



## Clinical trial results:

**Phase II trial studying the efficacy of a triplet combination of MLN9708, lenalidomide and dexamethasone as induction prior to, and as consolidation after high-dose therapy with peripheral stem cell transplantation followed by MLN9708 maintenance in the initial management of multiple myeloma in patients younger than 66 years.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-001443-31 |
| Trial protocol           | FR             |
| Global end of trial date | 17 March 2021  |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 19 August 2023 |
| First version publication date | 19 August 2023 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RC12_0447 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01936532 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                |
|------------------------------|--------------------------------------------------------------------------------|
| Sponsor organisation name    | CHU de Nantes                                                                  |
| Sponsor organisation address | 5 allée de l'île de Gloriette, Nantes, France, 44093                           |
| Public contact               | Département Promotion, CHU de Nantes, 33 253482835, bp-prom-regl@chu-nantes.fr |
| Scientific contact           | Département Promotion, CHU de Nantes, 33 253482835, bp-prom-regl@chu-nantes.fr |

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                       | 17 March 2021 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 17 March 2021 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 March 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective:

To evaluate the stringent Complete Response (sCR) rate of the combination of MLN9708, Lenalidomide and Dexamethasone in newly diagnosed multiple myeloma (MM) patients after extended consolidation therapy

Protection of trial subjects:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study.

Strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin) strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, érythromycine and posaconazole) strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), the dietary supplements St John's wort and Ginkgo biloba are prohibited.

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 12 November 2014 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy         |
| Long term follow-up duration                              | 3 Years          |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 42 |
| Worldwide total number of subjects   | 42         |
| EEA total number of subjects         | 42         |

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)                     | 38 |
| From 65 to 84 years                      | 4  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

46 patients are included in 10 centers. 42 patients are treated and 4 patients are in screening failure.

### Pre-assignment

Screening details:

Patients diagnosed with multiple myeloma, subjects must have symptomatic myeloma with CRAB criteria and they have measurable disease requiring systemic therapy defined by serum M-component  $\geq 5\text{g/l}$ , urine M-component  $\geq 200\text{ mg/24h}$  or serum FLC  $\geq 100\text{ mg/l}$  are included in this study.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 42 |
| Number of subjects completed | 42 |

### Period 1

|                              |                               |
|------------------------------|-------------------------------|
| Period 1 title               | essai global (overall period) |
| Is this the baseline period? | Yes                           |
| Allocation method            | Not applicable                |
| Blinding used                | Not blinded                   |

Blinding implementation details:

No blinded

### Arms

|           |         |
|-----------|---------|
| Arm title | One arm |
|-----------|---------|

Arm description:

There are one arm

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | MLN9708      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

4.0 mg weekly (Days 1, 8, and 15), followed by 1 week without study drug in a 28-day cycle during induction phase, post-transplant early and late consolidation phases and maintenance therapy.

| Number of subjects in period 1 | One arm |
|--------------------------------|---------|
| Started                        | 42      |
| Completed                      | 23      |
| Not completed                  | 19      |
| Physician decision             | 1       |
| progression                    | 7       |
| Adverse event, non-fatal       | 6       |
| patient decision               | 4       |

|                    |   |
|--------------------|---|
| Protocol deviation | 1 |
|--------------------|---|

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | essai global |
|-----------------------|--------------|

Reporting group description: -

| Reporting group values                                | essai global | Total |  |
|-------------------------------------------------------|--------------|-------|--|
| Number of subjects                                    | 42           | 42    |  |
| Age categorical                                       |              |       |  |
| Units: Subjects                                       |              |       |  |
| In utero                                              | 0            | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0            | 0     |  |
| Newborns (0-27 days)                                  | 0            | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0            | 0     |  |
| Children (2-11 years)                                 | 0            | 0     |  |
| Adolescents (12-17 years)                             | 0            | 0     |  |
| Adults (18-64 years)                                  | 38           | 38    |  |
| From 65-84 years                                      | 4            | 4     |  |
| 85 years and over                                     | 0            | 0     |  |
| Age continuous                                        |              |       |  |
| Units: years                                          |              |       |  |
| median                                                | 60           |       |  |
| full range (min-max)                                  | 43 to 66     | -     |  |
| Gender categorical                                    |              |       |  |
| Units: Subjects                                       |              |       |  |
| Female                                                | 21           | 21    |  |
| Male                                                  | 21           | 21    |  |

## End points

### End points reporting groups

|                              |         |
|------------------------------|---------|
| Reporting group title        | One arm |
| Reporting group description: |         |
| There are one arm            |         |

### Primary: sCR

|                        |                    |
|------------------------|--------------------|
| End point title        | sCR <sup>[1]</sup> |
| End point description: |                    |

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

End point timeframe:

To evaluate the sCR rate of the combination of MLN9708, lenalidomide and dexamethasone in newly diagnosed MM patients after extended consolidation therapy at the end of consolidation.

