



## Clinical trial results:

### A Double Blind, Randomized, Placebo Controlled, Multi-Center Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade®) in Combination with Methotrexate in Patients with Very Early Inflammatory Arthritis

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2006-002787-26    |
| Trial protocol           | AT NL DE ES GR GB |
| Global end of trial date | 31 August 2014    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 01 November 2018 |
| First version publication date | 01 November 2018 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | DINORA |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN21272423 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |                                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Medical University of Vienna                                                                                |
| Sponsor organisation address | Spitalgasse 23, Vienna, Austria, 1090                                                                       |
| Public contact               | Internal Medicine III, Rheumatology, Medical University of Vienna, 043 14040043010, josef.smolen@wienkav.at |
| Scientific contact           | Internal Medicine III, Rheumatology, Medical University of Vienna, +43 14040043010, josef.smolen@wienkav.at |

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                       | 23 February 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 31 August 2014   |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 31 August 2014   |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that patients with very early arthritis have a higher probability of achieving a state of clinical remission at end of infliximab therapy if treated with infliximab plus MTX when compared to MTX monotherapy or supportive treatment only.

Protection of trial subjects:

Personal data pseudonymized.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 01 May 2007 |
| 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 | Spain: 1        |
| Country: Number of subjects enrolled | Netherlands: 28 |
| Country: Number of subjects enrolled | Austria: 29     |
| Country: Number of subjects enrolled | Germany: 23     |
| Country: Number of subjects enrolled | Greece: 3       |
| Country: Number of subjects enrolled | Italy: 6        |
| Worldwide total number of subjects   | 90              |
| EEA total number of subjects         | 90              |

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) | 70 |
| From 65 to 84 years  | 20 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were eligible if they had symptom duration of 2 to 16 weeks with synovial swelling in at least 2 joints (66 joint count) of which a minimum of one joint must have been a metacarpophalangeal, proximal interphalangeal or a metatarsophalangeal (MTP) joint. However, two MTP-joints were considered not sufficient for inclusion.

### Pre-assignment

Screening details:

Two screening visits for symptom duration which must have been 2 weeks at least (subjects did not receive study treatment before 12 weeks of symptom duration) and 16 weeks at most. The 16 weeks included an observation period of at least 2 weeks, as reported by the subject.

### Period 1

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

Blinding implementation details:

A "double-dummy-like" administration of study medication was pursued. Every patient was treated with tablets containing methotrexate or placebo and with infusions containing infliximab or placebo. The study medication code was kept blinded in patients who discontinued prematurely.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | IFX+MTX |

Arm description:

Anti-TNF $\alpha$  chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)

|                                        |                                                                 |
|----------------------------------------|-----------------------------------------------------------------|
| Arm type                               | Experimental                                                    |
| Investigational medicinal product name | Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX) |
| Investigational medicinal product code |                                                                 |
| Other name                             |                                                                 |
| Pharmaceutical forms                   | Solution for infusion                                           |
| Routes of administration               | Intravenous use                                                 |

Dosage and administration details:

Infliximab is a chimeric IgG1 monoclonal antibody manufactured from a recombinant cell line cultured by continuous perfusion. Infliximab (IFX) was administered by intravenous infusions at a dose of 3 mg/kg at 0, 2 and 6 weeks, and at 5 mg/kg every 8 weeks thereafter.

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Methotrexate (MTX) |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Methotrexate (MTX) was dosed orally according to a rapid dose escalation scheme: start at 10 mg/week and increased to 25 mg/week in three steps with 2-week intervals except in cases of intolerance.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | MTX monotherapy |
|------------------|-----------------|

Arm description:

Methotrexate (MTX) monotherapy

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Methotrexate (MTX) |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Methotrexate (MTX) was dosed orally according to a rapid dose escalation scheme: start at 10 mg/week and increased to 25 mg/week in three steps with 2-week intervals except in cases of intolerance.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Placebo         |
| Investigational medicinal product name | Placebo         |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Capsule         |
| Routes of administration               | Intravenous use |

Dosage and administration details:

A "double-dummy-like" administration of study medication was pursued. Every patient was treated with tablets containing methotrexate (MTX) or placebo and with infusions containing infliximab (IFX) or placebo.

| <b>Number of subjects in period 1</b> | IFX+MTX | MTX monotherapy | Placebo |
|---------------------------------------|---------|-----------------|---------|
| Started                               | 38      | 36              | 16      |
| Completed                             | 14      | 11              | 7       |
| Not completed                         | 24      | 25              | 9       |
| Consent withdrawn by subject          | 6       | 9               | 1       |
| Adverse event, non-fatal              | 2       | 1               | 1       |
| Accidental unblinding                 | -       | -               | 1       |
| Unknown                               | 3       | 2               | -       |
| Lost to follow-up                     | 1       | 2               | -       |
| Unable to comply with protocol        | -       | 2               | -       |
| Lack of efficacy                      | 12      | 9               | 6       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                        |                 |
|----------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                  | IFX+MTX         |
| Reporting group description:<br>Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX) |                 |
| Reporting group title                                                                                                                  | MTX monotherapy |
| Reporting group description:<br>Methotrexate (MTX) monotherapy                                                                         |                 |
| Reporting group title                                                                                                                  | Placebo         |
| Reporting group description:<br>Placebo                                                                                                |                 |

| Reporting group values                                                                                                                                                                                                                                    | IFX+MTX    | MTX monotherapy | Placebo    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------|------------|
| Number of subjects                                                                                                                                                                                                                                        | 38         | 36              | 16         |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |            |                 |            |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |            |                 |            |
| Age continuous<br>Units: years                                                                                                                                                                                                                            |            |                 |            |
| arithmetic mean                                                                                                                                                                                                                                           | 52.1       | 52.9            | 54.4       |
| standard deviation                                                                                                                                                                                                                                        | $\pm 14.1$ | $\pm 14$        | $\pm 11.2$ |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |            |                 |            |
| Female                                                                                                                                                                                                                                                    | 26         | 28              | 9          |
| Male                                                                                                                                                                                                                                                      | 12         | 8               | 7          |

| Reporting group values                                                                                                                                                                                           | Total                           |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--|--|
| Number of subjects                                                                                                                                                                                               | 90                              |  |  |
| Age categorical<br>Units: Subjects                                                                                                                                                                               |                                 |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years) | 0<br>0<br>0<br>0<br>0<br>0<br>0 |  |  |

|                   |   |  |  |
|-------------------|---|--|--|
| From 65-84 years  | 0 |  |  |
| 85 years and over | 0 |  |  |

|                    |    |  |  |
|--------------------|----|--|--|
| Age continuous     |    |  |  |
| Units: years       |    |  |  |
| arithmetic mean    |    |  |  |
| standard deviation | -  |  |  |
| Gender categorical |    |  |  |
| Units: Subjects    |    |  |  |
| Female             | 63 |  |  |
| Male               | 27 |  |  |

## End points

### End points reporting groups

|                                                                                                                                        |                 |
|----------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                  | IFX+MTX         |
| Reporting group description:<br>Anti-TNF $\alpha$ chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX) |                 |
| Reporting group title                                                                                                                  | MTX monotherapy |
| Reporting group description:<br>Methotrexate (MTX) monotherapy                                                                         |                 |
| Reporting group title                                                                                                                  | Placebo         |
| Reporting group description:<br>Placebo                                                                                                |                 |

### Primary: Clinical remission

|                                    |                    |
|------------------------------------|--------------------|
| End point title                    | Clinical remission |
| End point description:             |                    |
| End point type                     | Primary            |
| End point timeframe:<br>At week 54 |                    |

| End point values                                | IFX+MTX           | MTX monotherapy   | Placebo           |  |
|-------------------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type                              | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed                     | 38 <sup>[1]</sup> | 36 <sup>[2]</sup> | 16 <sup>[3]</sup> |  |
| Units: Number of patients in clinical remission |                   |                   |                   |  |
| Clinical remission                              | 12                | 5                 | 0                 |  |
| No clinical remission                           | 26                | 31                | 16                |  |

Notes:

[1] - Intention to treat

[2] - Intention to treat

[3] - Intention to treat

### Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| Statistical analysis title              | Primary endpoint                    |
| Comparison groups                       | IFX+MTX v MTX monotherapy v Placebo |
| Number of subjects included in analysis | 90                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.05                              |
| Method                                  | Chi-squared                         |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During study period

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |                      |
|-----------------|----------------------|
| Dictionary name | Conducted by Janssen |
|-----------------|----------------------|

|                    |    |
|--------------------|----|
| Dictionary version | NA |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | IFX+MTX |
|-----------------------|---------|

Reporting group description:

Anti-TNFα chimeric monoclonal antibody infliximab (IFX) in combination with methotrexate (MTX)

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | MTX monotherapy |
|-----------------------|-----------------|

Reporting group description:

Methotrexate (MTX) monotherapy

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events                                                | IFX+MTX         | MTX monotherapy | Placebo         |
|-----------------------------------------------------------------------|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events                     |                 |                 |                 |
| subjects affected / exposed                                           | 6 / 38 (15.79%) | 3 / 36 (8.33%)  | 3 / 16 (18.75%) |
| number of deaths (all causes)                                         | 0               | 0               | 0               |
| number of deaths resulting from adverse events                        | 0               | 0               | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)   |                 |                 |                 |
| Haematuria, followed by a diagnosis of bladder cancer                 |                 |                 |                 |
| subjects affected / exposed                                           | 0 / 38 (0.00%)  | 1 / 36 (2.78%)  | 0 / 16 (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           |
| Vascular disorders                                                    |                 |                 |                 |
| Hypertensive episode one hour after the last infusion with study drug |                 |                 |                 |
| subjects affected / exposed                                           | 0 / 38 (0.00%)  | 1 / 36 (2.78%)  | 0 / 16 (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           |
| Cardiac disorders                                                     |                 |                 |                 |
| Myocardial infarction more than half a year after last study drug     |                 |                 |                 |

|                                                                        |                |                |                |
|------------------------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                                            | 0 / 38 (0.00%) | 1 / 36 (2.78%) | 0 / 16 (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          |
| Social circumstances                                                   |                |                |                |
| Fainted during blood collection, prior to administration of study drug |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 16 (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          |
| Endocrine disorders                                                    |                |                |                |
| Biliary pancreatitis in a time after the study medication              |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 16 (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          |
| Significantly raised transaminase levels                               |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all                        | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders                        |                |                |                |
| Significant flare of disease activity                                  |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 16 (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          |
| Infections and infestations                                            |                |                |                |
| Urinary tract infection                                                |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all                        | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0          | 0 / 0          |
| MTX pneumonitis (opportunistic) infection                              |                |                |                |
| subjects affected / exposed                                            | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all                        | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders                                     |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Hyperglycemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 0 / 36 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 38 (0.00%) | 0 / 36 (0.00%) | 1 / 16 (6.25%) |
| 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: 0.03 %

| <b>Non-serious adverse events</b>                                                       | IFX+MTX          | MTX monotherapy  | Placebo          |
|-----------------------------------------------------------------------------------------|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events                                   |                  |                  |                  |
| subjects affected / exposed                                                             | 34 / 38 (89.47%) | 32 / 36 (88.89%) | 13 / 16 (81.25%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                     |                  |                  |                  |
| Neoplasms                                                                               |                  |                  |                  |
| subjects affected / exposed                                                             | 0 / 38 (0.00%)   | 1 / 36 (2.78%)   | 0 / 16 (0.00%)   |
| occurrences (all)                                                                       | 0                | 1                | 0                |
| Vascular disorders                                                                      |                  |                  |                  |
| Diseases of circulatory system                                                          |                  |                  |                  |
| subjects affected / exposed                                                             | 6 / 38 (15.79%)  | 7 / 36 (19.44%)  | 3 / 16 (18.75%)  |
| occurrences (all)                                                                       | 8                | 10               | 6                |
| Pregnancy, puerperium and perinatal conditions                                          |                  |                  |                  |
| Diseases of genitourinary system (pregnancy, childbirth and puerperium)                 |                  |                  |                  |
| subjects affected / exposed                                                             | 2 / 38 (5.26%)   | 2 / 36 (5.56%)   | 0 / 16 (0.00%)   |
| occurrences (all)                                                                       | 2                | 4                | 0                |
| General disorders and administration site conditions                                    |                  |                  |                  |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified |                  |                  |                  |
| subjects affected / exposed                                                             | 11 / 38 (28.95%) | 11 / 36 (30.56%) | 5 / 16 (31.25%)  |
| occurrences (all)                                                                       | 21               | 22               | 6                |
| Social circumstances                                                                    |                  |                  |                  |
| External causes of morbidity                                                            |                  |                  |                  |

|                                                                                                                                                                                            |                        |                        |                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                           | 1 / 38 (2.63%)<br>1    | 0 / 36 (0.00%)<br>0    | 0 / 16 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Diseases of respiratory system<br>subjects affected / exposed<br>occurrences (all)                                                      | 23 / 38 (60.53%)<br>33 | 16 / 36 (44.44%)<br>32 | 4 / 16 (25.00%)<br>5 |
| Injury, poisoning and procedural complications<br>Injury, poisoning and certain other consequences of external causes<br>subjects affected / exposed<br>occurrences (all)                  | 6 / 38 (15.79%)<br>10  | 3 / 36 (8.33%)<br>3    | 0 / 16 (0.00%)<br>0  |
| Nervous system disorders<br>Disease of the nervous system<br>subjects affected / exposed<br>occurrences (all)                                                                              | 6 / 38 (15.79%)<br>9   | 9 / 36 (25.00%)<br>13  | 2 / 16 (12.50%)<br>2 |
| Blood and lymphatic system disorders<br>Disease of blood and blood-forming organs and certain disorders involving the immune mechanism<br>subjects affected / exposed<br>occurrences (all) | 1 / 38 (2.63%)<br>1    | 0 / 36 (0.00%)<br>0    | 0 / 16 (0.00%)<br>0  |
| Eye disorders<br>Diseases of the eye and adnexa<br>subjects affected / exposed<br>occurrences (all)                                                                                        | 1 / 38 (2.63%)<br>1    | 2 / 36 (5.56%)<br>3    | 0 / 16 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Diseases of the skin and subcutaneous tissue<br>subjects affected / exposed<br>occurrences (all)                                                 | 12 / 38 (31.58%)<br>18 | 8 / 36 (22.22%)<br>14  | 5 / 16 (31.25%)<br>8 |
| Endocrine disorders<br>Endocrine, nutritional and metabolic diseases<br>subjects affected / exposed<br>occurrences (all)                                                                   | 2 / 38 (5.26%)<br>2    | 5 / 36 (13.89%)<br>7   | 2 / 16 (12.50%)<br>2 |
| Musculoskeletal and connective tissue disorders<br>Diseases of musculoskeletal system and connective tissue<br>subjects affected / exposed<br>occurrences (all)                            | 15 / 38 (39.47%)<br>26 | 9 / 36 (25.00%)<br>16  | 6 / 16 (37.50%)<br>8 |

|                                                                                                                            |                        |                        |                       |
|----------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|-----------------------|
| Infections and infestations<br>Infections<br>subjects affected / exposed<br>occurrences (all)                              | 19 / 38 (50.00%)<br>30 | 9 / 36 (25.00%)<br>22  | 3 / 16 (18.75%)<br>4  |
| Metabolism and nutrition disorders<br>Diseases of the digestive system<br>subjects affected / exposed<br>occurrences (all) | 15 / 38 (39.47%)<br>29 | 17 / 36 (47.22%)<br>35 | 5 / 16 (31.25%)<br>10 |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported