



## Clinical trial results:

### A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-023015-33    |
| Trial protocol           | GB BE SE IT DE FR |
| Global end of trial date | 18 January 2018   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 03 February 2019 |
| First version publication date | 03 February 2019 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 114375 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01376310 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                                                        |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                                              |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

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                       | 18 January 2018 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 18 January 2018 |
| Was the trial ended prematurely? | No              |

Notes:

## General information about the trial

Main objective of the trial:

To provide continued treatment with trametinib (GSK1120212) for subjects who had previously participated in a trametinib study and who continued to receive clinical benefit as well as have an acceptable safety profile with trametinib.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 02 November 2010 |
| 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 | Canada: 3             |
| Country: Number of subjects enrolled | France: 3             |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Netherlands: 1        |
| Country: Number of subjects enrolled | Taiwan: 1             |
| Country: Number of subjects enrolled | United States: 150    |
| Worldwide total number of subjects   | 159                   |
| EEA total number of subjects         | 4                     |

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)      | 92 |
| From 65 to 84 years       | 66 |
| 85 years and over         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

159 subjects received treatment with GSK1120212 and were included in the safety set.

### Pre-assignment

Screening details:

Continued treatment with GSK1120212 was provided for subjects who had previously participated in a GSK1120212 study and who continued to receive clinical benefit as well as have an acceptable safety profile with GSK1120212.

### Period 1

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

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | Cohort A |

Arm description:

Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | GSK1120212   |
| Investigational medicinal product code | GSK1120212   |
| Other name                             | Trametinib   |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

The dose of study treatment administered to subjects were individualized based upon the dose/regimen received during their participation in the parent study at the time of transition to the rollover study.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort B |
|------------------|----------|

Arm description:

Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | GSK1120212   |
| Investigational medicinal product code | GSK1120212   |
| Other name                             | Trametinib   |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

The dose of study treatment administered to subjects were individualized based upon the dose/regimen received during their participation in the parent study at the time of transition to the rollover study.

| <b>Number of subjects in period 1</b> | Cohort A | Cohort B |
|---------------------------------------|----------|----------|
| Started                               | 126      | 33       |
| Completed                             | 90       | 22       |
| Not completed                         | 36       | 11       |
| Study closed/terminated               | 1        | 2        |
| Consent withdrawn by subject          | 8        | 2        |
| Physician decision                    | 26       | 7        |
| Lost to follow-up                     | 1        | -        |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                             |          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Reporting group title                                                                                                                                                                                       | Cohort A |
| Reporting group description:<br>Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.                                                                          |          |
| Reporting group title                                                                                                                                                                                       | Cohort B |
| Reporting group description:<br>Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial. |          |

| Reporting group values                                | Cohort A | Cohort B | Total |
|-------------------------------------------------------|----------|----------|-------|
| Number of subjects                                    | 126      | 33       | 159   |
| Age categorical<br>Units: Subjects                    |          |          |       |
| In utero                                              | 0        | 0        | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0        | 0        | 0     |
| Newborns (0-27 days)                                  | 0        | 0        | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0        | 0        | 0     |
| Children (2-11 years)                                 | 0        | 0        | 0     |
| Adolescents (12-17 years)                             | 0        | 0        | 0     |
| Adults (18-64 years)                                  | 74       | 18       | 92    |
| From 65-84 years                                      | 51       | 15       | 66    |
| 85 years and over                                     | 1        | 0        | 1     |
| Age Continuous<br>Units: years                        |          |          |       |
| arithmetic mean                                       | 61.0     | 61.7     | -     |
| standard deviation                                    | ± 12.34  | ± 11.30  |       |
| Sex: Female, Male<br>Units: Subjects                  |          |          |       |
| Female                                                | 66       | 17       | 83    |
| Male                                                  | 60       | 16       | 76    |
| Race/Ethnicity, Customized<br>Units: Subjects         |          |          |       |
| White                                                 | 116      | 28       | 144   |
| Black                                                 | 6        | 3        | 9     |
| Asian                                                 | 2        | 2        | 4     |
| Native American/Pacific Islander                      | 2        | 0        | 2     |

## End points

### End points reporting groups

|                                                                                                                                                                                                             |          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Reporting group title                                                                                                                                                                                       | Cohort A |
| Reporting group description:<br>Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.                                                                          |          |
| Reporting group title                                                                                                                                                                                       | Cohort B |
| Reporting group description:<br>Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial. |          |

### Primary: Number of participants with adverse events

|                                                                                                                                                                                                                                                                                       |                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                       | Number of participants with adverse events <sup>[1]</sup> |
| End point description:<br>Number of participants with adverse events as a measure of safety and tolerability                                                                                                                                                                          |                                                           |
| End point type                                                                                                                                                                                                                                                                        | Primary                                                   |
| End point timeframe:<br>Until 30 days after the last dose of study treatment. Subjects may have continued to receive study treatment until disease progression, death, unacceptable toxicity or until locally commercially available. The maximum duration of exposure was 76 months. |                                                           |

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: No statistical analyses were performed.

| End point values                         | Cohort A        | Cohort B        |  |  |
|------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                       | Reporting group | Reporting group |  |  |
| Number of subjects analysed              | 126             | 33              |  |  |
| Units: Participants                      |                 |                 |  |  |
| Adverse Events                           | 119             | 30              |  |  |
| Treatment-Related Adverse Events         | 101             | 26              |  |  |
| Serious Adverse Events                   | 26              | 13              |  |  |
| Treatment-Related Serious Adverse Events | 8               | 4               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort A |
|-----------------------|----------|

Reporting group description:

Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.

|                       |          |
|-----------------------|----------|
| Reporting group title | Cohort B |
|-----------------------|----------|

Reporting group description:

Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.

|                       |              |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All Patients

| Serious adverse events                               | Cohort A          | Cohort B         | All Patients      |
|------------------------------------------------------|-------------------|------------------|-------------------|
| Total subjects affected by serious adverse events    |                   |                  |                   |
| subjects affected / exposed                          | 26 / 126 (20.63%) | 13 / 33 (39.39%) | 39 / 159 (24.53%) |
| number of deaths (all causes)                        | 13                | 3                | 16                |
| number of deaths resulting from adverse events       | 0                 | 0                | 0                 |
| General disorders and administration site conditions |                   |                  |                   |
| General physical health deterioration                |                   |                  |                   |
| subjects affected / exposed                          | 0 / 126 (0.00%)   | 1 / 33 (3.03%)   | 1 / 159 (0.63%)   |
| occurrences causally related to treatment / all      | 0 / 0             | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            | 0 / 0             |
| Generalised oedema                                   |                   |                  |                   |
| subjects affected / exposed                          | 2 / 126 (1.59%)   | 0 / 33 (0.00%)   | 2 / 159 (1.26%)   |
| occurrences causally related to treatment / all      | 1 / 2             | 0 / 0            | 1 / 2             |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0            | 0 / 0             |
| Pyrexia                                              |                   |                  |                   |



|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Chronic obstructive pulmonary disease           |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Lung disorder                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pleural effusion                                |                 |                |                 |
| subjects affected / exposed                     | 2 / 126 (1.59%) | 2 / 33 (6.06%) | 4 / 159 (2.52%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2          | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumothorax                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 2 / 33 (6.06%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pulmonary embolism                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 2 / 33 (6.06%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory failure                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 2 / 33 (6.06%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 1           |
| Psychiatric disorders                           |                 |                |                 |
| Adjustment disorder with depressed mood         |                 |                |                 |

