy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rhabdomyolysis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Spondylolisthesis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Tendon discomfort			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	6 / 24 (25.00%)	5 / 15 (33.33%)
occurrences (all)	1	7	6
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 24 (12.50%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 24 (8.33%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Cystitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1

Upper respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Asymptomatic COVID-19			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Helicobacter gastritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Pustule			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Viral rhinitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	3 / 18 (16.67%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	4	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Increased appetite			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Decreased appetite			
subjects affected / exposed	1 / 18 (5.56%)	0 / 24 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gout			

subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 24 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 24 (4.17%)	0 / 15 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2019	Protocol Version 4.0, dated 01-Oct-2019, included 31 revisions to the first in all participating countries fully approved Protocol Version 3.0, dated 03-Dec-2018.
07 October 2020	Protocol Version 5.0, dated 07-Oct-2020, included 10 revisions to formerly fully approved Protocol Version 4.0, dated 01-Oct-2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported