# Clinical trial results:
# Abrogation of chronic monoclonal antibody treatment-induced T-cell exhaustion with DURVALUMAB (MEDI4736) in advanced HER-2 negative breast cancer: a pilot proof-of-concept trial

## Summary

| | |
|---|---|
| EudraCT number | 2015-005609-34 |
| Trial protocol | ES |
| Global end of trial date | 09 July 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 November 2020 |
| First version publication date | 30 November 2020 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CNIO-BR-008 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02802098 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Fundación CRIS de investigación para vencer el cáncer |
| Sponsor organisation address | Princesa de Eboli, 9, Madrid, Spain, 28050 |
| Public contact | Marta Cardona, Fundación CRIS de investigación para vencer el cáncer, +34 911161312, mcardona@criscancer.org |
| Scientific contact | Marta Cardona, Fundación CRIS de investigación para vencer el cáncer, +34 911161312, mcardona@criscancer.org |

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 | 16 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 July 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the immunodynamics in peripheral blood and in the tumor of combined administration of DURVALUMAB and the monoclonal antibody bevacizumab in advanced HER-2- negative breast cancer patients that have progressed to bevacizumab-based treatment.

Protection of trial subjects:

All patients have been treated according to GCP criteria.
Patients were entitled to withdraw from the study at any time and for any reason without prejudice of their future medical care on the part of the doctor or the center.
Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 May 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 25 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 25 |

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) | 19 |
| From 65 to 84 years | 6 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patient were recruited in the study from June 13th 2016 until July 9th 2018

### Pre-assignment

Screening details:

The patients underwent PDL-1 analysis before signing the study informed consent form in order to check if the patient was elegible. A physical examination, serology, hematology, biochemistry, ECG and a tumor evaluation and biopsy were performed to participating patients.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Study treatment |

Arm description:

Treatment with DURVALUMAB, if ≥ 30 kg, commences on day 1 following confirmation of eligibility into the study and continues on a Q2W schedule + Bevacizumab 15 mg/ Kg Q3W or 10 mg/ Kg Q2W, IV infusion for a maximum duration of treatment of 12 months. Study treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg administrated once every 3 weeks or 10 mg/kg administrated once every 2 weeks.

| | |
|---|---|
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

Patients with ≥ 30 kg, a fixed dose of 750 mg of DURVALUMAB was administered every 2 weeks (Equivalent dose of 10 mg/kg Q2W).

| **Number of subjects in period 1** | Study treatment |
|---|---|
| Started | 25 |
| Completed | 25 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall trial |