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: there are only one arm. We can't enter the data

| End point values            | One arm         |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 34              |  |  |  |
| Units: percentage           |                 |  |  |  |
| number (not applicable)     | 41              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During all study

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                                              | All patients     |  |  |
|---------------------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed                                         | 20 / 42 (47.62%) |  |  |
| number of deaths (all causes)                                       | 7                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Adenocarcinoma of colon                                             |                  |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Extradural neoplasm                                                 |                  |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Plasma cell leukaemia                                               |                  |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Plasma cell myeloma                                                 |                  |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Cardiac disorders                                                   |                  |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Atrial fibrillation                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Surgical and medical procedures                 |                |  |  |
| Cementoplasty                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Knee arthroplasty                               |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Prostatic operation                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Ischaemic stroke                                |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peroneal nerve palsy                            |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Radiculopathy                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Febrile bone marrow aplasia                     |                |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Febrile neutropenia                                  |                |  |  |
| subjects affected / exposed                          | 2 / 42 (4.76%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Thrombocytopenia                                     |                |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Influenza like illness                               |                |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain                                       |                |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Constipation                                         |                |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Rectal haemorrhage                                   |                |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Reproductive system and breast disorders             |                |  |  |
| Breast calcifications                                |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Genital prolapse                                |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Dermatitis exfoliative generalised              |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Bone pain                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Influenza                                       |                |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Periorbital cellulitis                          |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%) |  |  |
| occurrences causally related to treatment / all | 3 / 4          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia pneumococcal                          |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Varicella                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | All patients      |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by non-serious adverse events               |                   |  |  |
| subjects affected / exposed                                         | 42 / 42 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Melanocytic naevus                                                  |                   |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)    |  |  |
| occurrences (all)                                                   | 1                 |  |  |
| Plasmablastic lymphoma                                              |                   |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)    |  |  |
| occurrences (all)                                                   | 1                 |  |  |
| Vascular disorders                                                  |                   |  |  |
| Hot flush                                                           |                   |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)    |  |  |
| occurrences (all)                                                   | 2                 |  |  |
| Hypertension                                                        |                   |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)    |  |  |
| occurrences (all)                                                   | 1                 |  |  |
| Hypotension                                                         |                   |  |  |
| subjects affected / exposed                                         | 2 / 42 (4.76%)    |  |  |
| occurrences (all)                                                   | 2                 |  |  |
| Jugular vein thrombosis                                             |                   |  |  |
| subjects affected / exposed                                         | 2 / 42 (4.76%)    |  |  |
| occurrences (all)                                                   | 2                 |  |  |
| Orthostatic hypotension                                             |                   |  |  |
| subjects affected / exposed                                         | 1 / 42 (2.38%)    |  |  |
| occurrences (all)                                                   | 1                 |  |  |
| Peripheral venous disease                                           |                   |  |  |
| subjects affected / exposed                                         | 2 / 42 (4.76%)    |  |  |
| occurrences (all)                                                   | 3                 |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                   |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Raynaud's phenomenon<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1 / 42 (2.38%)<br>1                                                                                                                                                                                                                               |  |  |
| Surgical and medical procedures<br>Cataract operation<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1 / 42 (2.38%)<br>1                                                                                                                                                                                                                               |  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Feeling jittery<br>subjects affected / exposed<br>occurrences (all)<br><br>Inflammation<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site dermatitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Malaise<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema | 17 / 42 (40.48%)<br>33<br><br>1 / 42 (2.38%)<br>1<br><br>2 / 42 (4.76%)<br>6<br><br>1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1<br><br>4 / 42 (9.52%)<br>5<br><br>1 / 42 (2.38%)<br>1<br><br>1 / 42 (2.38%)<br>1<br><br>27 / 42 (64.29%)<br>29 |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Oedema peripheral                               |                  |  |  |
| subjects affected / exposed                     | 5 / 42 (11.90%)  |  |  |
| occurrences (all)                               | 7                |  |  |
| Pyrexia                                         |                  |  |  |
| subjects affected / exposed                     | 22 / 42 (52.38%) |  |  |
| occurrences (all)                               | 31               |  |  |
| Vaccination site inflammation                   |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Immune system disorders                         |                  |  |  |
| Drug hypersensitivity                           |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Bronchopneumopathy                              |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 6 / 42 (14.29%)  |  |  |
| occurrences (all)                               | 6                |  |  |
| Dyspnoea                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Dyspnoea exertional                             |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Emphysema                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Epistaxis                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Lung disorder                                   |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nasal polyps                |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pharyngeal disorder         |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pneumothorax                |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rhinitis allergic           |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rhinorrhoea                 |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Psychiatric disorders       |                 |  |  |
| Affective disorder          |                 |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Anxiety                     |                 |  |  |
| subjects affected / exposed | 7 / 42 (16.67%) |  |  |
| occurrences (all)           | 7               |  |  |
| Confusional state           |                 |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Depressed mood              |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Depression                  |                 |  |  |
| subjects affected / exposed | 4 / 42 (9.52%)  |  |  |
| occurrences (all)           | 4               |  |  |
| Insomnia                    |                 |  |  |
| subjects affected / exposed | 3 / 42 (7.14%)  |  |  |
| occurrences (all)           | 3               |  |  |

|                                                                                         |                     |  |  |
|-----------------------------------------------------------------------------------------|---------------------|--|--|
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 42 (4.76%)<br>2 |  |  |
| Investigations                                                                          |                     |  |  |
| Cytomegalovirus test positive<br>subjects affected / exposed<br>occurrences (all)       | 1 / 42 (2.38%)<br>1 |  |  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1 |  |  |
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)      | 1 / 42 (2.38%)<br>1 |  |  |
| Pseudomonas test positive<br>subjects affected / exposed<br>occurrences (all)           | 1 / 42 (2.38%)<br>1 |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 42 (4.76%)<br>2 |  |  |
| Injury, poisoning and procedural complications                                          |                     |  |  |
| Eschar<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 42 (2.38%)<br>2 |  |  |
| Radiation skin injury<br>subjects affected / exposed<br>occurrences (all)               | 1 / 42 (2.38%)<br>1 |  |  |
| Skin injury<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 42 (2.38%)<br>1 |  |  |
| Tooth avulsion<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 42 (2.38%)<br>1 |  |  |
| Congenital, familial and genetic disorders                                              |                     |  |  |
| Dolichocolon                                                                            |                     |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Cardiac disorders           |                 |  |  |
| Myocardial ischaemia        |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Tachycardia                 |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Ventricular extrasystoles   |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nervous system disorders    |                 |  |  |
| Carotid arteriosclerosis    |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Disturbance in attention    |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Dysaesthesia                |                 |  |  |
| subjects affected / exposed | 3 / 42 (7.14%)  |  |  |
| occurrences (all)           | 6               |  |  |
| Dysgeusia                   |                 |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Dyskinesia                  |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Headache                    |                 |  |  |
| subjects affected / exposed | 5 / 42 (11.90%) |  |  |
| occurrences (all)           | 10              |  |  |
| Neuralgia                   |                 |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Neuropathy peripheral       |                 |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 12 / 42 (28.57%) |  |  |
| occurrences (all)                    | 18               |  |  |
| Paraesthesia                         |                  |  |  |
| subjects affected / exposed          | 5 / 42 (11.90%)  |  |  |
| occurrences (all)                    | 6                |  |  |
| Peripheral sensory neuropathy        |                  |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Psychomotor hyperactivity            |                  |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Sciatica                             |                  |  |  |
| subjects affected / exposed          | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| Tremor                               |                  |  |  |
| subjects affected / exposed          | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 24 / 42 (57.14%) |  |  |
| occurrences (all)                    | 36               |  |  |
| Bone marrow failure                  |                  |  |  |
| subjects affected / exposed          | 4 / 42 (9.52%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Febrile bone marrow aplasia          |                  |  |  |
| subjects affected / exposed          | 9 / 42 (21.43%)  |  |  |
| occurrences (all)                    | 9                |  |  |
| Febrile neutropenia                  |                  |  |  |
| subjects affected / exposed          | 4 / 42 (9.52%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Leukopenia                           |                  |  |  |
| subjects affected / exposed          | 11 / 42 (26.19%) |  |  |
| occurrences (all)                    | 21               |  |  |
| Lymphopenia                          |                  |  |  |
| subjects affected / exposed          | 9 / 42 (21.43%)  |  |  |
| occurrences (all)                    | 18               |  |  |