|                                                       |                 |                |                 |
|-------------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                           | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| <b>Investigations</b>                                 |                 |                |                 |
| Blood bilirubin increased                             |                 |                |                 |
| subjects affected / exposed                           | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood creatinine increased                            |                 |                |                 |
| subjects affected / exposed                           | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| Ejection fraction decreased                           |                 |                |                 |
| subjects affected / exposed                           | 2 / 126 (1.59%) | 1 / 33 (3.03%) | 3 / 159 (1.89%) |
| occurrences causally related to treatment / all       | 2 / 2           | 1 / 1          | 3 / 3           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| <b>Injury, poisoning and procedural complications</b> |                 |                |                 |
| Fall                                                  |                 |                |                 |
| subjects affected / exposed                           | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| Pelvic fracture                                       |                 |                |                 |
| subjects affected / exposed                           | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| <b>Cardiac disorders</b>                              |                 |                |                 |
| Acute myocardial infarction                           |                 |                |                 |
| subjects affected / exposed                           | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |
| Bradycardia                                           |                 |                |                 |
| subjects affected / exposed                           | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all       | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0          | 0 / 0           |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| Cardiac arrest                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 1           |
| Left ventricular dysfunction                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 1 / 33 (3.03%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                 |                |                 |
| Sciatica                                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Seizure                                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Eye disorders                                   |                 |                |                 |
| Retinal vein occlusion                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                 |                |                 |
| Abdominal hernia                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Diarrhoea                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 2 / 33 (6.06%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                |                 |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 126 (0.79%) | 1 / 33 (3.03%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal obstruction                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal perforation                          |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Intra-abdominal fluid collection                |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Nausea                                          |                 |                |                 |
| subjects affected / exposed                     | 2 / 126 (1.59%) | 0 / 33 (0.00%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pancreatitis                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Small intestinal obstruction                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vomiting                                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                 |                |                 |
| Hepatitis acute                                 |                 |                |                 |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Purpura                                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                 |                |                 |
| Acute kidney injury                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                |                 |
| Back pain                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 1 / 33 (3.03%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Osteoarthritis                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                 |                |                 |
| Cellulitis                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 1 / 33 (3.03%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Clostridium difficile infection                 |                 |                |                 |
| subjects affected / exposed                     | 2 / 126 (1.59%) | 0 / 33 (0.00%) | 2 / 159 (1.26%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Erysipelas                                      |                 |                |                 |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastroenteritis                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Influenza                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Klebsiella sepsis                               |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Liver abscess                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Moraxella infection                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                 |                |                 |
| subjects affected / exposed                     | 2 / 126 (1.59%) | 3 / 33 (9.09%) | 5 / 159 (3.14%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3          | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pyelonephritis                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Sepsis                                          |                 |                |                 |

|                                                 |                 |                |                 |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 126 (0.00%) | 1 / 33 (3.03%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Wound infection                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                |                 |
| Dehydration                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 126 (0.79%) | 0 / 33 (0.00%) | 1 / 159 (0.63%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Cohort A           | Cohort B         | All Patients       |
|-------------------------------------------------------|--------------------|------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                  |                    |
| subjects affected / exposed                           | 115 / 126 (91.27%) | 28 / 33 (84.85%) | 143 / 159 (89.94%) |
| Vascular disorders                                    |                    |                  |                    |
| Deep vein thrombosis                                  |                    |                  |                    |
| subjects affected / exposed                           | 2 / 126 (1.59%)    | 2 / 33 (6.06%)   | 4 / 159 (2.52%)    |
| occurrences (all)                                     | 2                  | 2                | 4                  |
| Hypertension                                          |                    |                  |                    |
| subjects affected / exposed                           | 7 / 126 (5.56%)    | 0 / 33 (0.00%)   | 7 / 159 (4.40%)    |
| occurrences (all)                                     | 7                  | 0                | 7                  |
| General disorders and administration site conditions  |                    |                  |                    |
| Chills                                                |                    |                  |                    |
| subjects affected / exposed                           | 10 / 126 (7.94%)   | 2 / 33 (6.06%)   | 12 / 159 (7.55%)   |
| occurrences (all)                                     | 13                 | 2                | 15                 |
| Fatigue                                               |                    |                  |                    |