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 25 | 25 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 19 | 19 | |
| From 65-84 years | 6 | 6 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| median | 54.1 | | |
| full range (min-max) | 34.5 to 77.4 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 24 | |
| Male | 1 | 1 | |
| Race<br>Units: Subjects | | | |
| Caucasian | 23 | 23 | |
| Arabian | 1 | 1 | |
| Latin | 1 | 1 | |
| ECOG-PS at baseline<br>Units: Subjects | | | |
| ECOG-PS 0 | 15 | 15 | |
| ECOG-PS 1 | 10 | 10 | |
| TNM at diagnosis | | | |
| T | | | |
| Units: Subjects | | | |
| Tx | 2 | 2 | |
| T1 | 4 | 4 | |
| T2 | 10 | 10 | |
| T3 | 5 | 5 | |
| T4 | 2 | 2 | |
| ND | 2 | 2 | |
| TNM at diagnosis | | | |
| N | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Nx | 2 | 2 | |
| N0 | 6 | 6 | |
| N1 | 11 | 11 | |
| N2 | 1 | 1 | |
| N3 | 3 | 3 | |
| ND | 2 | 2 | |
| TNM at diagnosis | | | |
| M | | | |
| Units: Subjects | | | |
| M0 | 16 | 16 | |
| M1 | 8 | 8 | |
| ND | 1 | 1 | |
| Stage at diagnosis | | | |
| Stage | | | |
| Units: Subjects | | | |
| IA | 2 | 2 | |
| IIA | 4 | 4 | |
| IIB | 5 | 5 | |
| IIIC | 4 | 4 | |
| IV | 7 | 7 | |
| ND | 3 | 3 | |
| TNM at study inclusion | | | |
| T | | | |
| Units: Subjects | | | |
| Tx | 2 | 2 | |
| T0 | 1 | 1 | |
| T1 | 1 | 1 | |
| T2 | 4 | 4 | |
| T3 | 1 | 1 | |
| T4 | 2 | 2 | |
| ND | 14 | 14 | |
| TNM at study inclusion | | | |
| N | | | |
| Units: Subjects | | | |
| Nx | 2 | 2 | |
| N0 | 3 | 3 | |
| N1 | 4 | 4 | |
| N2 | 2 | 2 | |
| N3 | 1 | 1 | |
| ND | 13 | 13 | |
| TNM at study inclusion | | | |
| M | | | |
| Units: Subjects | | | |
| M1 | 24 | 24 | |
| ND | 1 | 1 | |
| Stage at study inclusion<br>Units: Subjects | | | |
| IV | 24 | 24 | |
| ND | 1 | 1 | |
| Histology | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Ductal | 18 | 18 | |
| Lobular | 4 | 4 | |
| Others | 3 | 3 | |
| Differentation grade<br>Units: Subjects | | | |
| G1 | 3 | 3 | |
| G2 | 10 | 10 | |
| G3 | 7 | 7 | |
| ND | 5 | 5 | |
| Estrogen hormonal receptors<br>Units: Subjects | | | |
| Positive | 16 | 16 | |
| Negative | 9 | 9 | |
| Previous surgery<br>Units: Subjects | | | |
| Yes | 21 | 21 | |
| No | 4 | 4 | |
| Sentinel node biopsy result<br>Units: Subjects | | | |
| Positive | 7 | 7 | |
| Negative | 2 | 2 | |
| Not biopsied | 16 | 16 | |
| Previous local chemotherapy<br>Units: Subjects | | | |
| Yes | 16 | 16 | |
| No | 9 | 9 | |
| Previous treatments: monotherapy and radiotherapy<br>Units: Subjects | | | |
| Yes | 18 | 18 | |
| No | 7 | 7 | |
| Number of previous lines to advanced/metastatic disease<br>Units: Subjects | | | |
| One | 4 | 4 | |
| Two | 8 | 8 | |
| Three | 4 | 4 | |
| Four | 6 | 6 | |
| Five | 2 | 2 | |
| Seven | 1 | 1 | |
| Number of locations<br>Units: Subjects | | | |
| One | 4 | 4 | |
| Two | 8 | 8 | |
| Three | 3 | 3 | |
| Four | 3 | 3 | |
| Five | 4 | 4 | |
| Six | 1 | 1 | |
| Seven | 1 | 1 | |
| Eight | 1 | 1 | |
| Number of cycles administered | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| One | 2 | 2 | |
| Two | 5 | 5 | |
| Three | 9 | 9 | |
| Four | 2 | 2 | |
| Five | 1 | 1 | |
| Six | 1 | 1 | |
| Eight | 2 | 2 | |
| Thirteen | 2 | 2 | |
| Fourteen | 1 | 1 | |
| Number of durvalumab infusion interruptions | | | |
| Non-hematological toxicity (N=4) | | | |
| Units: Subjects | | | |
| None | 22 | 22 | |
| One | 2 | 2 | |
| Two | 1 | 1 | |
| Number of bevacizumab infusion interruptions | | | |
| Non-hematological toxicity (N=6), treatment not related (1), not related AE (1) | | | |
| Units: Subjects | | | |
| None | 18 | 18 | |
| One | 6 | 6 | |
| Two | 1 | 1 | |
| Number of durvalumab infusions delayed | | | |
| Not related AE (N=3), Treatment not related reason (N=1) | | | |
| Units: Subjects | | | |
| None | 21 | 21 | |
| One | 4 | 4 | |
| Number of bevacizumab infusions delayed | | | |
| Not related AE (N=3), Treatment not related reason (N=2) | | | |
| Units: Subjects | | | |
| None | 20 | 20 | |
| One | 5 | 5 | |
| Progesterone receptors | | | |
| Units: Subjects | | | |
| Positive | 10 | 10 | |
| Negative | 15 | 15 | |
| Previous radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 14 | 14 | |
| No | 11 | 11 | |
| PDL-1 Expression | | | |
| Units: Subjects | | | |
| Positive | 4 | 4 | |
| Negative | 16 | 16 | |
| Unknow | 5 | 5 | |
| Cardiac frequency | | | |
| Units: bpm | | | |
| median | 75.0 | | |