|                                                                                             |                        |  |  |
|---------------------------------------------------------------------------------------------|------------------------|--|--|
| Macrocytosis<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 42 (2.38%)<br>1    |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                             | 25 / 42 (59.52%)<br>58 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                        | 33 / 42 (78.57%)<br>80 |  |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1    |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                                 | 3 / 42 (7.14%)<br>3    |  |  |
| Vertigo positional<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 42 (2.38%)<br>1    |  |  |
| Eye disorders<br>Dry eye<br>subjects affected / exposed<br>occurrences (all)                | 1 / 42 (2.38%)<br>1    |  |  |
| Keratitis<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 42 (2.38%)<br>1    |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 42 (2.38%)<br>1    |  |  |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 42 (2.38%)<br>1    |  |  |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 42 (2.38%)<br>1    |  |  |
| Gastrointestinal disorders                                                                  |                        |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 5 / 42 (11.90%)  |  |  |
| occurrences (all)           | 5                |  |  |
| Colitis                     |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 14 / 42 (33.33%) |  |  |
| occurrences (all)           | 19               |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 26 / 42 (61.90%) |  |  |
| occurrences (all)           | 44               |  |  |
| Diverticulum                |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dry mouth                   |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dyspepsia                   |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dysphagia                   |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Enterocolitis               |                  |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Gastric disorder            |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Gastritis                   |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Haematochezia               |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Haemorrhoidal haemorrhage   |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Haemorrhoids                |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Inguinal hernia             |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 27 / 42 (64.29%) |  |  |
| occurrences (all)           | 45               |  |  |
| Proctalgia                  |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| RECTAL HAEMORRHAGE          |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Tooth discolouration        |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Umbilical hernia            |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Vomiting                    |                  |  |  |
| subjects affected / exposed | 14 / 42 (33.33%) |  |  |
| occurrences (all)           | 16               |  |  |
| Hepatobiliary disorders     |                  |  |  |
| Cholestasis                 |                  |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hepatocellular injury       |                  |  |  |

|                                        |                  |  |  |
|----------------------------------------|------------------|--|--|
| subjects affected / exposed            | 4 / 42 (9.52%)   |  |  |
| occurrences (all)                      | 5                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Alopecia                               |                  |  |  |
| subjects affected / exposed            | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                      | 4                |  |  |
| Dermatitis contact                     |                  |  |  |
| subjects affected / exposed            | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Dry skin                               |                  |  |  |
| subjects affected / exposed            | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Eczema                                 |                  |  |  |
| subjects affected / exposed            | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Erythema                               |                  |  |  |
| subjects affected / exposed            | 5 / 42 (11.90%)  |  |  |
| occurrences (all)                      | 5                |  |  |
| Pruritus                               |                  |  |  |
| subjects affected / exposed            | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                      | 3                |  |  |
| Rash                                   |                  |  |  |
| subjects affected / exposed            | 13 / 42 (30.95%) |  |  |
| occurrences (all)                      | 28               |  |  |
| Rash maculo-papular                    |                  |  |  |
| subjects affected / exposed            | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Rash papular                           |                  |  |  |
| subjects affected / exposed            | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Rash pruritic                          |                  |  |  |
| subjects affected / exposed            | 2 / 42 (4.76%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Rosacea                                |                  |  |  |
| subjects affected / exposed            | 1 / 42 (2.38%)   |  |  |
| occurrences (all)                      | 1                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Skin mass                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Toxic skin eruption                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Urticaria                                       |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Renal and urinary disorders                     |                |  |  |
| Acute kidney injury                             |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Cystitis haemorrhagic                           |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Hypertonic bladder                              |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Renal colic                                     |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Renal cyst                                      |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Renal failure                                   |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Urinary hesitation                              |                |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Urinary retention                               |                |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Arthralgia                  |                 |  |  |
| subjects affected / exposed | 7 / 42 (16.67%) |  |  |
| occurrences (all)           | 7               |  |  |
| Back pain                   |                 |  |  |
| subjects affected / exposed | 8 / 42 (19.05%) |  |  |
| occurrences (all)           | 12              |  |  |
| Bone pain                   |                 |  |  |
| subjects affected / exposed | 3 / 42 (7.14%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Bursitis                    |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Flank pain                  |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Fracture delayed union      |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Muscle spasms               |                 |  |  |
| subjects affected / exposed | 9 / 42 (21.43%) |  |  |
| occurrences (all)           | 12              |  |  |
| Musculoskeletal pain        |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Myalgia                     |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Neck pain                   |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Osteoarthritis              |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Osteoporosis                |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |

|                                                                             |                        |  |  |
|-----------------------------------------------------------------------------|------------------------|--|--|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)       | 2 / 42 (4.76%)<br>2    |  |  |
| Periarthritis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 42 (2.38%)<br>1    |  |  |
| Tendon pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 42 (2.38%)<br>1    |  |  |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)              | 1 / 42 (2.38%)<br>1    |  |  |
| Infections and infestations                                                 |                        |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)              | 16 / 42 (38.10%)<br>17 |  |  |
| Catheter site infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1    |  |  |
| Clostridium colitis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 42 (2.38%)<br>1    |  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)          | 1 / 42 (2.38%)<br>1    |  |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 42 (2.38%)<br>1    |  |  |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)           | 1 / 42 (2.38%)<br>1    |  |  |
| Enterobacter infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 42 (2.38%)<br>1    |  |  |
| Enterococcal infection                                                      |                        |  |  |

|                                     |                |  |  |
|-------------------------------------|----------------|--|--|
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Enterocolitis bacterial             |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Epididymitis                        |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 2              |  |  |
| Escherichia urinary tract infection |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Fungal infection                    |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Fungal skin infection               |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Furuncle                            |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Gastroenteritis                     |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Gastroenteritis viral               |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Gingivitis                          |                |  |  |
| subjects affected / exposed         | 1 / 42 (2.38%) |  |  |
| occurrences (all)                   | 1              |  |  |
| Herpes zoster                       |                |  |  |
| subjects affected / exposed         | 3 / 42 (7.14%) |  |  |
| occurrences (all)                   | 4              |  |  |
| Klebsiella infection                |                |  |  |
| subjects affected / exposed         | 2 / 42 (4.76%) |  |  |
| occurrences (all)                   | 2              |  |  |
| Laryngitis                          |                |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Nasopharyngitis             |                 |  |  |
| subjects affected / exposed | 8 / 42 (19.05%) |  |  |
| occurrences (all)           | 9               |  |  |
| Oesophageal candidiasis     |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Onychomycosis               |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Oral candidiasis            |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Oral fungal infection       |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Orchitis                    |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Otitis externa              |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Paronychia                  |                 |  |  |
| subjects affected / exposed | 2 / 42 (4.76%)  |  |  |
| occurrences (all)           | 2               |  |  |
| parotitis                   |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pneumonia                   |                 |  |  |
| subjects affected / exposed | 3 / 42 (7.14%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Pseudomonas infection       |                 |  |  |
| subjects affected / exposed | 1 / 42 (2.38%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Respiratory tract infection |                 |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Rhinitis                           |                |  |  |
| subjects affected / exposed        | 4 / 42 (9.52%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Sepsis                             |                |  |  |
| subjects affected / exposed        | 2 / 42 (4.76%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Sinusitis                          |                |  |  |
| subjects affected / exposed        | 3 / 42 (7.14%) |  |  |
| occurrences (all)                  | 5              |  |  |
| Staphylococcal infection           |                |  |  |
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Staphylococcal sepsis              |                |  |  |
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Thrombophlebitis septic            |                |  |  |
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Tonsillitis                        |                |  |  |
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Upper respiratory tract infection  |                |  |  |
| subjects affected / exposed        | 3 / 42 (7.14%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Urinary tract infection            |                |  |  |
| subjects affected / exposed        | 4 / 42 (9.52%) |  |  |
| occurrences (all)                  | 8              |  |  |
| Viral infection                    |                |  |  |
| subjects affected / exposed        | 1 / 42 (2.38%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Decreased appetite                 |                |  |  |
| subjects affected / exposed        | 4 / 42 (9.52%) |  |  |
| occurrences (all)                  | 4              |  |  |

|                                      |                |  |  |
|--------------------------------------|----------------|--|--|
| Diabetes mellitus                    |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Diabetes mellitus inadequate control |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Hypokalaemia                         |                |  |  |
| subjects affected / exposed          | 4 / 42 (9.52%) |  |  |
| occurrences (all)                    | 4              |  |  |
| Hypomagnesaemia                      |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Hypophosphataemia                    |                |  |  |
| subjects affected / exposed          | 3 / 42 (7.14%) |  |  |
| occurrences (all)                    | 3              |  |  |
| Vitamin D deficiency                 |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |
| Vitamin K deficiency                 |                |  |  |
| subjects affected / exposed          | 1 / 42 (2.38%) |  |  |
| occurrences (all)                    | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                          |
|-------------------|------------------------------------|
| 09 September 2014 | dose modification                  |
| 06 January 2015   | center modification                |
| 06 December 2016  | investigator brochure modification |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35172566>