|                                                 |                   |                 |                   |
|-------------------------------------------------|-------------------|-----------------|-------------------|
| subjects affected / exposed                     | 43 / 126 (34.13%) | 3 / 33 (9.09%)  | 46 / 159 (28.93%) |
| occurrences (all)                               | 47                | 3               | 50                |
| Mucosal inflammation                            |                   |                 |                   |
| subjects affected / exposed                     | 7 / 126 (5.56%)   | 4 / 33 (12.12%) | 11 / 159 (6.92%)  |
| occurrences (all)                               | 10                | 7               | 17                |
| Non-cardiac chest pain                          |                   |                 |                   |
| subjects affected / exposed                     | 4 / 126 (3.17%)   | 2 / 33 (6.06%)  | 6 / 159 (3.77%)   |
| occurrences (all)                               | 4                 | 2               | 6                 |
| Oedema                                          |                   |                 |                   |
| subjects affected / exposed                     | 5 / 126 (3.97%)   | 2 / 33 (6.06%)  | 7 / 159 (4.40%)   |
| occurrences (all)                               | 5                 | 2               | 7                 |
| Oedema peripheral                               |                   |                 |                   |
| subjects affected / exposed                     | 27 / 126 (21.43%) | 6 / 33 (18.18%) | 33 / 159 (20.75%) |
| occurrences (all)                               | 33                | 7               | 40                |
| Pyrexia                                         |                   |                 |                   |
| subjects affected / exposed                     | 10 / 126 (7.94%)  | 3 / 33 (9.09%)  | 13 / 159 (8.18%)  |
| occurrences (all)                               | 12                | 4               | 16                |
| Respiratory, thoracic and mediastinal disorders |                   |                 |                   |
| Cough                                           |                   |                 |                   |
| subjects affected / exposed                     | 12 / 126 (9.52%)  | 3 / 33 (9.09%)  | 15 / 159 (9.43%)  |
| occurrences (all)                               | 13                | 3               | 16                |
| Dyspnoea                                        |                   |                 |                   |
| subjects affected / exposed                     | 17 / 126 (13.49%) | 5 / 33 (15.15%) | 22 / 159 (13.84%) |
| occurrences (all)                               | 18                | 5               | 23                |
| Dyspnoea exertional                             |                   |                 |                   |
| subjects affected / exposed                     | 2 / 126 (1.59%)   | 2 / 33 (6.06%)  | 4 / 159 (2.52%)   |
| occurrences (all)                               | 2                 | 2               | 4                 |
| Epistaxis                                       |                   |                 |                   |
| subjects affected / exposed                     | 5 / 126 (3.97%)   | 2 / 33 (6.06%)  | 7 / 159 (4.40%)   |
| occurrences (all)                               | 6                 | 2               | 8                 |
| Nasal congestion                                |                   |                 |                   |
| subjects affected / exposed                     | 8 / 126 (6.35%)   | 0 / 33 (0.00%)  | 8 / 159 (5.03%)   |
| occurrences (all)                               | 10                | 0               | 10                |
| Investigations                                  |                   |                 |                   |



|                                                                                                            |                        |                     |                        |
|------------------------------------------------------------------------------------------------------------|------------------------|---------------------|------------------------|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                     | 8 / 126 (6.35%)<br>8   | 1 / 33 (3.03%)<br>1 | 9 / 159 (5.66%)<br>9   |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 126 (5.56%)<br>8   | 1 / 33 (3.03%)<br>1 | 8 / 159 (5.03%)<br>9   |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                   | 9 / 126 (7.14%)<br>9   | 1 / 33 (3.03%)<br>1 | 10 / 159 (6.29%)<br>10 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 126 (1.59%)<br>2   | 2 / 33 (6.06%)<br>2 | 4 / 159 (2.52%)<br>4   |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 126 (1.59%)<br>2   | 2 / 33 (6.06%)<br>3 | 4 / 159 (2.52%)<br>5   |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 2 / 126 (1.59%)<br>2   | 2 / 33 (6.06%)<br>2 | 4 / 159 (2.52%)<br>4   |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 12 / 126 (9.52%)<br>15 | 3 / 33 (9.09%)<br>3 | 15 / 159 (9.43%)<br>18 |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                              | 8 / 126 (6.35%)<br>8   | 1 / 33 (3.03%)<br>1 | 9 / 159 (5.66%)<br>9   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                               | 9 / 126 (7.14%)<br>11  | 3 / 33 (9.09%)<br>3 | 12 / 159 (7.55%)<br>14 |
| Migraine<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 126 (0.00%)<br>0   | 2 / 33 (6.06%)<br>2 | 2 / 159 (1.26%)<br>2   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                           | 0 / 126 (0.00%)<br>0   | 2 / 33 (6.06%)<br>2 | 2 / 159 (1.26%)<br>2   |
| Sciatica                                                                                                   |                        |                     |                        |

|                                                                                                     |                         |                        |                         |
|-----------------------------------------------------------------------------------------------------|-------------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                                    | 0 / 126 (0.00%)<br>0    | 2 / 33 (6.06%)<br>2    | 2 / 159 (1.26%)<br>2    |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 15 / 126 (11.90%)<br>15 | 3 / 33 (9.09%)<br>3    | 18 / 159 (11.32%)<br>18 |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)          | 0 / 126 (0.00%)<br>0    | 2 / 33 (6.06%)<br>2    | 2 / 159 (1.26%)<br>2    |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 6 / 126 (4.76%)<br>6    | 5 / 33 (15.15%)<br>8   | 11 / 159 (6.92%)<br>14  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)                                         | 5 / 126 (3.97%)<br>5    | 2 / 33 (6.06%)<br>2    | 7 / 159 (4.40%)<br>7    |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                    | 14 / 126 (11.11%)<br>16 | 7 / 33 (21.21%)<br>7   | 21 / 159 (13.21%)<br>23 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                       | 36 / 126 (28.57%)<br>44 | 12 / 33 (36.36%)<br>19 | 48 / 159 (30.19%)<br>63 |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                                       | 13 / 126 (10.32%)<br>13 | 1 / 33 (3.03%)<br>1    | 14 / 159 (8.81%)<br>14  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 126 (0.79%)<br>1    | 2 / 33 (6.06%)<br>2    | 3 / 159 (1.89%)<br>3    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                          | 33 / 126 (26.19%)<br>38 | 7 / 33 (21.21%)<br>11  | 40 / 159 (25.16%)<br>49 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                      | 10 / 126 (7.94%)<br>10  | 2 / 33 (6.06%)<br>2    | 12 / 159 (7.55%)<br>12  |
| Vomiting                                                                                            |                         |                        |                         |

|                                                  |                         |                       |                         |
|--------------------------------------------------|-------------------------|-----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all) | 28 / 126 (22.22%)<br>30 | 6 / 33 (18.18%)<br>11 | 34 / 159 (21.38%)<br>41 |
| Skin and subcutaneous tissue disorders           |                         |                       |                         |
| Dermatitis acneiform                             |                         |                       |                         |
| subjects affected / exposed                      | 35 / 126 (27.78%)       | 1 / 33 (3.03%)        | 36 / 159 (22.64%)       |
| occurrences (all)                                | 45                      | 1                     | 46                      |
| Dry skin                                         |                         |                       |                         |
| subjects affected / exposed                      | 15 / 126 (11.90%)       | 2 / 33 (6.06%)        | 17 / 159 (10.69%)       |
| occurrences (all)                                | 20                      | 2                     | 22                      |
| Nail disorder                                    |                         |                       |                         |
| subjects affected / exposed                      | 1 / 126 (0.79%)         | 3 / 33 (9.09%)        | 4 / 159 (2.52%)         |
| occurrences (all)                                | 1                       | 3                     | 4                       |
| Pruritus                                         |                         |                       |                         |
| subjects affected / exposed                      | 12 / 126 (9.52%)        | 4 / 33 (12.12%)       | 16 / 159 (10.06%)       |
| occurrences (all)                                | 12                      | 5                     | 17                      |
| Rash                                             |                         |                       |                         |
| subjects affected / exposed                      | 28 / 126 (22.22%)       | 7 / 33 (21.21%)       | 35 / 159 (22.01%)       |
| occurrences (all)                                | 37                      | 10                    | 47                      |
| Rash maculo-papular                              |                         |                       |                         |
| subjects affected / exposed                      | 23 / 126 (18.25%)       | 5 / 33 (15.15%)       | 28 / 159 (17.61%)       |
| occurrences (all)                                | 25                      | 6                     | 31                      |
| Skin fissures                                    |                         |                       |                         |
| subjects affected / exposed                      | 5 / 126 (3.97%)         | 4 / 33 (12.12%)       | 9 / 159 (5.66%)         |
| occurrences (all)                                | 7                       | 9                     | 16                      |
| Skin ulcer                                       |                         |                       |                         |
| subjects affected / exposed                      | 0 / 126 (0.00%)         | 2 / 33 (6.06%)        | 2 / 159 (1.26%)         |
| occurrences (all)                                | 0                       | 2                     | 2                       |
| Renal and urinary disorders                      |                         |                       |                         |
| Dysuria                                          |                         |                       |                         |
| subjects affected / exposed                      | 1 / 126 (0.79%)         | 3 / 33 (9.09%)        | 4 / 159 (2.52%)         |
| occurrences (all)                                | 1                       | 3                     | 4                       |
| Musculoskeletal and connective tissue disorders  |                         |                       |                         |
| Arthralgia                                       |                         |                       |                         |
| subjects affected / exposed                      | 5 / 126 (3.97%)         | 2 / 33 (6.06%)        | 7 / 159 (4.40%)         |
| occurrences (all)                                | 5                       | 2                     | 7                       |
| Back pain                                        |                         |                       |                         |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 8 / 126 (6.35%) | 1 / 33 (3.03%)  | 9 / 159 (5.66%) |
| occurrences (all)           | 8               | 2               | 10              |
| Arthritis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 33 (6.06%)  | 2 / 159 (1.26%) |
| occurrences (all)           | 0               | 2               | 2               |
| Flank pain                  |                 |                 |                 |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 33 (6.06%)  | 2 / 159 (1.26%) |
| occurrences (all)           | 0               | 2               | 2               |
| Muscle spasms               |                 |                 |                 |
| subjects affected / exposed | 2 / 126 (1.59%) | 3 / 33 (9.09%)  | 5 / 159 (3.14%) |
| occurrences (all)           | 4               | 3               | 7               |
| Muscular weakness           |                 |                 |                 |
| subjects affected / exposed | 6 / 126 (4.76%) | 2 / 33 (6.06%)  | 8 / 159 (5.03%) |
| occurrences (all)           | 7               | 4               | 11              |
| Infections and infestations |                 |                 |                 |
| Cellulitis                  |                 |                 |                 |
| subjects affected / exposed | 3 / 126 (2.38%) | 2 / 33 (6.06%)  | 5 / 159 (3.14%) |
| occurrences (all)           | 3               | 2               | 5               |
| Folliculitis                |                 |                 |                 |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 33 (6.06%)  | 2 / 159 (1.26%) |
| occurrences (all)           | 0               | 4               | 4               |
| Conjunctivitis              |                 |                 |                 |
| subjects affected / exposed | 3 / 126 (2.38%) | 2 / 33 (6.06%)  | 5 / 159 (3.14%) |
| occurrences (all)           | 4               | 2               | 6               |
| Furuncle                    |                 |                 |                 |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 33 (6.06%)  | 2 / 159 (1.26%) |
| occurrences (all)           | 0               | 2               | 2               |
| Nail infection              |                 |                 |                 |
| subjects affected / exposed | 2 / 126 (1.59%) | 2 / 33 (6.06%)  | 4 / 159 (2.52%) |
| occurrences (all)           | 3               | 2               | 5               |
| Paronychia                  |                 |                 |                 |
| subjects affected / exposed | 2 / 126 (1.59%) | 5 / 33 (15.15%) | 7 / 159 (4.40%) |
| occurrences (all)           | 3               | 6               | 9               |
| Oral herpes                 |                 |                 |                 |
| subjects affected / exposed | 1 / 126 (0.79%) | 2 / 33 (6.06%)  | 3 / 159 (1.89%) |
| occurrences (all)           | 1               | 3               | 4               |

|                                    |                   |                 |                   |
|------------------------------------|-------------------|-----------------|-------------------|
| Pharyngitis                        |                   |                 |                   |
| subjects affected / exposed        | 2 / 126 (1.59%)   | 2 / 33 (6.06%)  | 4 / 159 (2.52%)   |
| occurrences (all)                  | 2                 | 2               | 4                 |
| Upper respiratory tract infection  |                   |                 |                   |
| subjects affected / exposed        | 3 / 126 (2.38%)   | 4 / 33 (12.12%) | 7 / 159 (4.40%)   |
| occurrences (all)                  | 3                 | 4               | 7                 |
| Urinary tract infection            |                   |                 |                   |
| subjects affected / exposed        | 6 / 126 (4.76%)   | 2 / 33 (6.06%)  | 8 / 159 (5.03%)   |
| occurrences (all)                  | 6                 | 2               | 8                 |
| Metabolism and nutrition disorders |                   |                 |                   |
| Decreased appetite                 |                   |                 |                   |
| subjects affected / exposed        | 18 / 126 (14.29%) | 2 / 33 (6.06%)  | 20 / 159 (12.58%) |
| occurrences (all)                  | 19                | 2               | 21                |
| Hypoalbuminaemia                   |                   |                 |                   |
| subjects affected / exposed        | 7 / 126 (5.56%)   | 3 / 33 (9.09%)  | 10 / 159 (6.29%)  |
| occurrences (all)                  | 7                 | 3               | 10                |
| Dehydration                        |                   |                 |                   |
| subjects affected / exposed        | 14 / 126 (11.11%) | 2 / 33 (6.06%)  | 16 / 159 (10.06%) |
| occurrences (all)                  | 15                | 2               | 17                |
| Hypokalaemia                       |                   |                 |                   |
| subjects affected / exposed        | 6 / 126 (4.76%)   | 2 / 33 (6.06%)  | 8 / 159 (5.03%)   |
| occurrences (all)                  | 6                 | 3               | 9                 |

## **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