| | | | |
|---|---|---|---|
| full range (min-max) | 58.0 to 96.0 | - | |
| Temperature<br>Units: celsius temperature<br>median<br>full range (min-max) | <br><br>36.1<br>35.1 to 36.7 | <br><br><br>- | |
| Sistolic blood pressure<br>Units: mmHg<br>median<br>full range (min-max) | <br><br>125.0<br>77.0 to 162.0 | <br><br><br>- | |
| Diastolic blood pressure<br>Units: mmHg<br>median<br>full range (min-max) | <br><br>75.0<br>61.0 to 90.0 | <br><br><br>- | |
| Respiratory frequency<br>Units: breaths per minute<br>median<br>full range (min-max) | <br><br>16.0<br>12.0 to 22.0 | <br><br><br>- | |
| Weight<br>Units: Kg<br>median<br>full range (min-max) | <br><br>57.0<br>47.0 to 75.2 | <br><br><br>- | |
| Height<br>Units: cm<br>median<br>full range (min-max) | <br><br>160.0<br>150.0 to 179.0 | <br><br><br>- | |
| Time from initial diagnosis<br>Units: months<br>median<br>full range (min-max) | <br><br>43.2<br>4.7 to 116.0 | <br><br><br>- | |
| Time from metastatic diagnosis<br>Units: months<br>median<br>full range (min-max) | <br><br>18.1<br>0.2 to 116.0 | <br><br><br>- | |
| Time from intial diagnosis to metastatic diagnosis<br>Units: months<br>median<br>full range (min-max) | <br><br>4.6<br>0.0 to 97.2 | <br><br><br>- | |
| Time of previous treatment with bevacizumab<br>Units: months<br>median<br>full range (min-max) | <br><br>7.9<br>1.6 to 24.7 | <br><br><br>- | |
| Time on treatment<br>Units: Weeks<br>median<br>full range (min-max) | <br><br>18.6<br>4.1 to 57.3 | <br><br><br>- | |
| Bevacizumab dose intensity<br>Units: mg/Kg/week<br>median<br>full range (min-max) | <br><br>4.5<br>2.4 to 4.95 | <br><br><br>- | |
| Durvalumab dose intensity | | | |

| | | | |
|---|---|---|---|
| Units: mg/week | | | |
| median | 332.7 | | |
| full range (min-max) | 181.03 to 375.0 | - | |
| Bevacizumab related dose intensity | | | |
| Units: NA | | | |
| median | 0.90 | | |
| full range (min-max) | 0.48 to 0.99 | - | |
| Durvalumab related dose intensity | | | |
| Units: NA | | | |
| median | 0.89 | | |
| full range (min-max) | 0.48 to 1.0 | - | |

## End points

### End points reporting groups

| Reporting group title | Study treatment |
|---|---|

Reporting group description:

Treatment with DURVALUMAB, if ≥ 30 kg, commences on day 1 following confirmation of eligibility into the study and continues on a Q2W schedule + Bevacizumab 15 mg/ Kg Q3W or 10 mg/ Kg Q2W, IV infusion for a maximum duration of treatment of 12 months. Study treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

