



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 $\geq 50\%$ 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 occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Reproductive system and breast disorders | | | |
| Gynaecomastia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 2 / 24 (8.33%) 2 | 0 / 15 (0.00%) 0 |
| Bronchostenosis subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Dysphonia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Nasal crusting subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Pulmonary pain subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 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 occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Investigations | | | |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 5 / 24 (20.83%) 5 | 0 / 15 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Blood sodium increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Cardiac murmur subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Hepatic enzyme abnormal subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Hepatic enzyme increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Intraocular pressure increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Liver function test increased subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Skin laceration subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 2 / 15 (13.33%) 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 occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 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 | | | |

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|--------------------------------------|-----------------|-----------------|-----------------|
| 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 occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Ear and labyrinth disorders Ear congestion subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Corneal erosion subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Dacryoadenitis acquired subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Eye pain subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 2 | 0 / 15 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Visual impairment subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 2 / 24 (8.33%) 2 | 1 / 15 (6.67%) 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 occurrences (all) | 2 / 18 (11.11%) 2 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 24 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| Haematuria subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Renal impairment subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 6 / 24 (25.00%) 7 | 1 / 15 (6.67%) 1 |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 18 (16.67%) 4 | 1 / 24 (4.17%) 1 | 3 / 15 (20.00%) 4 |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | 1 / 24 (4.17%) 1 | 2 / 15 (13.33%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 2 / 24 (8.33%) 4 | 0 / 15 (0.00%) 0 |
| Limb discomfort subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 1 / 24 (4.17%) 1 | 0 / 15 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 1 / 24 (4.17%) 2 | 0 / 15 (0.00%) 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 |

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