### Primary: Peripheral Blood Mononuclear Cells (PBMCS) differences after treatment between responders and non-responders

| End point title | Peripheral Blood Mononuclear Cells (PBMCS) differences after treatment between responders and non-responders[1] |
|---|---|

End point description:

Differences in CD4+, CD8+ and Treg cells

| End point type | Primary |
|---|---|

End point timeframe:

From treatment initiation to first evaluation (8 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: One arm clinical trial. Only descriptive analyses performed. No comparisons.

| End point values | Study treatment | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: p-value | | | | |
| number (not applicable) | | | | |
| CD4+ Naïve | 0.87 | | | |
| CD4+ Effector | 0.01 | | | |
| CD4+ Central memory | 0.09 | | | |
| CD4+ Effector Memory | 0.04 | | | |
| CD8+ Naive | 0.1 | | | |
| CD8+ Effector | 0.02 | | | |
| CD8+ Central memory | 0.02 | | | |
| CD8+ Effector memory | 0.78 | | | |
| T-reg | 0.11 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit rate at 4 months

| End point title | Clinical Benefit rate at 4 months |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

From treatment initiation to 4 months follow-up.

| **End point values** | Study treatment | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25[2] | | | |
| Units: Patients | | | | |
| Partial response | 2 | | | |
| Stable disease | 5 | | | |
| Not follow-up available | 18 | | | |

Notes:

[2] - Only 7 patients have a follow-up >=4 months

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the end of first treatment dose to 90 days after last dose of durvalumab.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Bevacizumab and Durvalumab treatment |

Reporting group description: -

| Serious adverse events | Bevacizumab and Durvalumab treatment | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | | |
| number of deaths (all causes) | 12 | | |
| number of deaths resulting from adverse events | 1 | | |
| Cardiac disorders | | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Bevacizumab and Durvalumab treatment | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 25 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 14 / 25 (56.00%) | | |
| occurrences (all) | 14 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)<br><br>Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucosal dryness<br>subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>2<br><br>2 / 25 (8.00%)<br>2<br><br>3 / 25 (12.00%)<br>3<br><br>2 / 25 (8.00%)<br>2 | | |
| Respiratory, thoracic and mediastinal disorders<br>Chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 25 (8.00%)<br>2<br><br>2 / 25 (8.00%)<br>2<br><br>5 / 25 (20.00%)<br>5 | | |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 25 (8.00%)<br>2<br><br>2 / 25 (8.00%)<br>2 | | |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | <br><br>5 / 25 (20.00%)<br>5<br><br>2 / 25 (8.00%)<br>2 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukopenia<br>subjects affected / exposed<br>occurrences (all) | <br>2 / 25 (8.00%)<br>2<br><br><br>2 / 25 (8.00%)<br>2 | | |
| Eye disorders<br>Xerophthalmia<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 25 (8.00%)<br>2 | | |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | <br><br>7 / 25 (28.00%)<br>7<br><br><br>5 / 25 (20.00%)<br>5<br><br><br>4 / 25 (16.00%)<br>4<br><br><br>3 / 25 (12.00%)<br>3<br><br><br>4 / 25 (16.00%)<br>4 | | |
| Hepatobiliary disorders<br>Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 25 (8.00%)<br>2 | | |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 25 (8.00%)<br>2 | | |
| Renal and urinary disorders<br>Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Proteinuria | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Bone pain | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | | |
| occurrences (all) | 5 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 25 (20.00%) | | |
| occurrences (all) | 5 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Hypothyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>2 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 January 2017 | Modification toxicity management guidelines |
| 26 October 2017 | Inclusion criteria modified |
| 18 December 2018 | Updating protocol safety information according to new Investigator Brochure. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The pilot design of the study and the sample size analyzed do not allow to detail a definitive conclusions. Only 7 patients of 25 could be followed up for 4 months.

Notes: